Williams Syndrome:

Genetics, Neuroimaging, Cognition, and Clinical Issues

Proceedings of the 12 International Professional Conference on Williams Syndrome

Inna Fishman, Terry Monkaba, Ursula Bellugi

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Nearly 50 years after the original two articles describing a few individuals with a particular disorder (Williams et al, 1961, and Beuren et al, 1962) followed by the discovery of its genetic basis in 1993 by Morris et al., the field of research on Williams Syndrome is clearly dynamic and expanding rapidly. It attracts growing numbers of researchers from an increasing variety of disciplines, including genetics, brain and neurosciences, psychology and linguistics, to name a few. The reason for such a wide cross-disciplinary interest in this unique and rare human condition is that Williams Syndrome provides a singular and exceptional framework for understanding the relationship between genes, brain circuits and behavior – a true goal of all sciences concerned with human life. Specifically, Williams Syndrome is one of the very few neurodevelopmental disorders that are associated with a known genetic etiology and an undoubtedly unique behavioral, social and cognitive profile. This combination of well defined behavioral features and known genotype offers a one of a kind opportunity for identifying the links between genotype, underlying brain mechanisms and the resulting altered trajectory of social and cognitive development.

The current volume summarizing the proceedings of the 12th International Professional Conference on Williams Syndrome reflects the wealth of current research and findings that can only be generated when scientists from such diverse disciplines as molecular genetics and psychology, animal models of behavior and social cognition – disciplines that traditionally carry out their investigations independently and in parallel to each other – come together to interact. The current collection of abstracts presented at the Conference attests to the synthesis of ideas and innovative methods spurred by such potential collaborations, as is amply illustrated throughout the monograph.

Part I, summarizing the first session of the Conference chaired by Dr. Julie Korenberg, of the Cedars-Sinai Medical Center at UCLA and the Brain Institute at University of Utah, is concerned with the recent developments in the filed of genotype-phenotype correlations in Williams Syndrome. The talks presented in this session described some recent findings on a family of transcription factors in the Williams region and presented a genome-wide array analyses of gene expression in Williams Syndrome. Part II, summarizing the second session of the Conference chaired by Dr. Lucy Osborne, of University of Toronto, presents the results of animal studies, in which the mouse genome is manipulated such that genes from the region commonly deleted in Williams Syndrome are knocked out. The talks included in this session review the phenotypic characterization of these mouse models.

Next, in her Keynote Address, Dr. Barbara Pober of the Massachusetts General Hospital and Harvard Medical School, discussed the current state of affairs regarding development of genetically informed treatments and novel therapies for individuals with Williams Syndrome. Her address was followed by a session on neuroimaging research co-chaired by Drs. Allan Reiss of the Stanford University School of Medicine and Karen Berman of the National Institutes of Health, summarized in Part III. The abstracts presented in this session described the recent findings pertaining to functional brain patterns evidenced by multimodal neuroimaging studies, including functional MRI, event-related potentials, diffusion tensor imaging and white-matter tractography.

Part IV summarizes a special session on the phenotype of a specific subgroup of Williams Syndrome, namely those with duplications of the typically deleted region

(dup7q11.23). The featured speakers of this session, Drs. Colleen Morris, of the University of Nevada School of Medicine, and Carolyn Mervis, of the University of Louisville, contrasted the profiles of these unique Williams Syndrome cases with the "typical" Williams group, concluding that one or more genes in the 7q11.23 region were dosage sensitive and were implicated in language and cognitive development.

Part V sums up a session on anxiety and other psychiatric conditions affecting persons with Williams Syndrome, chaired by Dr. Elisabeth Dykens of Vanderbilt University. Beyond specific findings in this domain, the abstracts included in this session also illustrate broader methodological complexities associated with research on psychopathology in individuals with developmental disabilities. This session was followed by a session on cognitive functioning in Williams Syndrome. Chaired by Dr. Klein-Tasman of University of Wisconsin – Milwaukee, this session included presentations on such diverse issues as the value of longitudinal approach to studying cognitive profile in neurodevelopmental disorders such as Williams syndrome, vulnerability of the dorsal visual stream in developmental disorders, and language learning patterns in toddlers with Williams Syndrome. The final platform session of the Conference chaired by Dr. Helen Tager-Flusberg, of the Boston University School of Medicine, is summarized in Part VII. These abstracts pertain to research on social cognition and the social phenotype of Williams Syndrome and touch upon such methodological challenges as what behavioral measures are best suited to investigating the social phenotype in Williams Syndrome or whether the cultural and ethnic context has an effect on the sociability associated with Williams Syndrome.

Lastly, the final section of this volume lists the abstracts of the posters presented at the Conference, ranging in the issues covered from behavioral interventions to improve cognitive functioning to the risk of hypertension associated with parental origin of the deletion; from understanding humor by individuals with Williams Syndrome to autonomic correlates of face processing; and from transcription factors implicated in sociability to amygdala volume and association between cerebral shape and social use of language.

One of our primary objectives in publishing this collection of abstracts is to illustrate the possibilities of scientific cross-fertilization made possible by bringing together researchers who cut across different fields and disciplines. We are grateful to our colleagues and collaborators who have taken part in the 12th International Professional Conference on Williams Syndrome and allowed us to learn from each other. We offer our special thanks to the Williams Syndrome Association and the Salk Institute, for their support of this effort.

Inna Fishman, Ursula Bellugi, and Terry Monkaba
Laboratory for Cognitive Neuroscience
The Salk Institute
and the Williams Syndrome Association

PROFESSIONAL CONFERENCE ABSTRACTS
TABLE OF CONTENTS

SESSION 1:
Genetics and Genotype-Phenotype Correlations **2**

***Featured Speaker*: Julie Korenberg**
Molecular Genetics of Williams Syndrome: Windows into Human Biology **3**

Function of TFII-I Family Factors Involved in Williams Syndrome **3**
A. Roy

Infantile Spasms in Individuals with Williams-Beuren Syndrome are Associated with Deletion of the MAGI2 Gene on Chromosome 7q11.23-7q21.11 **3**
C. R. Marshall, E. J. Young, A. M. Pani, M. L. Freckmann, K. Koch, et al.

Genome-Wide Analyses of Gene Expression in Williams Syndrome **5**
T. Tirosh-Wagner, R. Weiss, M. C. Gao, L. Dai, J. Korenberg, et al.

SESSION 2:
Animal Models of Williams Syndrome **6**

***Featured Speaker*: Lucy Osborne**
Mouse Models of Williams Syndrome **7**

Induced Chromosome 5G2 Deletions Cause Hypersociability and Other Features of Williams Syndrome in Mice **7**
H. H. Li, M. Roy, U. Kuscuoglu, C. M. Spencer, B. Halm, et al.

Phenotypic Analysis of a GTF2IRD1Mouse Model of Williams Syndrome **8**
E. J. Young, J. O'Leary, E. Tam, L. R. Osborne

***Keynote Address*: Barbara Pober**
New Approach to Genetically Informed Treatment **11**

SESSION 3:
Neuroimaging and Brain Functioning in Williams Syndrome **12**

Featured Speaker: **Allan Reiss**
Neuroimaging as a Tool to Elucidate Gene-Brain-Behavior Associations in Williams Syndrome **13**

Karen Berman
Update on the NIMH Multimodal Neuroimaging Study of Williams Syndrome **13**

Anomalous Neurofunctional Lateralization in Williams Syndrome **14**
K. Roe, C. Coutlee, C. Mervis, P, Kohn, K. Berman, et al.

The Mirror Neuron System Reflects Hypersociability in Williams Syndrome: Brain basis of Empathy, a Meta-Analytical Approach **15**
F. Hoeft, A. Karchemskiy, B. Haas, U. Bellugi, A. Reiss, et al.

Genetically Regulated Sociability: Hyper-Amygdala Reactivity and Event-Related Responses to Positive Social Stimuli in Williams Syndrome **16**
B. Haas, D. Mills, A. Yam, F. Hoeft, U. Bellugi, A. Reiss

SESSION 4:
Phenotype of the 7Q11.23 Duplication **17**

Featured Speakers: **Colleen Morris**
Copy Number Variation in the Williams Syndrome Region: Detection of 7q11.23Duplication by Microarray Allows Phenotypic Comparison **18**

Carolyn Mervis
Language and Cognitive Development of Children who have Williams Syndrome or Duplication of the Williams Syndrome Region **18**

SESSION 5:
Anxiety and Other Psychiatric Problems **20**

Featured Speaker: **Elisabeth Dykens**
Anxiety in Williams Syndrome: Beyond Diagnoses to Broader Conceptual and Therapeutic Challenges **21**

Anxiety Disorders in Children with Williams Syndrome, their Mothers, and Siblings: Implications for the Etiology of Anxiety Disorders **21**
O. Leyfer, J. Woodruff-Borden, C. Mervis

Emerging Executive Functioning: Relations to Behavioral Difficulties in Young Children with Williams Syndrome **23**
B. Klein-Tasman, F. J. Gallo

Hyperacusis and phonophobia in Williams Syndrome **23**
O. Zarchi, J. Attias, D. Gothelf

SESSION 6:
Updates on Cognition in Williams Syndrome **25**

***Featured Speaker*: Bonnie Klein-Tasman**
Updates on Cognition in Williams Syndrome **26**

A Longitudinal Study of Cognitive Functioning in Williams Syndrome **27**
M. Porter, H. Dodd

Assessing Attention in Children with Williams Syndrome and Down's Syndrome Using a New Comprehensive Attention Battery: Do These Problems Relate to Visual Dorsal Cortical Stream Deficits? **27**
K. Breckenridge, J. Atkinson

Statistical Language Learning and Face Processing by Infants and Toddlers with Williams Syndrome **28**
C. Cashon, C. Allen, O. Ha, G. Estes, J. Saffran, C. Mervis

Auditory Memory in Williams Syndrome: Is rote Memory Really a Strength? **29**
J. Marler, F. Wightman, D. Kisler, J. Roy, C. Mervis

SESSION 7:
Social Cognition and Social Phenotype of Williams Syndrome **31**

***Featured Speaker*: Helen Tager-Flusberg**
Investigating the Social Phenotype in Williams Syndrome: Methodological Challenges **32**

Comprehension of Communicative Intent Behind Pointing and Gazing Gestures by Young Children with Williams Syndrome or Down Syndrome **32**
A. John, C. Mervis

Observational Assessments of Attachment and Temperament in Young Children with Williams Syndrome: Toward a Profile of Early Socio-emotional Functioning **33**
D. Plesa-Skwerer, M. Lindeke, K. Ogrodnik, L. Ciciolla, H. Tager-Flusberg

Cross-Cultural Studies of Williams Syndrome **34**
C. Zitzer-Comfort, U. Bellugi, J. Reilly

Multidisciplinary Poster Session **36**

Do Children with Williams Syndrome have an Impairment in Declarative Function? **37**
K. Asada, K. Tomiwa, M. Okada, S. Itakura

Patterns of Early Language Development of Children with Williams Syndrome **37**
A. Becerra, C. Mervis

Understanding of Others' Intentions by Young Children with Williams Syndrome **39**
A. Becerra, A. John, C. Mervis

Reading Abilities of 9—17-Year-Olds with Williams Syndrome: Impact of Reading Method **40**
A. Becerra, A. John, E. Peregrine, C. Mervis

Self-Recognition by Toddlers with Williams Syndrome **41**
C. Cashon, A. John, C. Mervis

Sensory Processing Difficulties Predict Internalizing Symptoms, ADHD Symptoms, and Repetitive Behaviors in 4-10 year-old Children with Williams Syndrome **41**
N. Crawford, A. John, J. Woodruff-Borden, C. Mervis

Early Manifestation of the Social/non-Social Anxiety Distinction in Williams Syndrome **42**
H. Dodd, M. Porter, G. Peters, R. Rapee

Neuroplasticity in Williams Syndrome – Intervention on Attention Problems **43**
M. Férnandez-Prieto, A. Sampaio, M. Lens, E. Garayzábal, Ó. Gonçalves, & A. Carracedo

Reflexive Orienting to Non-Predictive Gaze and Arrow Cues in Williams Syndrome **44**
A. Fine, D. Skwerer, L. Ciciolla, R. Joseph, H. Tager-Flusberg

Hypertension: High Resolution Array Analyses Reveal the Risk in Williams Syndrome is Determined by Gender and Parent of Origin **45**
M. Gao, H. Wijesuriya, L. Dai, M. Appelbaum, X. Chen, A. Simon, J. Korenberg

Producing and Understanding Oral and Graphic Humour by Williams Syndrome People **46**
E. Garayzábal, M. Capo, A. Sampaio, M. Fernández

Feeding Disorders in Williams Syndrome **46**
S. Greis

Motor Function in Adults with Williams Syndrome: Is There Evidence for Basal Ganglia or Cerebellar dysfunction? **47**
D. Hocking, N. Rinehart, J. McGinley, J. Bradshaw

Question-Asking Behavior in Children and Adolescents with Williams Syndrome: Anticipation of Positive and Negative Events **48**
K. Janke, K. Phillips, B. Klein-Tasman

Genes, Neural systems, and Social Behavior: Autonomic Correlates of Processing Upright and Inverted Affective Faces in Williams Syndrome **49**
A. Järvinen-Pasley, N. Tsuchiya, M. K. Leonard, A. Yam, K. J. Hill, et al.

Sensory Modulation in Children with Williams Syndrome **50**
A. John, C. Mervis

Variability of Language Abilities of Young 4-Year-Olds Who Have Williams Syndrome **51**
A. John, A. Becerra, E. Peregrine, C. Mervis

Implicit Processing of Facial Expression During Interpretation of Gaze Direction in Adolescents and Adults with Williams Syndrome **52**
M. Kennedy, D. Plesa-Skwerer, L. Ciciolla, M. Lindeke, H. Tager-Flusbeg

Is it Williams Syndrome? GTF2I Implicated the Sociability and GTF2IRD1 in Visual-Spatial Construction Revealed by High Resolution Arrays **53**
L. Dai, U. Bellugi, X. Chen, A. Pulst-Korenberg, A. Järvinen-Pasley, et al.

Music Therapy Interventions for Difficulties-with Mathematics for Individuals with Williams Syndrome (WS) **53**
E. Kwak

Strangers and Spiders: How Young Children with Williams Syndrome Respond to Social and Non-social Fear-eliciting Events **54**
M. Lindeke, D. Plesa-Skwerer, L. Ciciolla, H. Tager-Flusberg

Amygdala Volume and Sociability in Williams Syndrome and Normal Controls **55**
M. Martens, S. Wilson, D. Reutens

Cognitive and Behavioral Profile of Australian Individuals with Williams Syndrome **56**
M. Martens, S. Wilson, D. Reutens

New Height, Weight and Head Circumference Charts for Children with Williams Syndrome in the United Kingdom **57**
N. Martin, W. Smith, M. Preece, T. Cole

Polysomnography Findings in Children with Williams Syndrome **57**
T. Mason, R. Arens, J. Sharman, A. Pack, P. Kaplan

Longitudinal Assessment of Receptive Vocabulary in Children and Adolescents with Williams Syndrome: A Multilevel Modeling Analysis **58**
C. Mervis, D. Kistler, E. Peregrine, A. John

Relations between Emotion Regulation and Adaptive Functioning in Children and Adolescents with Williams Syndrome **59**
K. Phillips, B Klein-Tasman

Association between Cerebral Shape and Social Use of Language in Williams Syndrome **60**
Y. Searcy, D. Gothelf, J. Reilly, U. Bellugi, A. Reiss, et al.

Growth Pattern in Japanese Children with Williams Syndrome. Does it Relate to the Neurobehavioral Phenotype? **60**
K. Tomiwa, K. Murashima, M. Okada, S. Okazaki

Face Processing Strength in Williams Syndrome Extends to Memory for Faces **61**
A. Yam, Y. Searcy, K. Hill, M. Grichanik, U. Bellugi

PROCEEDINGS
OF THE
WILLIAMS SYNDROME ASSOCIATION
PROFESSIONAL CONFERENCE
2008

Inna Fishman
Terry Monkaba
Ursula Bellugi

SESSION 1

GENETICS AND GENOTYPE-PHENOTYPE CORRELATIONS

Featured Speaker: **Julie Korenberg, M.D., Ph.D.:** Molecular Genetics of Williams Syndrome: Windows into Human Biology

Platform Presentations:

A. Roy:

Function of TFII-I Family Factors Involved in Williams Syndrome

L. Osborne:

Infantile Spasms in Individuals with Williams-Beuren Syndrome are Associated with Deletion of the MAGI2 Gene on Chromosome 7q11.23-7q21.11

L. Dai:

Genome-wide Analyses of Gene Expression in Williams Syndrome

Molecular Genetics of Williams Syndrome: Windows into Human Biology

J. Korenberg

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Genetics is my favorite way of thinking: Williams syndrome seen through the eyes of a geneticist.

Williams syndrome (WS) is the most compelling model in which to link the basis of human emotion and behavior to their biological origins. The explanatory power of human genetics in WS rests on the recent revolution in understanding the human genome but more specifically on the ability to link genetic with behavioral variation at high resolution. WS is due to the deletion of about 25 genes located in a stretch of genomic DNA located on chromosome 7q11.23. Further understanding of which genes may contribute to specific features of WS makes use of rare individuals with smaller deletions, of variation in gene expression remaining on the non-deleted chromosome 7, and of further study of the expression of WS region genes in non-human primate brain. The goal of this presentation is to describe some of these genetic mechanisms that appear to contribute to the features of Williams syndrome and to suggest how to use this information may inform brain development and adult function.

Function of TFII-I Family Factors, Involved in Williams-Bueren Syndrome

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Williams-Beuren Syndrome (WBS) is a rare developmental disorder that is caused by a hemizygous microdeletion of approximately 1.5 MB, spanning 17 genes at chromosomal location 7q11.23. However, we lack a complete understanding of molecular basis for WBS. Although this multisystem dysfunction with unusual craniofacial, behavioral and cognitive features occurs most likely due to haplo-insufficiency of several genes, rare cases with much smaller deletions have provided clues to identifying specific genes that may be causal to distinctive physical and cognitive defects. Two of these genes, *GTF2I* and *GTF3* encode the TFII-I family of transcription factors. TFII-I and its relative MusTRD1/BEN exhibit extensive and overlapping expression patterns in a variety of tissues during mouse pre- and post-implantation development, suggesting a functional role for these proteins in early development. These data strongly implicate TFII-I family proteins are causal to the craniofacial defects observed in WBS patients. To begin to understand the molecular basis for the craniofacial traits associated with WBS, it is thus imperative to elucidate the functional role of transcription factors TFII-I and BEN in cell culture and animal models. Here we discuss the biochemical properties of TFII-I and BEN and identify a host of target genes that can lead to elucidation of pathways important for the pathology of WBS.

Infantile Spasms in Individuals with Williams-Beuren Syndrome are Associated with Deletion of the MAG12 Gene on Chromosome 7q11.23-7q21.11

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Williams-Beuren syndrome (WBS) is characterized by numerous physical, cognitive and behavioral symptoms, but seizures have only rarely been reported. WBS-associated deletions larger than the common 1.55 Mb deletion have been reported, and are often associated with a more severe phenotype with serious impairments in cognitive function sometimes accompanied by Infantile Spasms.

Infantile spasms (IS, also known as West syndrome) is a disorder of the developing nervous system that begins in the first year of life, most commonly between 4 and 8 months of age. The spasms have a distinctive high-voltage, disorganized pattern on electroencephalogram (EEG), called hypsarrhythmia, that must be abolished if the prognosis is to be improved, otherwise the immature brain appears to remain hyper-excitable and proper neurodevelopment is impeded.

In order to determine whether a novel locus for IS could be identified near the WBS region, we mapped the deletion boundaries in a cohort of individuals with deletions of 7q11.23-q21, many of whom had a diagnosis of WBS. Using comparative intensity analysis with single nucleotide polymorphism microarrays we defined hemizygous deletions of 7q11.23-q21.1 ranging from 1.8 Mb to more than 25 Mb in size in 27 individuals. We defined a smallest region of overlap associated with IS of approximately 700 kb, spanning part of the 1.4 Mb membrane- associated guanylate kinase inverted-2 gene (*MAGI2*), suggesting this gene is a new, dominant locus for IS.

MAGI2 was originally characterized as a scaffold protein interacting with NMDA receptors at excitatory synapses but has since been shown to interact with many different proteins pre- and post-synaptically and at both excitatory and inhibitory synapses. Perhaps the most intriguing interaction of MAGI2 is that with stargazin, the protein mutated in the *stargazer* mouse, one of the first and best characterized mouse models of epilepsy.

The identification of this new locus for IS has implications for the clinical management of individuals with WBS who have large deletions of 7q11.23-q21.1. Infants with WBS and deletions that extend to *MAGI2* present with additional clinical features to those found in individuals with the classic deletion. These children exhibit very delayed motor and developmental milestones compared to children with typical WBS, often in combination with hypotonia and severe intellectual disability. Their prognosis is also complicated by the presence of IS which may further impact upon their neurological development. A longitudinal study of the outcome of these individuals would determine the extent and severity of their developmental impairment and help to establish some prognostic guidelines for other families of newly diagnosed children with similar deletions.

Genome-Wide Analyses of Gene Expression in Williams Syndrome

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Williams syndrome is a neurodevelopmental disorder due to the deletion of a ~1.5 Mb region of chromosome band 7q11.23. Although the features of WS are ultimately due to the decreased copy number of the ~25 genes, the critical downstream biological pathways that alter development and adult function are unknown. WS provides a unique human model in which to combine high-resolution array analyses to determine the components of these pathways.

In this study, we determined the deletion in a cohort of 21 subjects with WS and asked whether genome-wide approaches querying 22,000 genes at the single exon level, were capable of sensitively measuring alterations of two-fold reduction in single gene transcripts. Whole genome gene expression analysis was performed on total RNA samples from 21 WS DNAs with the common deletion and 6 normal controls. RNAs were labeled using a whole transcript sense target labeling assay after an rRNA reduction step. Biotinylated target was hybridized to Affymetrix GeneChip Exon 1.0 ST (sense target) arrays containing 6.5 million probe features. Probe level data was processed with RMA analysis (Robust Multiarray Analysis) for 22,000 RefSeq supported genes, and for exon-level results. Unexpectedly, rank products analysis (RP) revealed a 25-50% (1-2 fold) reduction in expression levels across chromosome 7 Williams region transcripts as the most significant genome-wide reduction observed between normal and affected groups. Of 22,000 gene transcripts queried, WS genes represented 10 of the top 11 transcripts with reduced expression. These data indicate that genome wide analyses can be used to establish both deleted genes and non-deleted genes whose transcription is altered, providing the opportunity to identify genetic networks that mediate the features of WS.

SESSION 2

ANIMAL MODELS OF WILLIAMS SYNDROME

Featured Speaker: **Lucy Osborne, Ph.D.**: Mouse Models of Williams Syndrome

Platform Presentations:

H. H. Li:

Induced Chromosome 5G2 Deletions Cause Hypersociability and other Features of Williams Syndrome in Mice

E. Young:

Phenotypic Analysis of a GTF2IRD1 Mouse Model of Williams Syndrome

Mouse Models of Williams-Beuren Syndrome

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In an attempt to dissect the contribution of individual genes to the complex and varied phenotype associated with Williams-Beuren syndrome (WBS), researchers have turned to mouse models. The mouse genome is easily manipulated to produce animals that are genetic copies of humans with genetic conditions, be it with null mutations, hypomorphic mutations, point mutations or even large deletions encompassing many genes.

Over the past few years, several mouse models knocking out genes from the region commonly deleted in WBS, have been generated. The first gene to be inactivated in the mouse was elastin (*Eln*), and this proved to be an excellent model for most, if not all, of the cardiovascular symptoms associated with ELN hemizygosity in humans. Subsequently, mouse models were generated for *Clip2*, *Limk1*, *Fkbp6, Stx1a, Fzd9*, and *Gtf2ird1* and they have provided valuable information about the potential role of theses genes in WBS.

The phenotypic characterization of these mouse models has been quite different but much of the analyses have concentrated on behavior and cognition, aspects that present unique difficulties for assessment in rodents. Not all genes that are haploinsufficient in humans prove to be so in mice, and the effect of the genetic background on which the mice are maintained can also have a significant effect on the penetrance of many phenotypes. So, although mouse models are powerful tools, the information garnered from their study must be carefully interpreted.

The existing mouse models certainly seem to implicate *CLIP2* and *GTF2IRD1* in WBS, however, even combined, the different models do not recapitulate the full phenotypic spectrum of WBS. This suggests either that an additional gene or genes are haploinsufficient in WBS, or that WBS is the combinatorial result of the deletion of multiple genes rather than solely the result of an additive effect. New mouse models with multiple gene deletions are now emerging and these will help to provide the answer.

Induced Chromosome 5G2 Deletions Cause Hypersociability and Other Features of Williams-Beuren Syndrome in Mice

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The neurodevelopmental disorder Williams-Beuren syndrome is caused by spontaneous ~1.5Mb deletions comprising 25 genes on human chromosome 7q11.23. To functionally dissect the deletion and identify dosage-sensitive genes, we created two half-deletions of the conserved syntenic region on mouse chromosome 5G2. Proximal deletion mice (PD) are missing *Gtf2i* to *Limk1,* distal deletion mice

(DD) lack *Limk1* to *Fkbp6*, and double heterozygotes (D/P) model the complete human deletion. We found that resulting transcript levels in brain are generally consistent with gene dosage. Increased sociability and acoustic startle response are associated with PD, and cognitive defects with DD. PD and D/P are growth-retarded, while skulls are shortened and brains are smaller in DD and D/P. Lateral ventricle volumes are reduced, and neuronal cell density in the somatosensory cortex is increased, in PD and D/P. Motor skills are most impaired in D/P. Together, these partial deletion mice model crucial aspects of the human disorder and serve to identify genes and gene networks contributing to the neural substrates of complex behaviors and behavioral disease.

Phenotypic Analysis of A GTF2IRD1 Mouse Model of Williams-Beuren Syndrome

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Williams-Beuren syndrome (WBS) is a complex disorder, caused by the hemizygous deletion of 26 genes on chromosome 7q11.23. WBS is characterized by a unique behavioral and cognitive profile, in addition to numerous physical symptoms, but although haploinsufficiency for the elastin gene has been shown to be responsible for the cardiovascular disease, no other gene has been unequivocally linked to this disorder. The common WBS deletion spans 1.55 million base pairs of DNA, and recent research has narrowed the region contributing to the major phenotypes to the telomeric portion, through the identification of individuals with smaller deletions.

We have generated a mouse model of one of the General Transcription Factor 2I (GTF2I) genes implicated in WBS and demonstrated neurological features similar to some of those seen in WBS. Mice with heterozygous or homozygous disruption of *Gtf2ird1* exhibit decreased fear and aggression and increased social behaviors, reminiscent of the hyper-sociability and diminished fear of strangers that are hallmarks of Williams-Beuren syndrome. In addition, we identified amygdala-based learning difficulties, although hippocampal-based learning remained intact as evidenced by performance in the Morris water maze that was comparable to wild-type littermates.

The interaction between the orbitofrontal cortex (OFC) and the amygdala is thought be crucial for making appropriate social judgments. Lesions of the OFC are associated with social disinhibition, and disturbance of the functional interaction between the OFC and amygdala in subjects with WBS is thought to be contributing to social disinhibition, reduced reactivity to social cues and an increased tendency to approach strangers. We assessed brain activity in the amygdala and frontal cortex in our mouse model, through the analysis of expression of the immediate-early transcription factor gene, *c-Fos*, which is activated transiently and rapidly in response to a wide variety of cellular stimuli. In this case we used the open field test as a fear stimulus, since the *Gtf2ird1*-/- mice showed marked differences in their level of anxiety in this test, when compared to wild-type mice. We analyzed both baseline *c-Fos* expression, where tissue was taken from animals in their home cage, and expression of *c-Fos* in response to fear/stress, where tissue was taken 30 minutes after exposure to the open field. We assessed expression of both mRNA and protein using quantitative real-time PCR analysis of brain regions and immunostaining of whole brain sections. We found that baseline *c-Fos* mRNA expression was equivalent in the *Gtf2ird1*-/- and wild- type

mice, but upon exposure to the open field, a 60% reduction in the expression of *c-Fos* was observed in the frontal cortex of *Gtf2ird1*-/- mice relative to wild-type mice. These results were confirmed by protein immunostaining, where we observed a decrease in c-Fos immunoreactivity in the medial prefrontal cortex, including the prelimbic and infralimbic cortex, and the cingulate cortex. These alterations in c-Fos protein correlate well with the changes in mRNA expression and suggest that there are significant differences in activation of the prefrontal cortex in response to fear/stress in our mouse model compared to wild type animals, which may correlate with the regionally reduced activity seen in subjects with WBS.

KEYNOTE ADDRESS

Keynote Speaker: **Barbara Pober, M.D.**: Genetically Informed Therapy

New Approach to Genetically Informed Treatment

B. Pober

Massachusetts General Hospital and Harvard Medical School

Recent advances in understanding the molecular of genetic disorders offer unheralded opportunities to develop genetically informed therapy. Such therapy can be viewed as consisting of either gene therapy, through replacement of absent or non-functioning genes, or pathway therapy, through regulation of the pathway perturbed by the genetic mutation.

To date, gene therapy successes have been few in number. However recent work replacing the *RPE65* gene in patients with a genetic form of severe retinal dystrophy is encouraging. This work will be discussed to highlight the possibilities as well as the challenges of gene replacement therapy. The most robust examples of pathway therapy consist of treatment of inborn errors of metabolism by implementation of special diets and/or cofactor supplementation. Exciting new approaches, such as treating Progeria with farnesyl transferase inhibitors, and treating Marfan syndrome with Losartin, will also be discussed.

Can insights be gained from the above precedents that will lead to novel therapies for patients with Williams syndrome? This question was the central focus of a recent meeting entitled "Cardiovascular Disease in Williams-Beuren Syndrome: Understanding Pathophysiology to Pioneer Treatment" held May 7-9, 2008, which brought clinical experts with a broad swath of laboratory scientists working in the field of vascular biology. The current state of knowledge is that deletion of one elastin allele is the major cause of cardiovascular disease in individuals with Williams syndrome. Experimental data indicate that increasing elastin protein levels, either in cells cultured from individuals with Williams syndrome or in elastin knock out mice, ameliorates the cardiovascular phenotype. Ways to supply additional elastin protein during vascular development such as through gene therapy or micro-RNAs to "turn on" the intact elastin allele were discussed as potential therapeutic targets. Although theoretically possible, the feasibility of introducing these therapies at the correct developmental stage and to the correct tissue remains daunting. Far less is known about pathway abnormalities triggered by elastin protein deficiency so that opportunities for targeted pharmacotherapy are currently elusive.

The cardiovascular disease that typifies Williams syndrome appears to be the easiest and most compelling target for development of novel therapies. If successful, then lessons learned from these pioneering efforts may set the foundation for developing treatments for other aspects of Williams syndrome.

SESSION 3

NEUROIMAGING AND BRAIN FUNCTIONING IN WILLIAMS SYNDROME

Featured Speakers: **Allan Reiss, M.D.:** Neuroimaging as a Tool to Elucidate Gene-Brain-Behavior Associations in Williams Syndrome
Karen Berman, M.D.: Update on the NIMH Multimodal Neuroimaging Study of Williams Syndrome

Platform Presentations:

K. Roe:
Anomalous Neurofunctional Lateralization in Williams Syndrome

F. Hoeft:
The Mirror Neuron System Reflects Hypersociability in Williams Syndrome: Brain Basis of Empathy, a Meta-analytical Approach

B. Haas:
Genetically Regulated Sociability: Hyper-amygdala Reactivity and Event-related Responses to Positive Social Stimuli in Williams Syndrome

Neuroimaging as a Tool to Elucidate Gene-Brain-Behavior Associations in Williams Syndrome

A. L. Reiss

Center for Interdisciplinary Brain Sciences Research (CIBSR), Stanford University School of Medicine

Williams syndrome is an intriguing and enigmatic neurodevelopmental condition that affects motor, sensory, language, cognitive, emotional and social development. Because the genetic risk factors for this condition have been identified, there is now the opportunity to begin to develop a better understanding of how genetic (and environmental) factors affect brain development and function, and how this ultimately translates into strengths and weaknesses in learning and behavior.

As a component of the multi-site program project grant based at the Salk Institute, the Stanford Center for Interdisciplinary Brain Sciences Research (CIBSR) has conducted multi-modal brain imaging studies in individuals affected by Williams syndrome for over 10 years. In the context of increased knowledge of the cognitive-behavioral phenotype associated with this condition as well as molecular genetic pathways, this neuroimaging research has begun to contribute to a better understanding of brain mechanisms in this condition.

This presentation will provide an overview of the progression of neuroimaging studies and results from the Stanford CIBSR, with an emphasis on how more recent studies have built upon previous research findings. I also will review how our present knowledge of brain structure and function in Williams syndrome is contributing to a more cohesive, integrated understanding of learning and behavioral function in affected individuals, as well as the generation of new questions for future research. Finally, I will present information pertaining to how neuroimaging research can help inform and facilitate new avenues for treatment of cognitive and behavioral problems associated with Williams syndrome.

Update on the NIMH Multimodal Neuroimaging Study of Williams Syndrome

K. F. Berman

Section on Integrative Neuroimaging, National Institutes of Mental Health, NIH

Brain function and dysfunction occurs at multiple levels of neural organization, the most basic of which is gene expression, which, in turn, works at the cellular and neural-system levels to confer individual variation in cognition and behavior. Neuroimaging can access each of these levels of neural function and elucidate the relationship between them in health and disease. With its unique profile of striking behavioral features, Williams syndrome provides a unique opportunity to explore fundamental questions about neurogenetic mechanisms and brain plasticity in development. Because the genes involved in WS are known, the study of neural mechanisms in WS affords a privileged setting for investigating genetic influences on complex brain functions in a "bottom-up" way.

The goals of the NIMH multimodal neuroimaging study of Williams syndrome are to 1) define the neural phenotype underlying the unique cognitive and behavioral features of WS, 2) define separable neural subsystems in this syndrome, specifying mechanisms for visuospatial cognition, social behavior, and memory that are under genetic control, and 3) use the identified brain phenotypes to investigate neurobiological effects of specific genes in 7q11.23. This presentation will provide an update on our findings, including three fundamental aspects of the brain phenotype in adults with Williams syndrome: 1) Underlying the syndrome's cognitive

hallmark, visuospatial construction impairment, is a neurostructural anomaly (decreased gray matter volume) and adjacent abnormal neural functional in the parietal sulcus region of the dorsal visual processing stream; 2) Also contributing to the visuospatial problems are hippocampal abnormalities in regional cerebral blood flow, neurofunctional activation, and N-acetyl aspartate concentration (measured *in vivo* with MR spectroscopy), as well as subtle structural changes; and 3) Underlying the syndrome's hallmark social cognition features are structural and functional abnormalities in the orbitofrontal cortex, an important affect and social regulatory region that participates in a fronto-amygdalar regulatory network found to be dysfunctional in WS. Identification of these brain phenotypes provides an avenue for linking specific genes to the neural, and thus, to the behavioral features of the syndrome.

The emerging results of our studies form a point of departure not only for a deeper understanding of Williams syndrome, but also, more generally, for a detailed and mechanistic investigation of dissociable genetic contributions to complex behavior in humans.

Anomalous Neurofunctional Lateralization in Williams Syndrome

K. Roe, K. Berman et al.

Section on Integrative Neuroimaging,
National Institute of Mental Health, NIH

Williams Syndrome (WS), a rare disorder caused by hemizygous microdeletion of approximately 1.6 megabases on chromosomal band 7q11.23, is associated with a distinct clinical profile of strengths and weaknesses within and across different cognitive domains, including marked visual-spatial constructional deficits, hypersociability, and relatively spared language processes. With non-invasive multimodal imaging -including structural MRI, functional MRI (fMRI), and oxygen-15 water Positron Emission Tomography (PET), we investigated neural systems associated with both impaired and preserved cognitive processing in individuals with Williams Syndrome.

Methods: BOLD fMRI was performed on a GE Signa 3T using gradient echo planar imaging (EPI) (36 axial slices, 3 mm thickness, repetition time/echo time = 3000md, field of view = 24 cm, matrix = 64 × 64). Twelve high-functioning individuals with WS and 12 healthy controls were scanned during passive viewing of pictures, during alternately object/location attention-demanding processing of pictures, and during a two-dimensional analog of the classic block-design task. We used oxygen-15 water PET (12 mCi/scan) to measure regional cerebral blood flow (rCBF) in 14 high-functioning WS participants and 16 age and IQ-matched healthy controls while they performed two paced fluency tasks. Participants were asked to produce exemplars from either standard categories (CAT, e.g., toys or sports), or over-learned categories (CON, days-of-the-week or months-of-the-year. High-resolution structural images were acquired on a 1.5T scanner (GE Signa, Milwaukee, WI). ROI definition was performed in the coronal plane with reference to the sagittal plane using the software MRIcro. FMRIB's *Brain Extraction Tool* (BET, [Smith, 2002]) was used in combination with MEDx's *Interactive Segmentation* (Medical Numerics, Sterling, VA) to remove extracranial matter from the averaged image. Freesurfer ver. 0.9 (Dale et al., 1999; Fischl et al., 1999a) was used to segment gray and white matter and to create white matter, "inflated white matter" and pial surface representations for each participant. Diffusion- weighted images were acquired with a single-shot echo-planar imaging sequence (six different gradient directions with *b*-value _1,100 s/mm2 plus one acquisition with *b*-value _0 s/mm2, 2-mm isotropic resolution, TE 82.7 ms, TR _10 s, cardiac-gated, gradient strength of 5G/cm) on a GE Signa 1.5T scanner. We used tractography to identify fiber bundles linked to these regions as well as all classical

major white matter tracts in the brain.

Results: Compared to healthy controls, individuals with WS displayed hypofunction in the dorsal stream of the right hemisphere while passively viewing pictures of houses during fMRI. During PET, though individuals with WS recruited similar networks as healthy controls during both verbal fluency tasks, analyses of hemispheric laterality (directly contrasting activity in one cerebral hemisphere with activity in contralateral hemisphere) indicates expected lateralization patterns in healthy participants but more distributed, bilateral activity in Williams syndrome participants. These functional patterns are consistent with structural findings indicating atypical hemispheric asymmetries in white matter tract integrity, gray matter volume and sulcal depth in temporal and parietal regions associated with typically- lateralized verbal and spatial processes. These data stress the importance of the interaction between cognitive and brain development in both typical and atypical neurofunctional organization.

The Mirror Neuron System Reflects Hypersociability in Williams Syndrome Individuals - A Meta-Analytical Approach –

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Statement of Purpose. Williams syndrome (WS) is a neurodevelopmental disorder caused by a hemizygous deletion of up to 28 genes on chromosome 7q11.23. One striking feature of the syndrome that distinguishes it from other disorders is excessive sociability and empathy for others (Meyer-Lindenberg et al. Nature Reviews Neuroscience 2006).

The mirror neuron system (MNS) including the inferior frontal gyrus (IFG) to ventral precentral gyrus (vPrCG) and inferior parietal lobule (IPL), as well as the posterior superior temporal gyrus (pSTG) which provides visual input to the MNS, have been linked to empathy and socialization (Rizzolatti and Craighero, Annual Review of Neuroscience, 2004). Further, in separate lines of studies, empathy has been linked to brain regions such as the sensorimotor regions, limbic and para-limbic regions (anterior cingulate cortex, ACC; insula) (Vignemont and Singer, Trends Cogn Sci, 2006), and theory of mind (ToM) to the medial frontal cortex (mPFC), temporal poles (TP), and temporoparietal junction (TPJ) (Ciaramidaro et al. Neuropsychologia, 2007).
In WS, it has been suggested that the cognitive component of theory of mind (ToM) is impaired whereas the perceptual component of ToM may be spared (Tager-Flusberg and Sullivan, Cognition, 2000). Therefore, it may be hypothesized that individuals with WS show differential impairment in brain regions implicated in cognitive and perceptual components of these systems.

Methods. In this preliminary study, we pooled previously collected functional magnetic resonance imaging (fMRI) data from 4 studies of affect and gaze processing. We compared brain activation in WS compared to typically developing (TD) control individuals. We also examined brain regions that are associated with empathy scores in WS and in TD individuals. Finally, diffusion tensor imaging (DTI) data was examined to test our hypothesis.

Results. Relative to TD individuals the WS group showed decreased activation in the "social brain", namely the IFG, vPrCG, insula, TP, fusiform and amygdala regions. On the other hand, WS compared to the TD group showed increased activation in the right IPL/pSTG. Regressing out task type, age, gender, task performance, and voxel-based gray matter morphometry did not change the results. Further, whereas the anterior "social brain" (mPFC, IFG/PrCG/insula, STG) showed positive correlation with empathy scores in TD individuals, WS patients showed positive correlation with more posterior and "perceptual" regions (IPL, occipital regions, thalamus). Finally, DTI of the superior longitudinal / arcuate fascicule showed negative association with empathy scores, similar to the previously found negative associations found with cognitive abilities (Hoeft et al. J Neurosci, 2007).

Discussion. This study shows promising initial results suggesting putative neural systems associated with empathy in WS. The results support the hypothesis of the dissociation between the cognitive and perceptual components of empathy in WS. Future studies using tasks that more effectively target the neural systems involved in empathy are warranted.

Genetically Regulated Sociability: Hyper Amygdala Reactivity and Event-Related Responses to Positive Social Stimuli in Williams Syndrome

B. W. Haas[1], D. Mills[2], A. Yam[3], F. Hoeft[1], U. Bellugi, & A. Reiss[1]

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The drive towards social engagement is a fundamental characteristic of the human species. Scientific pursuits have not yet fully determined the neural and genetic basis of social drive in humans. Williams syndrome (WS) is a genetic disorder caused by a hemizygous microdeletion on chromosome 7q11.23. WS is associated with a compelling symptom profile characterized by relative deficits in visuospatial function and preserved and in some cases enhanced social function. We examined the neural basis of social drive in WS by assessing brain function in WS participants during two types of social stimuli, negative (fearful) and positive (happy) emotional facial expressions. Here, we report a double dissociation such that WS participants exhibited absent amygdala reactivity to negative (fearful) social stimuli, and heightened amygdala reactivity to positive (happy) social stimuli compared to controls. Furthermore, by using ERP we report that WS participants exhibited reduced N200 response to negative (fearful) social stimuli and heightened P300-500 response to positive (happy) social stimuli compared to controls. This study provides evidence that specific genetic deletions (such as in WS) may not only influence the reduction (or absence) of brain function, but in some cases enhance brain function during psychological processing.

SESSION 4

PHENOTYPE OF THE 7Q11.23 DUPLICATION

Featured Speakers:

Colleen Morris, M.D.: Copy Number Variation in the Williams Syndrome Region: Detection of 7q11.23 Duplication by Microarray Allows Phenotypic Comparison

Carolyn Mervis, Ph.D.: Language and Cognitive Development of Children who have Williams Syndrome or Duplication of the Williams Syndrome Region

Copy Number Variation in the Williams Syndrome Region: Detection of 7q11.23 Duplication by Microarray Allows Phenotypic Comparison

C. A. Morris[1], S. L. Velleman[2], C. B. Mervis[3], A. E. John[3], A. Currier[3], E. Peregrine[3], C. Rios[1], K. Kimberley[1], H. Hobart[1], & G. Gowans[3] & M. Gulbronson[3]

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Williams syndrome (WS) is caused by a deletion of ~25 genes on chromosome 7q11.23 mediated by nonallelic homologous recombination. The advent of chromosome microarray technology has resulted in detection of the reciprocal duplication of the region. The purpose of this report is to define the WS region duplication phenotype, and to compare it to WS in order to identify traits that are sensitive to copy number/gene dosage.

Method: Physical examinations and cognitive and language assessments were performed on 8 children and one adult (mother of 2 of the children) with duplications of the classic WS region (dup7q11.23), and on 2 children with longer duplications including *HSP27* (deletion of which is associated with more severe intellectual disability in individuals with WS with long deletions). Phenotypic features were compared to individuals with classic WS.

Results: Dysmorphic features included prominent forehead (65%), high broad nose (70%), long columnella (41% of total, but 90% of those over age 8), short philtrum (54%), and facial asymmetry (95%). Birth defects were rare, including one person each with ASD/VSD, microcephaly, hydrocephaly, and severe micrognathia. About 50% had ADHD, and 82% had anxiety (social and separation anxiety). Interestingly, all individuals with a duplication had language delay and current or former difficulty with motor speech.

Discussion: The facial phenotype of duplication of the WS region is subtle, but recognizable. *GTF2IRD1* has been implicated in the facial asymmetry in WS, and may be copy number sensitive, since it is a trait shared by the dup7 group. Both groups share anxiety as a behavioral problem, but those with WS typically have specific phobia (loud noises), while those with dup7 have separation and social anxiety. These findings suggest that one or more genes in the Williams syndrome region are dosage sensitive, including genes that contribute to facial and language development.

Language and Cognitive Development of Children Who Have Williams Syndrome or Duplication of the Williams Syndrome Region

C. B. Mervis[1], S. L. Velleman[2], A. E. John[1], A. Currier[3], E. Peregrine[1], A. M. Becerra[1], & C. A. Morris[4]

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Purpose: Williams syndrome (WS) is caused by a deletion of ~25 genes on chromosome 7q11.23, typically leading to mild to moderate intellectual disability. WS is associated with a specific cognitive profile involving relative strengths in verbal short-term memory and (concrete) language and severe weakness in visuospatial construction. For every syndrome caused by a deletion, there is hypothesized to be a syndrome caused by a duplication of the same region. The first child with duplication7q11.23 syndrome (dup7q11.23)

was phenotyped by our research group in 2005. This child evidenced severe expressive speech and language delay. However, his standard scores for nonverbal reasoning and spatial ability were similar to those for his unaffected sister. The purpose of the present research was to further investigate the cognitive and linguistic phenotype for dup7q11.23 by studying additional individuals with this syndrome and to compare this phenotype to that for WS. In addition we provide a case comparison of two boys with dup7q11.23 demonstrating the importance of speech and language intervention.

Method: For the "group" study, seven children and one adult (the mother of two of the children) with duplications of the classic WS region (dup7q11.23) and two children with longer duplications (long-dup) including *HSP27* (deletion of which is associated with more severe intellectual disability in individuals with WS with long deletions) participated. Performance on standardized assessments was compared to that of the participants with WS (classic deletions) whom we have assessed on the same measures. Ns for the major assessments range from 52 – 88. For the "case comparison," participants were two 8½-year-old boys with dup7q11.23 with similar IQs from similar SES and parental education backgrounds. Child 1 had only had sporadic speech therapy, beginning at age 3 years. Child 2 had consistent speech therapy (both private and through early intervention or his school system) beginning as a toddler.

Results: Mean standard scores on most measures were higher for the dup7q11.23 group than the WS group. The most striking differences were for measures of visuospatial construction, with DAS-II Spatial Cluster and VMI standard scores averaging ~20 points higher than for WS. Verbal standard scores averaged ~10 points higher than for the WS group on the DAS-II, the PPVT-4, the EVT-2, and the TROG-2. In contrast, mean performance for DAS-II Recall of Digits was at the same level for the two groups. Mean PPVT-4 and TROG-II standard scores for the long-dup group were similar to the dup7q11.23 group, but EVT-2 mean standard score was ~35 points lower than for the dup7q11.23 group and 25 points lower than for the WS group.

A particularly striking characteristic of the children in both duplication groups was current or former difficulty with speech. Every participant had or had had severe speech delay. All but one child in the 7q11.23 group had or once had problems with motor speech and/or oral-motor movements. Some had phonological delay and others had phonological disorder. Some had symptoms of Childhood Apraxia of Speech (CAS). Both children with long duplications had CAS. Results of the case comparison strongly demonstrated the impact of early and intensive speech therapy: Child 1 communicated primarily in sentences that were, with effort, comprehensible to most listeners. In contrast, Child 2 communicated primarily by single poorly pronounced words, gestures, pantomime, and drawing.

Discussion: The strong differences in language (including speech) and cognitive abilities between children with WS and children with duplications of 7q11.23 suggest that one or more genes in the 7q11.23 region are dosage sensitive and that these genes, in transaction with other genes and the environment, are important for language and cognitive development.

SESSION 5

ANXIETY AND OTHER PSYCHIATRIC PROBLEMS

Featured Speaker: **Elisabeth Dykens, Ph.D.:** Anxiety in Williams syndrome: Beyond Diagnoses to Broader Conceptual and Therapeutic Challenges

Platform Presentations:

O. Leyfer:

Anxiety Disorders in Children with Williams Syndrome, their Mothers, and Siblings: Implications for the Etiology of Anxiety Disorders

B. Klein-Tasman:

Emerging Executive Functioning: Relations to Behavioral Difficulties in Young Children with Williams Syndrome

O. Zarchi:

Hyperacusis and Phonophobia in Williams Syndrome

Anxiety in Williams Syndrome: Beyond Diagnoses to Broader Conceptual and Therapeutic Challenges

E. M. Dykens

Vanderbilt Kennedy Center for Research on Human Development, Vanderbilt University

This presentation reviews salient aspects of anxiety in people with Williams syndrome, thereby setting the stage for subsequent papers in this section of the conference. In reviewing findings to date, we provide a brief summary of our research on anxiety in persons with Williams syndrome. Beyond specific findings, however, this presentation also addresses broader methodological and conceptual complexities involved in research on psychopathology in persons with intellectual or developmental disabilities.

Non-social anxiety in people with Williams syndrome is increasingly well-studied using psychiatric nosology, standardized behavioral measures, and fMRI techniques (Dykens, 2003; Lefyer et al, 2006; Meyer-Lindberg et al., 2005). We recently extended these observations by examining correlates of anxiety in 35 adults with Williams syndrome (M age = 24 years; 19M, 16F). We did not find strong associations between anxiety in WS adults and their medical status or history, family psychiatric histories, or current maternal anxiety. Compared to males, females generally had higher levels of anxiety, depression, and salivary cortisol levels. In ongoing fMRI studies, we are also examining neurological aspects of anxiety. We find that the amygdala and areas implicated in empathy are differentially activated in WS subjects versus typical controls in response to viewing anxiety-provoking faces and images. We also find evidence for increased functional connectivity between sensory cortices in Williams syndrome.

Beyond these studies, this presentation also addresses broader conceptual and methodological issues involved in the study of anxiety or other psychiatric problems in persons with Williams syndrome or other developmental disabilities. These broader points will address: issues related to the accurate diagnosis or measurement of symptoms in persons with cognitive and developmental delay; the extent to which risk and protective factors for psychiatric illness in the general population apply to those with Williams syndrome or other disabilities; and disparities in basic psychiatric research or treatment studies in those with disabilities versus the general population. Solutions for closing these psychiatric research and treatment gaps will be discussed in relation to Williams syndrome.

Acknowledgements: This work was supported by the Vanderbilt Kennedy Center for Research on Human Development's NICHD Grant P30HD15052; a Vanderbilt University Discovery Grant, the Biobehavioral Intervention Training Program, NIH Roadmap Post-Doctoral Training Grant; and the Vanderbilt Institute for Clinical and Translational Research. Special thanks to Elizabeth Roof, Tricia Thornton-Wells, and the staff, families, and campers involved in the Vanderbilt Kennedy Center's Williams Syndrome Music Camp.

Anxiety Disorders in Children with Williams Syndrome, Their Mothers, and Siblings: Implications for the Etiology of Anxiety Disorders

O. Leyfer, J. Woodruff-Borden, & C. B. Mervis

Department of Psychological and Brain Sciences, University of Louisville

Purpose: Genetic factors play an important role in the etiology of anxiety disorders. Williams syndrome (WS), a genetic disorder caused by a deletion on chromosome 7q11.23 and associated with increased prevalence of anxiety disorders relative to the general population and many other genetic disorders associated with intellectual disability, can be used in the search for susceptibility genes for anxiety disorders. This study examines the prevalence of anxiety disorders in children with WS, their mothers, and their siblings as well as predictors of anxiety in these groups, in order to facilitate the use of WS in studies of the genetics of anxiety disorders.

Method: The prevalence of anxiety disorders in a sample of 132 4 – 16 year-old children with WS, their mothers, and 84 siblings in the same age range was assessed using the ADIS-P, a structured diagnostic interview.

Results: Prevalence of anxiety disorders was compared to the general population (Table 1, next page).
The children with WS had a significantly higher prevalence of specific phobia, generalized anxiety disorder (GAD), and separation anxiety in comparison to children in the general population. Their mothers had a significantly higher prevalence of GAD than women in the general population, but the prevalence rate for GAD in this group prior to the birth of the child with WS was comparable to that for women in the general population. The siblings had a significantly higher prevalence of specific phobia than children in the epidemiological study used for comparison, but the prevalence for siblings was similar to the rates reported in other studies of specific phobia in typically developing children. The odds of a child with WS having an anxiety disorder increased with the severity of maternal anxiety.

Discussion: This is the first study to examine familial aggregation of anxiety disorders in individuals with WS. The elevated prevalence rates of anxiety disorders in children with WS suggest a connection between the deletion found in WS and anxiety disorders. Given the increased prevalence of anxiety disorders in children with WS, genetic studies examining possible links between particular gene(s) deleted in WS and anxiety are warranted. It would also be worthwhile to investigate relations between genes deleted in WS and genes previously implicated in anxiety disorders.

Table 1: Prevalence of anxiety disorders in children with WS, their mothers, and their siblings
[1] $p < .001$; [2] $p < .0$

Type of Anxiety Disorder	WS		Population Prevalence	Siblings		Mothers		Population Prevalence
	N	%	%	N	%	N	%	%
Separation anxiety disorder	8	6.1[1]	2.3	3	3.6	--		15.7
Social phobia	3	2.3	4.5	6	7.1	15	11.4	8.1
GAD	10	7.6[2]	3.1	5	6.0	31	23.5[1]	1.6
OCD	2	1.5	--	0	0	3	2.3	17.9
Specific phobia	74	56.1[1]	1.3	14[1]	16.7	27	20.5	10.9
Post traumatic stress disorder	2	1.5	--	0		5	3.8[2]	7.7
Panic disorder	--					4	3.0	

Emerging Executive Functioning: Relations to Behavioral Difficulties in Young Children with Williams Syndrome

B. Klein-Tasman & F. J. Gallo

University of Wisconsin-Milwaukee

Background: Williams syndrome is a genetically-based neurodevelopmental disorder, characterized by mild to moderate intellectual ability. Research about the behavioral phenotype of children with Williams syndrome has found that children often show socio-communicative deficits that overlap with those seen in children with autism spectrum disorders (Klein-Tasman et al., 2007). They also show heightened levels of inattention and hyperactivity, with symptoms meeting criteria for ADHD at a rate higher than generally seen for children with intellectual disabilities (Leyfer et al., 2006). Although executive functions, complex cognitive processes associated with pre-frontal cortical functioning, show robust correlations to symptoms of ASD and ADHD in the literature (Pennington & Ozonoff, 1996), their role in the WS behavioral phenotype has yet to be explored. The current study examines emerging executive functions and their relation to parent reports of attention problems and social responsiveness in young children with WS.

Methods: Participants were 27 children with Williams syndrome (9 male, 18 female), ranging from 4-7 years (M= 69.87 months, SD=11.89). Each child was administered a brief measure of verbal and nonverbal reasoning (KBIT-II), as well as a battery of developmentally-appropriate executive function measures: A-not-B, Delayed Alternation, NEPSY Statue, Dimensional Change Cart Sort (DCCS). Parents of each participant were also asked to complete the Social Responsiveness Scale (SRS), a measure of social-cognitive and socio-communicative difficulties characteristic of ASD, and the Conners Parent Rating Scales-Revised (Conners), a measure of behavioral symptoms associated with ADHD.

Results: On measures with age-based norms (A-not-B and Statue), participants demonstrated borderline to mild impairment. Passing scores on the DCCS Post-switch phase were also well below age-expected levels. With the exception of Delayed Alternation, performance on executive function tasks was significantly correlated with age. No correlations with verbal or nonverbal standard scores were found. After controlling for age, DCCS performance correlated with parent ratings on the Conners ADHD Index (r = -.409, p <.05), SRS Social Communication (r = -.441, p <.05), and SRS Autistic Mannerisms (r = -.444, p <.05). Total raw scores for Statue correlated significantly with SRS Social Motivation (r = -.460, p <.05).

Discussion: To date, research has largely focused on documenting the occurrence of atypical behaviors that characterize individuals with Williams syndrome, with few investigations exploring dysfunctional brain-based processes that may contribute to their presence. The current study provides an analysis of emerging executive functions in Williams syndrome, and findings suggest that pre-frontal dysfunction may contribute to problem behaviors often characteristic of children in this population. Further implications regarding the relationship between executive function deficits and problem behavior in this population will be discussed.

Hyperacusis and Phonophobia in Williams Syndrome

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Hyperacusis and phonophobia are among the most salient features of Williams syndrome (WS) and affect the life of most children carrying the syndrome. We have investigated the clinical characteristics and neuroaudiological pathways mediating the hyperacusis in 49 children and adolescents with WS. Compared to controls, subjects with WS showed 20dB lower discomfort level thresholds, high-frequency cochlear hearing, distortion products otoacoustic emission, higher prevalence of ipsilateral acoustic reflex (AR) absence, and prolonged wave I latency of the BAER. Subjects with WS also showed increased suppression effect of the MOC reflex. The findings of the study suggest that hyperacusis in WS is associated with a high-frequency hearing loss resembling the configuration of noise induced hearing loss. The hyperacusis and hearing loss in WS may stem from a deficiency in AR, resulting from auditory nerve dysfunction. Hyperexcitability of the medial olivocochlear efferent system coupled with AR absence further enhance hyperacusis in subjects with WS. Additionally, we present preliminary results suggesting abnormal central auditory processing in WS as evident by mismatch negativity ERP findings.

SESSION 6

UPDATES ON COGNITION IN WILLIAMS SYNDROME

Featured Speaker: **Bonnie Klein-Tasman, Ph.D.:** Updates on Cognition in Williams Syndrome

Platform Presentations:

M. Porter:

A Longitudinal Study of Cognitive Functioning in Williams Syndrome

K. Breckenridge:

Assessing Attention in Children with Williams Syndrome and Down's Syndrome Using a New Comprehensive Attention Battery: Do These Problems Relate to Visual Dorsal Cortical Stream Deficits?

C. Cashon:

Statistical Language Learning and Face Processing by Infants and Toddlers with Williams Syndrome

J. Marler:

Auditory Memory in Williams Syndrome: Is rote Memory Really a strength?

Updates on Cognition in Williams Syndrome

B. Klein-Tasman

University of Wisconsin – Milwaukee

Foundational research about cognition in Williams syndrome has examined cognitive strengths and weaknesses to hone in on a distinct phenotype to Williams syndrome (e.g., Bellugi, Bihrle, Jernigan, Trauner, & Doherty, 1990; Bellugi, Lichtenberger, Mills, Galaburda, & Korenberg, 1999; Klein & Mervis, 1999; Mervis et al., 2000). Research had indicated that language abilities generally fall at the level of overall intellectual functioning, with some specific areas of relative strength and weakness. Auditory rote memory has been identified as an area of relative strength (Robinson, Mervis, & Robinson, 2003; Wang & Bellugi, 1994). While face-processing is generally seen as a strength (Bellugi, Marks, Bihrle, & & Sabo, 1988; Udwin & Yule, 1991), some studies find abnormal processing of faces (Gagliardi et al., 2003; Karmiloff-Smith, Scerif, & Thomas, 2002), whereas others indicate that people with Williams syndrome largely process faces holistically, as do typically developing individuals (Tager-Flusberg, Plesa-Skwerer, Faja, & Joseph, 2003). There is general agreement that visuospatial constructive ability is an area of specific and significant weakness for people with Williams syndrome. This set of presentations builds on the established unique cognitive profile, extending our knowledge both developmentally and conceptually.

Potential neural mechanisms underlying task performance are being examined in Williams syndrome. A large body of research has supported the presence of deficits in dorsal stream processing (e.g., Atkinson et al., 2003; e.g., Atkinson et al., 2006; Atkinson et al., 1997; Nakamura, Kaneoke, Watanabe, & Kakigi, 2002; Paul, Stiles, Passarotti, Bavar, & Bellugi, 2002). As mentioned, visuospatial construction is an area of relative difficulty on standardized tests. Even within the language domain, specific difficulties with relational concepts, that likely involve spatial cognition, have been reported. Atkinson and colleagues have documented deficits on experimental tasks requiring dorsal stream processing. Neuroimaging findings have confirmed abnormality in the neural systems underlying dorsal stream processing in adults with Williams syndrome (Meyer-Lindenberg et al., 2004). Breckenridge and Atkinson will present results of an investigation of performance on a battery of experimental attention tasks and how attention difficulties may relate to dorsal stream functioning in Williams syndrome. We will also hear from Marler and his colleagues about how the dorsal/ventral stream distinction may be important for understanding auditory functioning of people with Williams syndrome.

A second theme of this set of presentations is consideration of development in our understanding of the cognitive phenotype in Williams syndrome. First, there has been little published longitudinal research about the cognitive phenotype in Williams syndrome. Such research is important to demonstrating the stability of patterns of cognitive strength and weakness across development. In this session, we will hear from Porter and Dodd about one such study, finding considerable stability across a 7-year time-span. Second, Williams syndrome is now getting recognized and diagnosed by physicians at very young ages, presenting the opportunity to examine patterns of functioning early in development, so that the developmental timing of peaks and valleys can be explored. We will hear about research from Cashon and her colleagues examining cognitive functioning in infants and toddlers with Williams syndrome related to both language functioning and face processing.

A Longitudinal Study of Cognitive Functioning in Williams Syndrome

M. A. Porter[1] & H. Dodd[2]

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2. Macquarie Centre for Cognitive Science, Macquarie University, Sydney, Australia

Our research represents the first longitudinal study of cognitive functioning in Williams syndrome using the same cognitive test battery at time 1 and time 2, and the same cognitive test battery for all individuals, regardless of age or ability level. The aim of this study was to explore whether cognitive abilities remain stable over time in individuals with Williams syndrome.

Twenty-seven individuals with Williams syndrome participated; all had tested positive for the elastin gene deletion (FISH test), and were aged between 5 and 43 years at initial assessment. There were 14 females and 13 males in the study.

The participants were assessed using the Woodcock Johnson Test of Cognitive Ability – Revised (WJ-R COG, Woodcock & Johnson, 1989, 1990) at time 1, and again at time 2, during follow up approximately five years later. The WJ-R COG assesses seven broad cognitive domains: Long-term Retrieval; Short-term Memory; Processing Speed; Fluid Reasoning; Comprehension-knowledge, Visual Processing and Auditory Processing. The test publishes norms for typically developing individuals aged 2 to 95 years.

Results showed that the gap in ability levels between Williams syndrome individuals and the normal population had not changed significantly in the five year period from time 1 to time 2, neither had their individual patterns of cognitive strength and weakness.

Discussion: These results suggest that cognitive functions remain stable in individuals with Williams syndrome, both in terms of their general level of ability and their personal profiles of strength and weakness, at least on the cognitive domains assessed using the WJ-R COG. The fact that cognitive functions did not change significantly substantiates continued research efforts into exploring the relationship between heterogeneous cognitive and genetic abnormalities in Williams syndrome and related chromosome 7 disorders.

Assessing Attention in Children with Williams Syndrome and Down's Syndrome Using a New Comprehensive Attention Battery: Do These Problems Relate to Visual Dorsal Cortical Stream Deficits?

K. Breckenridge & J. Atkinson

Visual Development Unit, University College London

Purpose: There are many anecdotal reports of attention problems in both Williams syndrome (WS) and Down's syndrome (DS), with some recent studies suggesting difficulties on frontal lobe executive function tasks (e.g. Atkinson et al, 2003). However, for many children with WS and DS who have a mental age below 6 years, there has been no standardized single battery to assess the different components of attention (selective attention, sustained attention and attentional / executive control) which are thought to be underpinned by different neural networks of brain areas in the adult brain and in typically developing older children (e.g. Posner & Petersen, 1990; Manly et al, 2001). In the Visual Development Unit, we have recently devised and normalized a new battery designed to assess different attention components in children of 3-6 years mental

age (MA), including children with developmental disorders. We report the results of a study using this battery to map profiles of attention in children with WS and DS and consider the relationship between attentional deficits and dorsal stream deficits, as manifested in the comparison of motion and form coherence thresholds (e.g. Atkinson et al, 1997; Braddick et al, 2003).

Methods: There were 8 short subtests in the battery, each test lasting between 2 and 10 minutes. These subtests included a visual search and a flanker task, intended to tap selective attention; vigilance-type sustained attention tasks in visual and auditory modalities; and tests of verbal inhibition, motor inhibition, and sorting with rule shifts to assess aspects of attentional / executive control. Children in the current study completed these new attention tasks, plus measures of verbal and non-verbal intelligence, dorsal and ventral stream processing (motion and form coherence computer game), and global vs. local level visual processing with Navon figures.

Results and discussion: Results to date confirm earlier preliminary data showing marked delays for both groups compared to chronological age and MA, and suggest that sustained attention is less affected than selective or executive attention in both syndrome groups. We will discuss how profiles of attention in these groups relate to (i) the changes in attention seen over the preschool years in typical development, (ii) vulnerability of the dorsal visual stream in developmental disorders, and (iii) known structural and functional brain abnormalities in these groups.

Statistical Language Learning and Face Processing by Infants and Toddlers with Williams Syndrome

C. H. Cashon[1], C. L. Allen[1], O. R. Ha[1], K. G. Estes[2], J. R. Saffran[3], & C. B. Mervis[1]

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Background and Purpose: Williams syndrome (WS) is a rare genetic disorder caused by a microdeletion of ~25 genes on chromosome 7q11.23. Although most people with WS have mild to moderate intellectual disability, some individuals have average intelligence or severe intellectual disability. WS is associated with a specific cognitive profile of relative strengths in language and verbal short-term memory and severe weakness in visuospatial construction. Because WS is rarely diagnosed at birth, research with infants and toddlers with WS is scarce. In this talk, two studies will be presented that include samples of children with WS younger than 3-years-old: the first is on statistical language learning and the second is face processing.

Statistical Language Learning Study: Although individuals with WS eventually acquire reasonably good language skills, the development of these skills is delayed (Mervis, 2003). Despite these delays, it has been argued that children with WS may still acquire language in a similar pattern to that of typically developing (TD) children (Mervis, 2006). One of the early linguistic tasks of a young child is to discern where the word boundaries are in continuous speech in their native linguistic environment. TD 8-month-old infants are able to identify word boundaries by attending to the statistical regularities in linguistic input (Saffran, Aslin, & Newport, 1996). The purpose of this study was to determine if infants and toddlers with WS are also sensitive to the statistical properties of linguistic input. Participants were 7 children with WS (4 girls, 3 boys), all who had classic-length deletions. The mean age was 1.08 years (*SD* = .36 years; range 0.82 – 1.72 years); 5 of the 7 participants were <1

year old. We used an experimental method and stimuli similar to those of Saffran et al. (1996). Results indicate that older infants and toddlers with WS are sensitive to the statistical regularities in the language environment and can use this information to segment words from novel linguistic input.

Face Processing Study: The "face inversion effect" is a well-known phenomenon that describes the fact that adults in the general population are better at recognizing, remembering and discriminating faces in the upright, canonical orientation compared to inverted faces (e.g., Valentine, 1988). It is thought that this 'inversion effect' is due to a difference in the modes of processing used for the different orientations, specifically that holistic, 1st-order and 2nd-order configural processing are used for upright faces, but featural processing is used for inverted faces (Maurer, LeGrand, & Mondloch, 2002). The effect has been seen as early as 7 months of age in TD infants (Cashon & Cohen, 2004). Although research indicates that adolescents and adults with WS encode and recognize faces holistically and show the 'inversion effect' (Tager-Flusberg, Plesa-Skwerer, Faja, & Joseph, 2003), there is no such research on face processing by infants or toddlers with WS. In this set of studies, we tested holistic vs. featural face processing for upright (Experiment 1) and inverted (Experiment 2) face orientations by infants and young toddlers with WS. Participants were 13 (7 males, 6 females) infants and toddlers with WS, all who had the classic-length deletion. The mean age was 1.66 years (*SD* = .82; range: 0.46 - 2.80 years). A visual habituation "switch" task similar to that of Cohen and Cashon (2001; Cashon & Cohen, 2004), which was previously used with TD infants to evaluate face processing, was used. The results indicate that infants and toddlers with WS demonstrate differential face processing for upright vs. inverted faces. Specifically, they processed upright faces holistically and inverted faces featurally, the same pattern of findings as for older TD infants and toddlers.

Auditory Processing in Williams Syndrome: Does Normal Behavioral Hearing Indicate Normal Auditory Function?

J. A. Marler[1], F. L. Wightman[2], D. J. Kistler[3], J. L. Roy[1], & C. B. Mervis[2]

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2. Department of Psychological & Brain Sciences, University of Louisville
3. Heuser Hearing Institute, University of Louisville

Introduction: Williams syndrome (WS) is a genetic disorder caused by a heterozygous microdeletion on chromosome 7. As individuals with WS present with a hypersensitivity to sound they have historically been assumed to have normal hearing sensitivity. Only recently has it been documented that many individuals with WS actually have a mild to moderate sensorineural hearing loss; in addition, preliminary cross-sectional data suggest that the hearing loss is progressive. With prevalence rates of poorer behavioral thresholds ranging from 60% of children to 100% of adults, there is likely to be a strong genetic component to the hearing loss. Our purpose was to further investigate the peripheral auditory functioning of individuals with WS.

Methods: Auditory functioning was assessed through tympanometry (middle-ear function), behavioral auditory, a distortion production otoacoustic emissions screening task (DPOAE; a measure of outer hair-cell function of the inner ear), and a more audiometrically stringent input/output (I/O) functions at 4000 Hz. I/O functions are understood to be an objective, physiologic correlate to behavioral loudness growth function, which may help to explain the hypersensitivity to sound evidenced in this population. And when these DPOAE I/O functions are measured at 4000

Hz, they are also extremely sensitive to possible noise-induced hearing loss.
Forty-six individuals with WS participated in the behavioral pure-tone task, 41 participated in the DPOAE screening task, and 11 individuals with WS who had "normal" behavioral hearing participated in the DPOAE I/O function. This final group (WS with normal hearing) will be compared to age- and gender-matched controls with normal behavioral hearing. Participants ranged in age from 6 years to 53 years (Median=15.25).

Results: On the tympanometric condition, 26% of individuals with WS displayed tympanograms indicative of middle ear pathology. Additionally, 85% of individuals failed a behavioral hearing screening and 66% displayed DPOAEs below the 5th percentile according Gorga et al.. Gorga reports that such depressed (poor) outer hair cell activity is indicative of impaired cochlear function (impaired inner ear function). This interpretation finds further support in the DPOAE I/O function. Those individuals with WS who also had "normal" hearing showed significantly depressed outer hair-cell function within the 4000 Hz range as compared to normal-hearing controls [$F(1,12) = 23.812$, $p < 0.01$, $\eta_p^2 = 0.665$]. This phenomenon is most frequently seen in individuals with noise-induced hearing loss.

Discussion: Individuals with WS displayed a peripheral auditory impairment greater than that found in the general population. Specifically, pathology was found in both middle ear and cochlear hair cell functioning as evidenced by abnormal tympanograms, poorer behavioral thresholds, poorer DPOAEs, and poorer I/O function. The impaired I/O function may assist in explaining the hypersensitivity to sound in WS. Clinically, our data suggest that a large number of special needs, school-aged children with WS have undiagnosed hearing loss. Theoretically, WS ears may be an experimental model for what has been referred to as "fragile ears".

SESSION 7

SOCIAL COGNITION AND SOCIAL PHENOTYPE OF WILLIAMS SYNDROME

Featured Speaker: **Helen Tager-Flusberg, Ph.D.:** Investigating the Social Phenotype in Williams Syndrome: Methodological Challenges

Platform Presentations:

A. John:
Comprehension of Communicative Intent Behind Pointing and Gazing Gestures by Young Children with Williams Syndrome or Down Syndrome

D. Plesa-Skwerer:
Observational Assessments of Attachment and Temperament in Young Children with Williams Syndrome: Toward a Profile of Early Socio-emotional Functioning

C. Zitzer-Comfort:
Cross-cultural Studies of Williams Syndrome

Investigating the Social Phenotype in Williams Syndrome: Methodological Challenges

H. Tager-Flusberg

Boston University School of Medicine

The earliest descriptions of individuals with WS remarked on their unusual sociability, interest and engagement with other people, especially strangers. For the past 15 years researchers have focused their investigations on elucidating this aspect of the WS phenotype addressing several key questions: Is the social phenotype unique to WS? How can we define the social phenotype of WS? What are the cognitive mechanisms that underlie the social phenotype? What is the neurobiological basis of the social phenotype? Is the social phenotype related to other components of the WS phenotype? What are the developmental origins of the social phenotype?

As research has progressed, the picture of social functioning in WS has become more complex. Early on studies focused on the social component of the WS phenotype as a unique "strength" arguing that in WS theory of mind was spared, in contrast to autism. More recently, the pendulum has swung in the other direction: not only is theory of mind impaired in WS, in many respects the social adaptive skills of people with WS have been viewed by some researchers as being quite impaired, in ways similar to what is seen in autism spectrum disorders.

In this presentation, I will focus on four key issues related to research on the social phenotype of WS:

(1) How should we formulate hypotheses about the social phenotype? Discussion will focus on defining hypotheses in terms of strengths or weaknesses; relative or absolute sparing or impairment.

(2) What behavioral measures are best suited to investigating the social phenotype in WS? Discussion will focus on the use of explicit and implicit measures; measures that confound assessing social processing with language or other general cognitive skills; use of different types of social stimuli (e.g., pictures; video; real world people); use of different types of measures (behavioral performance; eye-tracking; physiological measures).

(3) How can cognitive neuroscience contribute to our understanding of the social phenotype in WS? Discussion will focus on the remarkable studies that have been conducted as well as limitations in use of cognitive neuroscience approaches with this population.

(4) How have developmental studies advanced our understanding of the social phenotype in WS? Discussion will focus on what kinds of developmental changes in social behavior are seen, and whether in this respect, WS is a *developmental* disorder.

In the final segment of the presentation I will explore future directions in research on the social phenotype in WS.

Comprehension of Communicative Intent Behind Pointing and Gazing Gestures by Young Children with Williams Syndrome or Down Syndrome

A. E. John & C. B. Mervis

Department of Psychological and Brain Sciences, University of Louisville

Background and Purpose: Although individuals with WS evidence a relative strength in concrete vocabulary, recent research has documented significant

weaknesses in pragmatic abilities even in very young children. For example, the communicative behavior of toddlers and preschoolers with WS (e.g., gaze shifting, participation in joint attention, production of gestures, tracking distal pointing gestures) is well below both chronological age (CA) and mental age (MA) expectations. To further explore pragmatic abilities during the preschool period, we conducted a study comparing the ability of young children with WS or Down syndrome (DS) to recognize communicative intent as expressed through non-linguistic gestures (eye gaze or pointing) in the context of a hiding game modeled after Behne, Carpenter, & Tomasello (2005).

Methods: Participants were 33 children with WS (17 boys, 16 girls) aged 3.00 to 5.32 years (m = 4.14 years, SD = .68) and 25 children with DS (11 boys, 14 girls) aged 3.02 to 5.40 years (m = 4.34, SD = .73) matched on CA (p = .29). Mean DQ on the Mullen Scales of Early Learning was significantly higher for the WS group (59.0) than the DS group (52.5); the WS group also scored significantly higher on the Mullen Receptive and Expressive Language Scales. During the hiding game, the experimenter hid a toy in one of two identical containers, established eye contact, and then provided a communicative or non-communicative cue (involving gaze shifting or pointing) to indicate the container in which the object was hidden. Each child participated in four conditions formed by crossing Communicative style (communicative vs. non-communicative) and Gesture type (point vs. eye gaze shift). The non-communicative conditions were presented first to avoid biasing the child's attention. Order of presentation of Gesture type was counterbalanced.

Results: Comparisons of performance in the communicative and non-communicative conditions to chance indicated that communicative cues were used significantly more often than expected by chance ($p < .005$) to find the hidden toy for both the WS (point: m = 4.57, gaze: m = 3.83) and DS (point: m = 5.04, gaze: m = 4.48) groups but non-communicative cues were not. Binomial tests examining individual performance on communicative trials indicated that significantly more children with DS (60%) than WS (27%) found the toys at a rate greater than that expected by chance (≥10/12 trials correct). Results of a mixed ANOVA indicated significant main effects of Communicative style ($p < .001$, $\eta^2 = .60$) and Diagnostic Group ($p = .03$, $\eta^2 = .08$) but not Gesture ($p = .15$; $\eta^2 = .04$). In addition, the interaction term between Communicative style and Gesture was significant ($p = .02$, $\eta^2 = .10$), indicating a significantly greater discrepancy between performance on the two communicative style conditions for pointing than for eye gaze.

Discussion: As groups, preschoolers with WS or DS have begun to distinguish communicative intent from non-communicative intent for non-linguistic pointing and gazing gestures. However, despite significantly lower DQs and language levels, the DS group evidenced significantly stronger pragmatic skills than the WS group. This finding provides further evidence that young children with WS have more difficulty with socio-communication than expected for CA or level of intellectual or language ability. Theoretical implications and applications will be addressed.

Observational Assessments of Attachment and Temperament in Young Children with Williams Syndrome: Toward a Profile of Early Socio-Emotional Functioning

D. Plesa-Skwerer, M. Lindeke, K. Ogrodnik, L. Ciciolla & H. Tager-Flusberg

Lab of Developmental Cognitive Neuroscience, Boston University School of Medicine

Background/Purpose: Anecdotal evidence, parental reports and observational data from free-play sessions suggest that children with Williams syndrome (WS) show a strong propensity to approach strangers and indiscriminate friendliness (Doyle, Bellugi, & Korenberg, 2004; Jones et al., 2000). A pattern of indiscriminate friendliness toward strangers has been reported in children who failed to form preferential attachment relations due to unusual child-rearing circumstances, such as being raised in orphanages with multiple and inconsistent caregivers. In typical development in the family context, the emergence of focused attachments is marked by the appearance of separation protest and stranger anxiety, while the absence of either may be interpreted as a potential symptom of attachment disorders (Zeanah & Fox, 2004). In this study we used a combination of laboratory based assessments and parental interview/questionnaires to examine possible contributions of attachment relations and temperamental characteristics to the development of social behavior in young children with WS.

Methods: Fifteen children with WS ages 2.11 to 5.10 years, 15 children with Down syndrome (DS) matched on chronological and mental age with the WS group, and 20 age-matched typically developing children (TD) and their primary caregivers were administered the preschool attachment Strange Situation Procedure (SSP; Cassidy & Marvin, 1995), followed by 9 episodes from the Laboratory Temperament Assessment Battery (LabTAB; Goldsmith et al., 1999), designed to elicit behavioral and emotional reactions to novel objects and people, social and nonsocial fear, pleasure/exuberance, etc. Qualitative coding of attachment into standard categories (B, A, C, D) was done by certified coders, while a detailed coding of behavioral observations using the Noldus Observer program was conducted to obtain quantitative measures of social-interactive behaviors (e.g., duration of eye contact and proximity with mother/stranger, affective expressions, activity level, style of interactive behavior/play type, and indices of specific separation/reunion-related behaviors such as reaction to mother's leaving, greeting, waiting behavior). Scoring behaviors in LabTAB episodes followed standard instructions.

Results: Qualitative coding of the SSP showed 87% of the WS group, 93% of the DS group and 76% of the TD children to be securely attached. Groups were similar on the majority of quantitative measures of interactive behaviors; However children with WS spent proportionally more time 'very close' to the social partner than the DS group, $p < .05$. Both the WS and DS children showed proportionally more eye-contact with mother across episodes compared to TD controls ($p<.05$), but groups did not differ significantly in looking time to the 'stranger'. Significant group differences emerged in the LabTAB episodes that elicit reactions to unfamiliar people and objects: children with WS showed less fear and more approach to both social and nonsocial fear-eliciting stimuli than controls ($p <.05$).

Discussion: These results suggest that the pattern of relatively indiscriminate friendliness toward strangers shown by children with WS is not related to the absence of focused attachment bonds or characteristics of the child's rearing environment. Differential responses to fear-eliciting situations revealed a complex pattern of temperamental tendencies in the three groups, which cannot be unequivocally divided according to the social or nonsocial nature of the stimulus or context/event. Findings will be discussed in relation to defining the profile of social-emotional functioning in children with WS, stressing the need for a multi-method investigational approach to advance our understanding of the developmental roots of hypersociability in WS.

Cross-Cultural Studies of Williams Syndrome

C. Zitzer-Comfort[1], U. Bellugi[2], & J. Reilly[2, 3]

1. California State University, Long Beach
2. The Salk Institute for Biological Studies
3. San Diego State University

This work is concerned with ways in which children with Williams syndrome (WS), a rare neurodevelopmental disorder arising from a hemizygous deletion in chromosome band 7q11.23, are affected by social experiences of markedly differing cultures: the United States and Japan in one study, and France, Italy as well as the United States in another study. WS presents a compelling model for this investigation because its genetic phenotype is well defined and results in an uneven cognitive and social profile, including overt over-friendliness toward strangers. While a number of research groups have been studying the cognitive strengths and weaknesses of individuals with WS in various countries, there have been no studies to date that explore the social phenotype in WS across different cultures.

We describe two studies examining the ways in which social behavior in WS, stemming from specific genetic underpinnings, can be mediated by cultural expectations. In the first study, we conducted a cross-cultural comparison using an instrument that measures aspects of sociability commonly found among people with WS (the Salk Institute Sociability Questionnaire). Quantitative analyses revealed a significant effect of diagnostic category in that in both countries (Japan and the U.S.), children with WS were rated as significantly higher in global sociability and more likely to approach strangers than were their normal counterparts. There was also an effect of culture, in that regardless of diagnostic category, both WS and normal children in Japan were rated lower than their counterparts in the U.S. In another cross-cultural study, we examined the use of language for social purposes, using a narrative task for individuals with WS in the U.S., Italy and France. We examined aspects of language structure (morphology and syntax) as well as the evaluative language, which refers to lexically conveyed affect used for social purposes (e.g., emphatics, intensifiers, character speech and sound effects). We found that WS were significantly higher than age matched normal controls in the use of language that conveyed affect and sociability. At the same time, there was also a significant effect of culture across groups, with the Italians exceeding the levels of evaluative language found in the U.S., and the French using significantly less social evaluation. We, thus, conclude that the excessively social phenotype of children with Williams syndrome, although markedly present across cultures, appears to vary in its intensity by culture. These are intriguing illustrations of the interactions between the effects of a genetic predisposition and the effects of different cultural experiences.

Multidisciplinary Poster Session

Do Children with Williams Syndrome have an Impairment in Declarative Function?

K. Asada[1], K. Tomiwa[1, 2], M. Okada[2], & S. Itakura[1]

1. Kyoto University
2. Osaka City General Hospital

Williams syndrome (WS) is a rare genetic disorder. Individuals with WS have relatively intact language ability, talk fluently and like to interact with others. However, they are known to have several problems with daily communication. There might be discrepancies in the domain of sociability such as their approachability. To investigate the characteristics of their communication we focused on the imperative (to obtain an object) and declarative (to direct other's attention to an event or object) function of their language. These two are thought to be important functions in development of communication. A previous study of preverbal communication showed that toddlers with WS produced fewer imperative and declarative pointing than typically developing (TD) children. We investigated whether children with WS had impairments in both functions in spontaneous verbal communication which was assumed to be fluent in WS. We analyzed children's verbalizations and compared them between WS and TD group with a matching verbal age.

In Experiment 1 we investigated imperative function. Children were asked to choose the toys they liked. Then the experimenter played with each of the toys but never handed it to the children. During the toy presentation phase the amounts of verbal requests by children did not differ in both groups. The result indicated that children with WS were able to use the imperative function as equally well as TD children.

In Experiment 2 we investigated declarative function. Children were asked to accomplish several tasks (e.g. fishing game). While and after they accomplished the tasks, the experimenter attended (Attention condition) or did not attend (Ignore condition) to children. TD children were predicted to talk about their accomplishment more when ignored than attended in order to draw the experimenter's attention. Children's verbalizations, following successful completion of the task, about their own accomplishment were counted. The results showed that in both groups children produced the same amount of verbalizations in general. However, TD children produced more verbalizations in the ignore condition than the attention condition but children with WS showed the opposite pattern. The result indicated that children with WS did not often obtain attention from the experimenter or share it with him and possibly that they did not often use the declarative function.
These results suggest that children with WS have difficulty with the declarative function but not with the imperative function. We discuss these results that may demonstrate the discrepancies in their approachability, social cognition and motive to share attention and interest with others.

Patterns of Early Language Development of Children with Williams Syndrome

A. M. Becerra & C. B. Mervis

Department of Psychological and Brain Sciences, University of Louisville

Introduction: Individuals with Williams syndrome (WS) evidence a characteristic cognitive profile: relative strength in verbal short-term memory and in language (including vocabulary and grammar) and extreme weakness in visuospatial construction. Despite their relatively good language abilities, the onset of language acquisition is delayed for most children with WS. The purpose of this

study is to provide a longitudinal investigation of the early lexical and grammatical development of 21 children with WS. Five questions were addressed: (1) How similar are the early vocabulary growth curves of children with WS to those of typically developing (TD) children? (2) Is the relation between receptive vocabulary size and productive vocabulary size for children with WS the same as for TD children? (3) Is the relation between expressive vocabulary size and grammatical development for children with WS the same as for TD children? (4) Once grammatical development begins, how does rate of grammatical development compare to that for TD children? (5) At age 4 years, are there differences in overall intelligence, verbal intelligence, nonverbal intelligence, or digit span between children who evidenced logistic expressive vocabulary growth curves and those who evidenced other types of expressive vocabulary growth curves?

Methods: 21 children participated in the study. The children had a mean age of 17 months at the start of the study and have been/were enrolled in the study for an average of 53 months. Expressive vocabulary size at the start of the study was ≤5 words for all but one child. Four children had comorbid diagnoses on the autism spectrum (1 PDD-NOS, 3 autism). Parents completed the MacArthur-Bates Communicative Development Inventory (CDI), a parental report measure of early language development, on a monthly basis. Intellectual ability at age 4 years was assessed using the Differential Ability Scales (DAS).

Results: Onset of vocabulary was delayed for almost all children. Analyses of vocabulary growth curve data indicated that 14 children (including the child with PDD-NOS) evidenced logistic growth (the type of growth characteristic of TD children), 5 (including the 3 children with autism) evidenced very slow linear growth, and 2 evidenced an unusual pattern we refer to as double-linear (very slow linear growth followed by a sudden very steep change in slope). The relation between receptive and expressive vocabulary size was within the normal range for all children. Onset of grammatical development (defined as a score of at least 1 on the CDI Early Sentence Checklist) was within the normal range for 3 of the 21 children, mildly delayed (onset between 31 and 41 months) for 8 children, seriously delayed (onset between ages 42 and 52 months) for 6 children (1 with PDD-NOS, 1 with autism) and extremely delayed (onset at >66 months) for 4 children, including 2 children with autism who have expressive vocabulary sizes of <10 words at age 6 years. Once grammatical development began, rate of grammatical acquisition was within the normal range for all children. The relation between expressive vocabulary size and grammatical complexity was also consistently within the normal range. To consider the relation between type of vocabulary growth curve and intellectual development at age 4 years, the three group-curve groups were compared on overall cognitive ability (DAS GCA), verbal ability (DAS Verbal Cluster standard score), nonverbal ability (DAS Nonverbal Cluster standard score), and digit span. The logistic growth group had significantly higher DAS GCA and Verbal standard scores than did the linear and double-linear groups. The logistic and double-linear groups had significantly higher DAS Nonverbal standard scores and significantly longer digit spans than the linear group.

Discussion: Most children with WS evidence delayed lexical and grammatical development, but once development begins, follow the same path as TD children, including evidencing the same type of expressive vocabulary growth curve. This group of children also performs significantly better than the remaining children with WS on measures of intellectual ability and verbal short-term memory at age 4 years. The impact of a comorbid PDD-NOS or autism diagnosis on language acquisition and cognitive development will be considered, as will theoretical implications and applications of the overall pattern of findings.

Understanding of Others' Intentions by Young Children with Williams Syndrome

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Background and Purpose: The social phenotype of children with Williams syndrome (WS) includes gregariousness, high sociability, and high empathy. At the same time, they show significant problems in social interaction, including difficulty with peer relationships and poor social judgment. Difficulties in understanding others' intentions could be an underlying factor for these social-communicative difficulties. In this study we considered the question of whether young children with WS understand the intentions of others in two different tasks: (1) a helping task and (2) an intentionality task.

Methods: Participants were 15 children with WS (9 girls, 6 boys) aged 4.05 to 6.89 years (m= 5.82, SD= .95). In the helping task (developed from Meltzoff, 1995) the child and a puppet played with a series of 12 sets of toys. During play, the puppet either successfully (6 trials) or unsuccessfully (6 trials) manipulated the toys in a manner with which the child would be familiar. To determine if children understood the puppet's intentions, responses were coded to indicate if the child imitated the puppet's successful actions (imitate) or helped when the puppet was unsuccessful (help). For the intentionality task (modified from Carpenter et al., 1998) 13 boxes were constructed (one was used for warm up/training). Each box had two moveable attachments (e.g., protrusions that could be slid or turned) and an outcome (e.g., lights flashing, music playing). , For each box, one experimenter demonstrated both an intentional (I) action with a verbal cue of "There!" and an accidental (A) action with a verbal cue of "Whoops!," both with the appropriate intonation. Actions were presented in one of two orders: I-A or A-I, after which a second experimenter secretly activated the outcome related to the intentional action. Orders were counterbalanced across participants and boxes. Responses were coded based on actions produced by the child after watching the experimenter: first action only (FAO), second action only (SAO), both actions same order (BASO), and both actions reversed order (BARO).

Results: In the helping task, comparisons of performance on the imitating (m = 5.11, SD = 1.57) and helping trials (m = 5.05, SD = 1.51) indicated no significant difference between conditions (p = .82), with high performance on both. For the intentionality task, results from a 2 (condition: I-A, A-I) x 4 (response: FAO, SAO, BASO, BARO) mixed ANOVA indicated a significant effect of response (p=.003) and a significant interaction between condition and response (p<.001). In both conditions, the most common response was the correct one (production of the intentional action but not the accidental action). However, children were more likely to perform correctly in the A-I condition (66%) than in the I-A condition (49%). The results of a paired-t test suggest that performance was better on the helping task than on the intentionality task (p = .05).

Discussion: By age 6 years, most children with WS showed an understanding of others' intentions by providing help when needed (after the puppet was unsuccessful) in a familiar context. However, they had difficulty applying this knowledge to a novel learning task that required them to differentiate between the impact of an action that an adult intended and one that occurred accidentally in determining what made the novel boxes produce the desired outcome. Although the most common response was to produce the intentional action without the accidental action (the correct pattern), 43% of the time the children produced the accidental action (either with or without the intentional action), suggesting difficulty using verbal pragmatic cues provided by the adult to distinguish between intentional and accidental actions in a novel situation. These results contribute to our

understanding of the social-communicative difficulties of children with WS. Data collection is ongoing for the WS group in addition to a control group of younger typically developing children. Theoretical implications will be discussed.

Reading Abilities of 9 – 17-Year-Olds with Williams Syndrome: Impact of Reading Method

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Purpose: Williams syndrome (WS) is characterized by a specific cognitive profile including relative strengths in verbal short-term memory and language and considerable weakness in visuospatial construction. Although there have been many studies of the language abilities of children with WS, very few studies have focused on reading ability. Furthermore, the age range included in each study has been very broad, analyses were often based on age equivalents rather than standard scores making interpretation of the findings problematic, and information regarding reading instruction methods was not included. The purpose of the present study was to consider the impact of reading method on the reading abilities of 9 – 17-year-olds with WS.

Methods: Participants were 44 children with WS aged 8.93 – 17.71 years (mean: 12.49 years, SD: 2.61 years). Children completed the Differential Ability Scales-II (DAS-II) School Age version and the Wechsler Individual Achievement Test-II (WIAT-II) Reading subtests. Mean DAS-II GCA (similar to IQ) was 63.14 (SD: 11.58, range: 39 – 98). Mean WIAT-II Reading standard scores were: Word Reading: 73.00 (SD: 20.58, range: 40 – 112), Pseudoword Decoding: 78.75 (SD: 15.83, range: 40 – 113), Reading Comprehension: 64.61 (SD: 18.97, range: 40 – 102), Reading Composite: 67.27 (SD: 18.84, range: 40 – 102).

Results: To consider the impact of reading method on the reading abilities of children with WS, participants were divided into two groups based on primary reading approach, which was determined from the child's IEP, parental report, and when necessary discussion with the child's teacher. 24 children were classified as using primarily a phonics approach and 20 as using primarily a sight-word approach. The DAS-II manual provides predicted WIAT-II standard scores based on the child's DAS-II GCA. Using this information, discrepancy scores (obtained WIAT-II standard score minus predicted WIAT-II standard score) were calculated for each child for each Reading subtest and the Reading Composite and used as the dependent variable in a series of *t* tests. Discrepancy score means and standard deviations are shown in Table 1. Significant and large differences favoring the Phonics group were found for all measures: Word Reading: $t(42) = 9.36$, $p < .001$; Pseudoword Reading: $t(42) = 6.84$, $p < .001$; Reading Comprehension: $t(42) = 6.27$, $p < .005$; Reading Composite: $t(42) = 9.01$, $p < .001$. Eight of the 20 children in the Sight-word group earned a raw score of 0 on Pseudoword Decoding.

Group	Word Reading		Pseudoword Decoding		Reading Comprehension		Reading Composite	
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
Phonics	9.08	(9.53)	6.67	(9.46)	-0.96	(10.22)	3.50	(8.97)
Sight	-17.75	(9.39)	-10.60	(6.72)	-19.45	(9.15)	-18.45	(6.76)

Table 1. WIAT-II Reading Discrepancy Scores as a Function of Reading Group

Discussion: In summary, results indicated a very wide range of reading ability for children with WS relative to their age peers in the general population. Similarly to the general population, IQ was strongly related to reading ability. Reading method had a major impact on reading ability; children who were taught to read with phonics on average read at or above the level expected for their GCA. In contrast, children taught to read using a sight-word approach on average read well below the level expected for their GCA. Theoretical and applied implications will be discussed.

Self-Recognition by Toddlers with Williams Syndrome

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Background and Purpose: The development of self-recognition is considered an important marker of cognitive development (Howe & Courage, 1997) and language development (Lewis & Ramsay, 2004) and may also be related to the development of empathy (Bishof-Kohler, 1988). Self-recognition is traditionally tested with the Rouge Task (Amsterdam, 1972) in which a child, after a spot of rouge was unobtrusively placed on his or her nose, is positioned in front of a mirror. Children who reach for the spot on their face instead of reaching for the spot on the mirror or not reaching at all are considered to recognize themselves. Despite eventual relative strengths in verbal short-term memory and language and a gregarious and overly friendly personality, young children with WS are delayed in their language acquisition and evidence some socio-communicative difficulties that overlap those of children with autism spectrum disorders. Children with WS also have considerable difficulty with visuospatial construction and more generally, with eye-hand coordination and fine motor skills. The present study explores self-recognition in toddlers with WS. Because of the unusual developmental profile of children with WS, data from these children provide an important test of the universality of the relation between the development of self-recognition and the development of symbolic (pretend) play.

Method: Participants were 26 children with WS (mean chronological age = 29.85 months, range: 21.95 to 37.75 months) for self-recognition using the Rouge Task. In addition, the children completed the Mullen Scales of Early Learning (mean = 59.19, *SD* = 9.54) and their parents completed the Communication and Symbolic Behavior Scales Developmental Profile (CSBS DP) Caregiver Questionnaire, which includes a measure of symbolic play.

Results and Discussion: Children who passed the Rouge Task did not differ significantly from those who did not pass the Task on chronological age (29.67 months vs. 30.12 months, $p = .67$) or on overall Mullen Composite score ((61.80 vs. 54.91, $p = .07$). A Fisher's Exact Test indicated a significant relation between success on the Rouge Task and the ability to engage in symbolic play involving "object-directed" actions (e.g., brushing a doll's hair, feeding a teddy bear with a spoon) (Figure 1, $p < .001$). This finding is consistent with Lewis and Ramsay (2004)'s results for TD toddlers.

Discussion: In sum, the present findings indicate that self-recognition, when tested by the Rouge Task, is delayed for children with WS. The results also suggest that self-recognition is related to object-related symbolic play, as has been shown for TD children. Within the age range tested, chronological age and expressive vocabulary were not found to be significantly related to performance on the Rouge Task. Theoretical implications will be discussed.

Sensory Processing Difficulties Predict Internalizing Symptoms,

ADHD Symptoms, and Repetitive Behaviors in 4 – 10-year old Children with Williams Syndrome

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Purpose: Children with Williams syndrome (WS) frequently meet DSM-IV diagnostic criteria for psychiatric disorders. For example, Leyfer et al. (2006) found that 54% of 119 children aged 4 – 16 years met DSM-IV criteria for specific phobia, 12% for generalized anxiety disorder, and 65% for Attention Deficit Hyperactivity Disorder (ADHD). McNally & Mervis (2006) found that based on parent report, 95% of children with WS engage in at least one type of repetitive behavior. As there is likely significant co-morbidity among these symptoms, it is important to investigate factors which may help explain the links between them. 52% of children with WS with specific phobia have a phobia of loud noises, suggesting sensory processing as a possible predictor. The purpose of this study was to investigate the relations between sensory abnormalities in children with WS and internalizing symptoms (IS; includes anxiety and depression), ADHD symptoms (ADHD), and repetitive behaviors (RB), using path analysis.

Methods: Participants were 42 children with WS aged 4.12 – 10.95 years (mean: 8.12 years, SD=1.79). Children's scores for IS, ADHD, RB, and SP were determined based on questionnaires completed by their parents. IS was operationalized as the Internalizing Problems T score from the Child Behavior Checklist-Parent Report (Achenbach, 2001), ADHD as the ADHD index T score from the Conner's Parent Rating Scale-Revised (Conners, 1997). RB as the total raw score for the Repetitive Behavior Scale-Revised (Bodfish et al., 1999), and SP as the total raw score for the Short Sensory Profile (Dunn, 1999).

Results: Correlational analyses were conducted to examine the relations among SP, IS, ADHD, and RB. Significant correlations were found between all of the variables, with the exception of RB and ADHD, which approached significance. To test the hypothesis that sensory processing abnormalities predicted IS, ADHD, and RB, a path analysis was conducted. The resulting model provided a significant fit to the data (χ^2 = 2.80, $p > .05$; CFI = 1.0; RMSEA < .05), with each individual path yielding a significant contribution (β = -.60 for IS, $p < .001$; β = -.45 for ADHD, $p < .01$; β = -.63 for RB, $p < .001$; see figure). Given the bivariate relations between the dependent variables, a second model was conducted to estimate the correlation among error terms for IS, ADHD symptoms, and RB. All error correlations within the model were nonsignificant, suggesting that these variables do not share any additional variance not accounted for by SP.

Discussion: The path analysis results indicate that much of the shared variance in the comorbid symptoms of IS, ADHD, and RB may be explained by sensory-related processing difficulties. Theoretical implications and applications will be discussed.

Early Manifestation of the Social/non-Social Anxiety Distinction in Williams Syndrome

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Despite evidence of high rates of non-social anxiety disorders in Williams Syndrome (Dykens, 2003), population rates of Social Phobia are exceptionally low (Leyfer et al., 2006) and WS individuals are renowned for their outgoing, sociable personalities (for example, Gosch & Pankau, 1994, 1997). The aim of the present study was to examine early manifestations of this dissociation in young children with WS by observing behavior in response to both socially and non-socially threatening situations. In light of findings suggesting the face is particularly motivating for children with WS (Mervis et al., 2003), we were also interested to compare the children's behavior when a stranger's face was visible with their behavior when it was covered.

A group of ten children with Williams syndrome, aged 3 to 6 years, and two typically-developing control groups, matched on chronological and mental age respectively, took part in individual 30-minute play sessions. During the play session, children's behavior in response to situations designed to be either physically or socially threatening was assessed. The physical threat component involved the child hiding alone in a cupboard and unstructured playtime with three 'threatening' toys. The social threat aspect of the play session incorporated a number of components. Firstly, the child's behavior towards an adult stranger was observed, both during unstructured and structured play. Secondly, the child's behavior towards an adult stranger with their face completely covered was observed. Finally, the child's behavior in social performance situations (karaoke and impressions games) was observed.

No group differences were found on the physical threat component of the play session. In contrast, a number of group differences emerged on the social threat component. The WS group were more likely to initiate interaction and engage with the stranger in both the masked and unmasked conditions. Interestingly, the WS group spent a larger proportion of time engaged with the stranger during the unstructured play session but no group differences were found for the structured play session. Observation of behavior on the social performance tasks showed that the WS group were more likely to sing along to the karaoke but were comparable to both control groups in their behavior on the impressions tasks.

In contrast to the hypothesis, there was no evidence to suggest that young children with WS differed from controls in their anxiety toward non-social threat. However, the results suggest that the sociability characteristic of older children and adults with WS is already evident in young children, even when a stranger's face is covered. This indicates that the salience of the face does not entirely drive social approach behaviors in WS. Consistent with a two-factor model of social inhibition (Asendorf, 1990), the results further suggest that children with WS may primarily differ from typically developing children with respect to their behavior towards strangers rather than their behavior in social performance or evaluative situations.

Neuroplasticity in Williams Syndrome – Intervention on Attention Problems

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Williams Syndrome (WS) is a rare neurodevelopmental disorder (1/7500) caused by a submicroscopic delection in the band q11.22-23 of chromosome 7 and involves a highly unusual set of clinical characteristics. WS patients exhibit a very distinctive cognitive profile, with relative strengths in language and facial processing, contrasting with profound impairments in visuo-spatial cognition. In addition, specific emotional and behavioural features have been described, being attention and concentration the most common problems (Davies, Howlin, & Udwin, 1997). Indeed, these deficits are corroborated by parents reports and our clinical assessment with Luria Neuropsychological Investigation (Christensen, 1989). This specific cognitive architecture reinforces the need of designing specific intervention strategies to improve these weak areas. Thus, the objective of this work is to present the intervention work that we have accomplished in the last 5 years in the regional Galician Williams Syndrome Association (ASWG) in Santiago de Compostela (Northwest of Spain) with 20 patients with WS.

Our cognitive stimulation program developed in this association is a bottom up approach that consists in training programmes involving multimodal stimulation characterized by repetitive practice of specific cognitive exercises designed to strengthen basic skills that are essential for more complex cognitive function. Taking into account that attention is a cognitive process that mediates other cognitive skills, as memory, executive functions and visuo-perceptive abilities, one approach of our intervention program was focused on attention. Thus, we developed specific psycho-educative material (in both paper and digital versions) to work attention problems, in order to have a major impact in other cognitive processes and ultimately in promoting a scholar, social and occupational adjustment.

Reflexive Orienting to Non-Predictive Gaze and Arrow Cues in Williams Syndrome

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Background: Previous studies have shown reflexive attentional orienting to gaze in typically developing individuals (e.g. Friesen & Kingstone, 1998; Frischen & Tipper, 2004; Hietanen, 1999). Orienting of attention has not been systematically examined in Williams syndrome (WS), a neurodevelopmental disorder characterized by mild mental retardation, specific impairments in spatial ability, and heightened social interest. Measuring attentional processes engaged in orienting tasks may elucidate low-level mechanisms of face perception and social cognition in this population.

Methods: We administered a standard cueing paradigm with non-predictive, centrally-presented schematic faces and arrows at two stimulus onset asynchronies (200, 600 SOA) to 13 individuals with WS and to 10 mental age-matched normal controls (NC). Gaze and arrow cues were presented in separate blocks, with target location (left or right side of the central stimulus), cue validity, and SOA counter-balanced across trials. Each trial consisted of a central fixation point, followed by a centrally-located cue, with a target (asterisk) appearing either 200 or 600 ms after the appearance of the cue. In each block half of the trials were valid (direction of cue toward the subsequent target) and half were invalid (direction of cue away from subsequent target); Valid and invalid trials were randomized. Manual response time (via button-press) to target location was measured to assess effects of cue-direction on attention deployment.

Results: Reaction time analyses were conducted on correct trials only. Accuracy was not significantly different between the

two groups. In the arrow condition, NC participants were able to locate validly cued targets significantly faster ($p<.05$) than invalidly cued targets at the 200 ms SOA; however, the RT advantage disappeared at the longer SOA, replicating earlier findings (e.g. Senju et al. 2004). In the arrow condition, participants with WS showed a validity effect at both SOAs ($p<.05$). The validity effect for arrows at the 600 ms SOA was also of a greater magnitude for individuals with WS overall than for controls ($p<.05$). For the schematic faces the NC group showed a validity effect at 200ms ($p<.05$), but again this decayed at 600ms. The opposite was true for the participants with WS, who showed a validity effect for gaze cues at the longer SOA ($p<.05$) but not the shorter one.

Discussion: This is the first study to demonstrate attentional orienting effects in WS using gaze and arrow cues. These results suggest that individuals with WS may have more difficulty using top-down attention control mechanisms to disengage from the "rule-like" directional quality of the arrows. Our findings indicate that orienting to gaze is preserved in individuals with WS, although proceeding on a different time-course, which may be influenced by domain-general processing constraints.

Hypertension: High Resolution Array Analyses Reveal the Risk in Williams Syndrome is Determined by Gender and Parent of Origin

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Hypertension (HTN) is the leading independent risk factor for stroke and cardiovascular disease. Despite intensive study, the genetic origins of essential hypertension are largely unknown although it accounts for more than 95% of cases. We have combined high resolution SNP array analyses with phenotypic analyses of WS and report that the elevated risk of HTN in Williams Syndrome (WS) is significantly modified by both gender and parental origin of the deletion and that the size of the deletion does not correlate with the risk. We initially determined the parental origin of the deletion and HTN in 53 families with WS (ages 12-51y) and 32% reported HTN. We found HTN in 21% (6/29) of those with maternally derived deletions in contrast to 46% (11/24) of those with paternally derived deletions. To better model the HTN risk factors found in the normal population, we reasoned that gender might also affect the risk of HTN in WS, independent of parental origin of the deletion. Unexpectedly, we found a highly significant effect in females with 0% (0/17) HTN in those with maternally derived deletions vs 40% (6/15) in those with paternally derived deletions. In contrast, males had an increased risk of HTN regardless of the parental origin of the deletion with HTN found in 56% (5/9) with paternally derived and 50% (6/12) with maternally derived deletions. To test the significance of these findings, we examined a second independent population of 30 WS families and observed a similar trend: in females, only 10% (1/10) of maternal but 29% (2/7) of paternal deletions had HTN in contrast to 67% (2/3) of paternal and 40% (4/10) of maternal males. Molecular extent of the deletion was measured by using the 1M Illumina SNP array. Combining both populations in a multivariate model, we find that the risk of HTN is independently related to gender ($p=0.0002$), age ($p=0.0002$), and parental origin of the deletion ($p=0.0107$). In summary, the risk of HTN appears to be dramatically affected by gender and the parental origin of the deletion in WS. This suggests an imprinted gene(s) in the WS region affecting HTN as well as a potential role for gender specific epigenetic imprinting

in HTN. We propose that incorporating this in current models may improve the ability to define genes for essential HTN in the normal population.

Producing and Understanding Oral and Graphic Humour by Williams Syndrome People

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In this work we try to value how do Williams syndrome people understand and produce humour. Do they maintain the traditional parts of a joke? Is funny to them what must be funny? What strategies that make a joke be funny are left out? Do they infer properly in order to enjoy the humorous situation? Can they organize and explain correctly a cartoon?

We assess humour in 8 people with Williams syndrome (four adults and four adolescents). Regarding oral humour, they must tell a joke and hear different jokes in which linguistic and non-linguistic devices were used and afterwards they had to explain the joke.

In relation to graphic humour, different cartoons were presented. They had to put in order the different frames of the cartoons to get a funny result. Then they had to tell what the funny interpretation was for them. Next the correct order was presented and three different interpretations were given (literal, non literal but incorrect, the correct one) and they had to choose the one who fitted best to the cartoon.

Results show difficulties in telling jokes and understanding them. Graphic humour was also misunderstood. Literal interpretations were mostly given; identifying the relevant element of a frame of the cartoon is especially important to get the correct sense and enjoy the situations and was very difficult to them. Jokes and cartoons need of special comprehensive strategies (world knowledge, interpretation of the situation from cultural and environmental patterns) to be properly understood. So, pragmatic knowledge must be applied, in order to get the funny meaning. A deficient pragmatic competence in WS restricts seriously their integration in social and everyday communicative situations.

Feeding Disorders in Williams Syndrome

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Statement of Purpose: Children with Williams Syndrome are at risk for a myriad of developmental disabilities because of the complicated medical and neurological conditions. Little has been written about the specific types of feeding problems in these children. A better understanding of how this syndrome affects a child's ability to manipulate increasingly complex food textures and advance oral motor function could provide improved outcomes for feeding and swallowing development and optimal growth in children with Williams Syndrome.

Methods: Children with identified feeding and swallowing problems were evaluated by the Speech Pathologist, with over 15 years experience in dysphagia, as a member of an Interdisciplinary Feeding Clinic and a Multi-specialty Williams Syndrome Clinic. Oral motor function and swallowing patterns were assessed in children with complex medical conditions, which predisposed them to feeding and swallowing problems. Williams syndrome is associated with oral motor delay and feeding difficulty in infancy and early childhood. Experience in treating these

children has contributed to the identification of specific problems, therapeutic interventions, and parent education, which improve feeding ability.

Results: Identified feeding problems included disordered sucking in infancy, inefficient oral motor patterns, delay in chewing skill acquisition, limited volume, growth failure, and dysphagia. The constellation of conditions in Williams Syndrome, which are associated with feeding disorders, were identified and correlated with the occurrence and severity of the feeding disorder. Those conditions include developmental delay, cardiovascular disease, neurological abnormalities, failure to thrive, and gastrointestinal problems. Hypotonia and GI dysmotility were prevalent in the children evaluated and significantly contributed to decreased sucking strength and endurance, inadequate strength for chewing, food refusal, difficulty drinking, poor appetite, limited interest in eating, and drooling, which impacted sufficient oral intake and weight gain. Treatment strategies to improve function included identifying adequate seating and positioning to support optimal oral motor function; providing specialized bottle/nipple systems; and modifying food texture and consistency to decrease effort and increase volume at mealtime.

Discussion: Children with Williams Syndrome are predisposed to feeding problems and reduced oral motor function impacted by hypotonia, which has been shown to affect a child's ability to suck and swallow, manipulate solid food, and acquire developmental feeding milestones. In addition, gastrointestinal conditions can affect a child's physiological state of comfort during feeding and impact hunger and motivation to eat. Experience has provided consistent information with earlier findings that corroborate the need for appropriate assessment and intervention to establish positive growth and optimize development in children with William's Syndrome.

Motor Function in Adults with Williams Syndrome: Is There Evidence for Basal Ganglia or Cerebellar Dysfunction?

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Despite early reports of neurological 'soft' signs in Williams syndrome (WS), there has not yet been any systematic investigation of the developmental progression of motor dysfunction in this disorder. These individuals are often described as 'clumsy', and show poor motor coordination, for instance when walking across uneven surfaces or negotiating obstacles. The few clinical reports of motor problems in WS have described subtle neurologic signs of cerebellar dysfunction such as mild dysmetria and poor balance during cerebellar sensitization tests (tandem walking). However, the precise neuroanatomical loci for the motor impairments seen in WS are as yet unclear, with some evidence that motor impairments resembling basal ganglia dysfunction appear to increase and persist into adulthood. The aim of this study was to systematically examine neuromotor dysfunction in adults with WS, by employing a kinematic analysis of upper-limb and gait function to determine whether the motor profile is consistent with basal ganglia or cerebellar dysfunction. A further aim of the study was to examine the impact of attention and executive deficits on visuomotor

performance in WS. The relationship between cognitive function (assessed on standardized tests of attention and executive function) and motor control was explored using visuomotor tasks with varying levels of task difficulty for individuals with WS. Preliminary results suggest a more pervasive functional impairment that involves deficits in movement control when compared to matched controls, implicating frontostriatal deficits in WS. The results will be discussed in the context of the important interaction between higher-level cognitive function and motor control in WS. Further, we speculate about the possible genetic influences on early brain development that may contribute to the visuomotor deficits seen in individuals with WS.

Question-Asking Behavior in Children and Adolescents with Williams Syndrome: Anticipation of Positive and Negative Events

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Background: Williams syndrome (WS) is a rare genetic neurodevelopmental disorder (1 in 7500 births) caused by a hemizygous deletion of chromosome 7q11.23. One aspect of the behavioral phenotype that has received some attention is the tendency of people with WS to be anxious (Dykens, 2003; Klein-Tasman & Mervis, 2004; Leyfer et al., 2006), which commonly manifests as repeated thoughts and questions about upcoming events. This question-asking behavior may fall at the "intersection of worry and obsessiveness" (Leyfer et al., 2006, p. 620), and is not adequately captured by the diagnostic categories of Generalized Anxiety Disorder (GAD) or Obsessive-Compulsive Disorder (OCD). The question-asking behavior of people with WS has not been examined empirically. The present study was designed to take a closer look at this behavior and parents' perceptions of the anticipatory anxiety in their children with WS.

Methods: Participants were 30 children with WS, ranging in age from 8 to 15 years (mean = 12.03). The sample group consisted of 14 males and 16 females. Participants were administered the Kaufman Brief Intelligence Test—Second Edition; Attention Deficit/Hyperactivity Disorder (ADHD), Specific Phobia, GAD and OCD sections of the Anxiety Disorders Interview Schedule for DSM-IV Parent version (ADIS-IV Parent); and the *Anticipation of Upcoming Events* survey, which was developed for this study. The survey included a quantitative portion in which items were coded to measure the frequency of question-asking (frequency rated from 1-4; 1 = never, 4 = very often), and a scale was created from these questions (α = .86). Qualitative data were also gathered about how problematic the behavior has been for the family and parents were asked how well the terms "anxiety," "anticipation," and "worry" characterize this behavior.

Results: Parents of 26 of the 30 children reported that anticipatory question-asking occurs often or very often. The children frequently (i.e., often or very often) ask questions about both positive (N=26) and negative (N=25) upcoming events. Of the 26 parents who reported that question-asking is occurring, 15 reported that it is problematic. Most parents (n = 23) reported that "anticipation" best characterized the question-asking behavior. Sixteen participants (53.3%) met criteria for comorbid ADHD diagnoses and 12 (40%) for Specific Phobia; 7 (23.3%) participants had both diagnoses. Only one child met the criteria for GAD. Though scale scores were not influenced by gender, IQ, or diagnosis of Specific Phobia, scores were significantly higher for the children with ADHD [t (35.99) = 2.69, p = .011]. Higher scores were also associated with parental reports that the question-asking behavior is problematic [t (28) = 2.12, p = .043] and an

increasing difficulty in redirecting the child [t (22.4) = 2.75, p = .012].

Discussion: Anticipatory anxiety in the form of repeated thoughts and question-asking is a common phenomenon in children and adolescents with WS. When this behavior is present, a majority of parents report that it is problematic for their family. Though Specific Phobias were fairly common in these children with WS, the repeated question-asking is more prevalent than anxiety disorder diagnoses. As noted in prior research, this anticipatory anxiety may lie at the intersection of worry and obsessiveness and is therefore not adequately captured by diagnoses of GAD or OCD. High scores on the survey scale can serve as a signal that parents may need assistance in managing their child's anticipatory anxiety. There is evidence that the anxiety experienced by children with WS increases as they move into adulthood (Dykens, 2003; Einfeld, Tonge & Rees 2001). Further research about the role of question-asking behavior as an early indicator for vulnerability to anxiety is needed.

Genes, Neural Systems, and Social Behavior: Autonomic Correlates of Processing Upright and Inverted Affective Faces in Williams Syndrome

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Williams syndrome (WS) is a neurogenetic disorder caused by a hemizygous deletion of approximately 25 genes on chromosome 7q11.23. Behaviorally, WS is associated with heightened appetitive social drive (e.g., tendency to indiscriminately approach strangers), a preference for viewing and increased skill in identifying faces, and language features that increase the likelihood of social interaction with others (e.g., Järvinen-Pasley et al, 2008; Meyer-Lindenberg et al, 2006). Neuroanatomical data indicate relative enlargement in the amygdala and prefrontal cortical structures (Reiss et al, 2004). Almost nothing is known about autonomic nervous system function in WS. In typical development, different temperament profiles have been linked to distinct patterns of autonomic responding that reflect individual differences in cortical arousal, thereby regulating social and emotional behavior (Eysenck, 1967, 1981). It may therefore be hypothesized that individuals with WS show similar autonomic responding to extroverts with regard to social stimuli, manifested as smaller skin conductance responses (SCRs), lower heart rate (HR) reactivity, lower overall skin conductance level, and faster electrodermal habituation, compared to introverts. We examined autonomic responses (SCR, HR) of 21 individuals with WS, 21 typically developing controls (TD), and 5 family members with a partial WS deletion (PWS), to 92 upright and inverted affective and neutral faces (Ekman & Friesen, 1976). The experimental groups exhibited significantly different patterns of autonomic reactivity across the upright and inverted stimuli, with individuals with WS uniquely showing a greater SCR to the upright than the inverted faces. Whereas individuals with WS, relative to both TD and PWS, showed the greatest magnitude of SCR to the upright face and the lowest magnitude of SCR to the inverted face, those with TD and PWS showed the opposite pattern, with the PWS group presenting the most dramatic contrast to the WS group. Behaviorally, the WS group showed significantly poorer affect identification ability compared to the TD controls. No significant between-group differences were found in baseline skin conductance level or HR reactivity. This pattern suggests atypical organization of autonomic function in WS, with increased responsiveness to upright faces, and decreased responsiveness to inverted faces. Marked

differences between the WS and PWS groups show that the atypical pattern observed in WS is not due to intellectual impairment alone. These data provide promising initial evidence of increased autonomic reactivity to upright face stimuli in individuals with the full WS deletion, which may be linked to their unique social phenotype.

Sensory Modulation in Children with Williams Syndrome

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Background and Purpose: Recently there has been interest in understanding the similarities and differences between the phenotypes associated with autism and Williams syndrome (WS). Although the popular press and some researchers have argued that the phenotypes associated with these developmental disorders are opposites of one another, careful examination of the WS phenotype has yielded several similarities (e.g., difficulties with pragmatics and with socio-communicative behaviors). However there are many areas yet to be explored. For example, although sensory issues are often found in children with autism, to date, little is known about the nature of sensory issues in children with WS. Klein-Tasman et al. (2007) examined children with WS between 30 and 63 months of age in a structured interaction (ADOS-G) and found that 28% demonstrated definite unusual responses to sensory aspects of toys or surroundings. The purpose of the present study was to further investigate the nature of sensory abnormalities in children with WS and examine their relation to cognitive ability and adaptive functioning.

Methods: Participants were 72 children with WS aged 4.00 - 10.95 years for whom three types of data were available: parental report data for the Short Sensory Profile (SSP; Dunn, 1999) designed to examine sensory modulation, cognitive ability, and adaptive functioning. Mean IQ on the Kaufman Brief Intelligence Test, 2nd edition was 70.26 (*SD* = 17.32). Mean overall adaptive functioning as measured by the Scales of Independent Behavior – Revised was 49.06 (*SD* = 20.10). Nine children had comorbid diagnoses on the autism spectrum (ASD) based on clinical judgment following administration of the ADOS-G and ADI-R.

Results: Based on caregiver report, most children were classified as having definite sensory modulation issues (Table 1). To assess the relations between SSP total score, overall intellectual ability, and adaptive functioning, a series of correlations was computed. Overall Sensory score was not significantly related to cognitive ability ($r = .21$) but was related to adaptive functioning ($r = .46$, $p < .001$). This correlation remained significant even when the children with ASD were excluded. Interestingly, the children with ASD were not clustered at the low (severe problem) end of the distribution of Sensory Profile Total Score. Most children with and without ASD demonstrated impairments on Auditory Filtering, Energy, Under-responsive/Sensation Seeking, and Visual/Auditory Sensitivity.

Discussion: In summary, based on parental report most children with WS demonstrate sensory modulation problems. Most children with WS both with and without comorbid diagnoses of ASD demonstrated definite abnormalities in the ability to use and screen out sounds, the ability to use muscles to move, noticing sensory events, and responding to sounds and sights. Overall sensory score was moderately correlated with overall adaptive functioning but was not significantly related to cognitive ability. Theoretical implications will be discussed.

Variability of Language Abilities of Young 4-Year-Olds who have Williams Syndrome

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Background and Purpose: The intellectual level of individuals with Williams syndrome (WS) ranges from severe intellectual disability to average intelligence, with most people in the mild to moderate intellectual disability range. Despite initial reports that WS provided a paradigmatic example of the independence of language from cognition, subsequent research indicated that language and cognitive ability are strongly correlated. Consistent with the wide range of intellectual ability, performance of school-aged children on standardized language assessments is as variable as for the general population, with mean level of performance in the low average to mild impairment range on most measures (see review in Mervis & Becerra, 2007). Prior studies of children with WS have included a wide range of ages in a single sample. In this study, we have taken a different approach, focusing on a large group of children who vary in age by only a few months to consider the early manifestations of variability in language ability.

Methods: Participants were 38 children with WS aged 4.0 – 4.33 years for whom three types of data were available: transcripts from free play sessions with a parent, standardized developmental assessments, and parental-report data for the CDI: Words and Sentences. Mean General Conceptual Ability (similar to IQ) on the Differential Ability Scales (DAS) was 61.03 (*SD* = 18.01, range: 26 – 91). Mean Peabody Picture Vocabulary Test-III standard score was 76.72 (*SD* = 24.22, range: 34 – 107). Seven children had comorbid diagnoses on the autism spectrum (ASD) based on clinical judgment following completion of the ADOS-G and ADI-R.

Results: Although children varied in age by only a few months, their language skills varied greatly. CDI Expressive Vocabulary size ranged from 2 to 679 (maximum possible) words (*M* = 359.16, *SD* = 232.45). Seven children (five with ASD) had expressive vocabularies of <30 words and six (two with ASD) had expressive vocabularies of 60 – 199 words. Play session transcripts confirmed that all children had expressive grammar delays. Six children (five with ASD) did not produce any word combinations and 11 (two with ASD) only rarely produced word combinations. The utterances produced by the remaining children, although longer on average, were shorter than expected for their age. Bound morphology was also limited. For nouns, 66% of the children produced the plural and 8% produced the possessive. For verbs, 66% produced –ing, 24% produced –ed, and 34% produced the third person singular. 53% produced the uncontracted copula (e.g., is, are).

Measures of expressive vocabulary and syntactic ability were available from both the play session transcripts and parental report on the CDI. Correlations between play session and CDI measures were very strong (*rs* = .61 - .92) indicating that, as for typically developing children, vocabulary growth was closely linked to grammatical development.

To examine the relations between language and cognitive development, correlations among performance on the DAS, vocabulary ability, and grammatical ability were computed. All were strong ($p \leq .002$). Correlations with GCA ranged from .62 – .83, correlations with DAS Nonverbal standard score ranged from .55 – .73, and correlations with DAS Recall of Digits T score ranged from .48 – .77. Correlations remained significant even when the children with ASD were excluded.

Discussion: The variability in language abilities evidenced by school-age children and adults with WS is apparent by age 4 years. Furthermore, as for typically developing children, vocabulary ability and grammatical ability are highly correlated and both are strongly related to verbal and nonverbal intellectual abilities. Theoretical implications will be discussed.

Implicit Processing of Facial Expression during Interpretation of Gaze Direction in Adolescents and Adults with Williams Syndrome

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Statement of Purpose: Studies have shown that gaze direction and emotional expression interact during processing of facial information in typically-developing (TD) individuals (Adams & Kleck, 2003; Ganel et al., 2005). Individuals with Williams syndrome (WS), a neurodevelopmental disorder characterized by heightened sociability, are relatively spared in facial identity recognition, but impaired in identification of facial expressions. Given the unique social phenotype of WS, we aimed to examine whether the interaction between gaze and affect processing observed in typical development is differentially manifested behaviorally and/or at the level of autonomic responsiveness in this population.

Methods: Participants included 11 individuals with WS (mean age 20:11) and 23 TD controls (mean age 23:8). Participants were presented a set of faces for passive viewing during which skin conductance responses (SCRs) were collected, followed by a gaze direction recognition task. Stimuli consisted of images of 6 male faces selected from the Karolinska Directed Emotional Faces set (KDEF; Lundqvist, 1998). Each face was presented with 3 eye gaze directions (direct, right averted, and left averted) and three facial expressions (neutral, fearful, and angry) counter-balanced across trials for a total of 108 trials over four randomized blocks. SCRs were collected on one block and reaction time (RT) data were collected for the remaining three blocks. During the SCR block, stimuli were presented for 5 seconds with a variable 5-7 second inter-stimulus interval, while during the RT blocks, participants judged gaze direction as "looking at you" or "looking away" by responding on a button box.

Results: Individuals with WS showed fewer SCRs to both averted and direct-gaze fearful faces than to direct-gaze neutral faces ($p<.05$). There were no differences in SCR frequency by condition in the TD group. RT analyses were conducted on correct trials only and groups did not differ significantly on accuracy. ANOVA for the RT data showed an effect of condition, $F(5,28) = 7.09$, $p<.001$, and a significant group by condition interaction, $F(5,28) = 5.01$, $p<.01$. Though there was an effect of facial expression on judgment of gaze direction in both groups, the pattern of influence within the groups differed. Both the WS and TD groups judged gaze direction more quickly for angry faces than neutral faces ($p<.01$). However, in the WS group judgment of gaze direction was delayed for both direct and averted-gaze neutral expressions compared to direct-gaze angry expressions ($p<.05$), while in the TD group, only responses to averted-gaze neutral expressions were delayed compared to angry expressions ($p<.05$). Judgment of gaze direction was also faster for fearful expressions compared to averted-gaze neutral expressions in the TD group ($p<.05$), but this effect was not significant in the WS group.

Discussion: The delayed response to neutral faces suggests implicit processing of facial expression during the explicit task of gaze interpretation in both groups. The ambiguity of neutral expressions interfered more with the explicit gaze direction judgment than the more readily interpretable angry and fearful expressions in the TD group. Though present for anger, this effect was not found for fearful expressions in WS, consistent with previous findings of atypical processing of fear in WS. Moreover, increased autonomic responsiveness to neutral stimuli compared to fearful stimuli in the WS group, which parallels the delayed RT to neutral expressions, may suggest alternative modes of processing ambiguous facial expression in WS.

Is it Williams Syndrome? GTF2I Implicated in Sociability and GTF2IRD1 in Visual-Spatial Construction Revealed by High Resolution Arrays

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Genetic contributions to human cognition and behavior are clear but difficult to define. Williams syndrome (WS) provides a unique model for relating single genes to visual-spatial cognition and social behavior. We defined a ~1.5 Mb region of ~25 genes deleted in >98% of typical WS and then small deletions in rare cases, showing that visual-spatial construction (VSC) in WS was associated with the genes GTF2IRD1 and GTF2I 1. To distinguish the roles of GTF2IRD1 and GTF2I in VSC and social behavior, we developed multiple genomic reagents (a custom high resolution oligonucleotide array spanning 14Mb of the WS and flanking duplicated regions, multicolor FISH and somatic cell hybrids analyzed by PCR) to identify individuals deleted for either gene but not both. We analyzed genetic, expression, cognitive and social behavior in atypical and typical deletion WS. The results indicate a rare individual with WS features (heart disease, small size, facies), but atypical deletion of all genes from FKBP6 through GTF2IRD1, but not GTF2I. At sub-exon resolution, the centromeric breakpoint localized to 72.38 Mb within intron 2 of the gene FKBP6 and the telomeric to 72.66 Mb, 10 kb downstream of the gene for GTF2IRD1. Cognitive testing (WPPSI-R, K-BIT, and PLS-3) revealed striking deficits in VSC (Block Design, Object Assembly) but overall performance 1.5-3 SD above WS means. Social behavior, evaluated quantitatively, revealed decreased global sociability and approach to strangers, less eye contact and more involvement in non-social activities than typical WS. These results define WS breakpoints, indicate the gene GTF2IRD1 is responsible for a large part of typical WS facies and VSC, and that GTF2I contributes to WS social behaviors including increased gaze and attention to strangers.

Music Therapy Interventions for Difficulties with Mathematics for Individuals with Williams Syndrome (WS)

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This presentation is based on an instrumental case study describing the interactions between a music therapist and three individuals with WS, specifically addressing the relationship between cognition in mathematics and music therapy interventions. Affinity for music is described as the one of the fundamental characteristics across the WS population. Music has been used more as a recreational tool or possibly for vocational purposes in some cases. Difficulty in basic mathematical skills has been documented in WS patients. This inquiry is designed to identify the possibility of using WS patients' affinity toward music as a strategy for addressing their mathematical difficulties. Based on literature reviews in special education, neuroscience, and WS research, attention problems, lack of strategies, and learned hopelessness appear to magnify the cognitive impairment in individuals with WS. Accordingly, four aspects of music are theorized to be effective in facilitating and expediting the learning process with WS patients: music (a) as a means to gain and maintain attention, (b) used as a learning aid can help with the memorization and retrieval of information, (c) can provide systematic sequence strategies for task accomplishment, and (d) can provide a positive self-statement for alleviating the high frustration levels and learned hopelessness aspects commonly found among the WS population. Approximately 12 weekly meetings with three informants had been conducted. The result indicates that individualized and specialized music therapy interventions for individuals with WS is necessary because of their differences in the manner in which visual and auditory information is processed, and difficulties in mathematics appear to be somewhat overlooked and basic numerical concepts must be mastered before working on addition and subtraction.

Strangers and Spiders: How Young Children with Williams Syndrome Respond to Social and Non-social Fear-eliciting Events

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Statement of Purpose: An abundance of research consistently describes children with Williams syndrome (WS) as extremely social and eager to approach and interact with strangers (Jones et al., 2000; Mervis et al., 2003). Children with WS are also reported to have high levels of anxiety and to exhibit specific fears and even phobias (Dykens, 2003). These behavioral tendencies suggest that children with WS may respond differently when confronted with social and non-social fear-evoking situations. Because previous findings were almost exclusively based on parental reports, the need remains for observational and laboratory-based measures of temperamental propensities in children with WS. This study explores behavioral responses to social and non-social fear-eliciting stimuli in children with WS using standardized laboratory-based assessment methods.

Methods: Participants were 14 children with WS (mean age = 50.1 mos., range 26 – 74 mos.), compared to 12 age- and IQ-matched children with Down syndrome (DS) and 15 age-matched typically developing (TD) children. Participants were administered 9 episodes from a lab-based assessment of temperament (Lab-TAB, Preschool Version, Goldsmith et al., 1999), including episodes designed to elicit social and non-social fear. In the "Stranger Approach" episode children encounter an unfamiliar person, in the "Scary Mask" episode they meet a research assistant wearing a wolf mask, and in two other episodes they are asked to touch fear-eliciting

objects (a jumping spider toy and a large gorilla mask). These episodes were videotaped and behaviors were coded according to manual instructions for emotional responses including: fearful facial affect, approach and avoidance behaviors, vocal distress, and postural fear.

Results: As expected, in a social context children with WS exhibited significantly less facial fear than the TD or DS groups ($p<.01$) and were more likely to approach the stranger than children in either control group ($p<.05$). Somewhat surprisingly, WS children were also less tentative than controls towards both "non-social" stimuli ($p<.05$), i.e. the jumping spider and gorilla mask. In response to a person wearing a wolf mask, children with WS responded similarly to TD controls and showed less postural fear than the DS group ($p<.05$). When compared across episodes, however, both WS and DS children showed significantly more facial and postural fear to the masked person than to the non-social stimuli ($p<.05$).

Discussion: These results suggest a complex pattern of responses to fear-eliciting situations in children with WS that may not fall neatly along social and non-social lines. Confirming prior research on sociability in WS children, this group showed the least fear when confronted with an unfamiliar person. Contrary to what was expected, children with WS were also less fearful when presented with non-social stimuli. The ambiguity of the situation of encountering a familiar masked person may have been particularly troubling to the children with developmental disorders relative to the other stimuli, though the WS and TD groups may have been better able to puzzle out the socially "playful" nature of the situation than the DS group. The complex pattern of results in this study points to a need for further systematic laboratory-based investigations of social and non-social fear-related behaviors and the need to clarify how temperamental dispositions (e.g. disinhibition) and anxiety influence this behavior in children with WS.

Amygdala Volume and Sociability in Williams Syndrome and Normal Controls

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The amygdala has been implicated in recognition of emotions in facial expression. Individuals with Williams syndrome (WS) have been found to view unfamiliar faces as more approachable than normal controls. The current research investigated the relationship between amygdala volume and approachability in both normal controls and individuals with WS. Twenty-two individuals with WS (mean age 17.1, SD 7.3 years; range 8-41 years) and 22 healthy controls matched for age, sex, and handedness (mean age 17.1, SD 7.3 years; range 8-41 years) underwent T1-weighted high-resolution MRI brain scans and rated the approachability of unfamiliar faces (Adolphs, 1998). The results showed that individuals with WS rated the unfamiliar faces as significantly more friendly than controls [$t(40)=2.29$, $p=.02$], supporting the trait of hypersociability in WS. Despite an 18% reduction in overall brain volume for individuals with WS, the volumes of left and right amygdala were similar in individuals with WS and controls. The average approachability rating of all faces for each participant in both groups was regressed against right and left amygdalar volume. Both group and right amygdalar volume contributed

significantly to the variance in the approachability ratings. Furthermore, in comparison to controls, individuals with WS made significantly fewer comments about features of the eyes and mouth than controls [t(39)=-3.30, p=.002] and significantly more comments about peripheral features [t(39)=3.47, p=.003], suggesting that WS individuals may use atypical facial processing when determining how friendly a person appears.

Cognitive and Behavioral Profile of Australian Individuals with Williams Syndrome

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We examined the cognitive and behavioral profile of 29 Australian individuals with Williams syndrome (mean age = 17 years, SD 7.3 years; range 8-41 years) and compared their results with that of 29 typical controls matched for age, sex, and handedness. We used a standardized effect measure, based on Cohen's "d", which indicated that the difference in the Full Scale IQ scores between the groups was approximately 5.5 standard deviations. The largest differences between the groups were noted in overall general intelligence, visuospatial skills, and mathematical abilities. Smaller differences were evident between the groups in receptive vocabulary, word associations, and musical ability. Individuals with Williams syndrome showed evidence of hypersociability compared to controls. An analysis of the word associations task indicated that although the controls were able to state more animal names that the individuals with WS[F(1,56) = 34.07, p < .001], the individuals with WS were more likely to name specific species, such as African Wild Dog, European Wash, Hopping Mouse, and Red-Bellied Black Snake. In comparison to their siblings, the participants with WS were reported to enjoy music significantly more than controls (z = -4.10, p < .001]. Similarly, when compared to peers, the participants with WS were reported to enjoy music significantly more than the control participants [z = -3.60, p < .001]. The results of a musical task (Specimen Aural Tests) indicated that there was a subgroup of six individuals with WS who scored significantly higher than the remaining participants with WS (z = -3.47, p < .001), and similar to the mean performance of the typical controls. Finally, the results of a hypersociability task (Adolphs) indicated that the participants with WS rated both positive and negative faces as more approachable than controls [F(1,53) = 5.29, p = .025]. In order to explore whether there were any differences in how the faces were rank ordered based on age group, the participants were divided into three broad developmental age ranges: (8-13 years; 14-18 years, and 19-41 years). The results suggest a possible developmental shift in rank ordering. The 8-13 year-olds rating both the negative and positive faces with a more positive bias than controls. The 14-18 year-olds rated only the positive faces as more approachable than similar aged controls. The 19-41 year-olds continued to rate the positive faces as more approachable than controls, but they rated the negative faces with a more negative bias than controls. Interestingly, the youngest group tended to use atypical features to determine approachability (such as hair and earrings), but this tendency was not as evident among the older participants with WS. This study shows evidence that the cognitive and behavioral profile of Australian individuals with WS is consistent with previous findings described in the WS literature. The results also provide new findings that younger individuals with

WS tend to use atypical features when determining whether or not someone appears approachable.

New Height, Weight and Head Circumference Charts for Children with Williams Syndrome in the United Kingdom

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Aim: To produce a growth reference for children in the UK with Williams syndrome.

Method: The children and adults were all affiliated to the Williams Syndrome Foundation a parent support group founded in 1979. They have all been shown to have a deletion of chromosome 7q,11,23. Prospective measurements were made by one growth nurse (WRS) from 19 regions in the UK, including Scotland, England and Wales. 176 children and adults were measured on up to 4 occasions between 2001 and 2004 (635 measurements). In addition retrospective data was obtained from the hospital notes of 67 of these same individuals (333 measurements). Centile curves were constructed using Cole's LMS method (1).

Results: The centile charts differ from charts previously derived in the USA and Germany and provide more appropriate standards for the UK population (2,3).

Conclusions: We propose that these charts be adopted for routine clinical practice as abnormalities in growth are an important feature of this syndrome.

Polysomnography Findings in Children with Williams Syndrome

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Purpose: Parents of children with Williams Syndrome (WS) often report that their children have sleep difficulties. A prior study of 7 WS subjects at the Children's Hospital of Philadelphia (CHOP) supported an association between WS and periodic limb movements in sleep, as well as increased wake time, less time in sleep stages 1 and 2, and more time in sleep stages 3 and 4 than control subjects (Arens et al. 1998). We wanted to expand the analysis of sleep in children with WS with a larger sample size, unselected for a history of sleep disturbance, to determine whether particular sleep features may be characteristic of WS.

Methods: Eligible subjects were males and females ages 2-18 years who met clinical criteria for WS, and who had haplo-insufficiency for the elastin gene as determined by fluorescent *in situ* hybridization (FISH). WS patients were recruited from the CHOP Multispecialty Center for Williams Syndrome. An equal number of healthy control subjects without sleep problems (matched for gender, age, race, and ethnicity) were enrolled. The test series included overnight polysomnography as well as parent-completed questionnaires.

Results: 35 WS subjects and 35 matched control children were studied. In each group, there were 15 males and 20 females; the majority (89%) was white. The median age was 8.4 years. WS subjects had significantly decreased sleep efficiency compared to control children (paired $t = -2.67$, $df = 34$, $p = 0.01$); the mean difference was 4.5% (9.9%). The standardized effect size was -0.45. Children with WS also significantly increased slow

wave sleep (non-REM stage 3 and 4 sleep), as a percentage of total sleep time, compared to control children (paired t=-2.67, df=34, p=0.01); the mean difference was 4.6% (10%). The standardized effect size was 0.45. No statistically significant differences were seen in REM sleep latency, REM sleep as a percentage of total sleep time, the obstructive apnea/hypopnea index, or the periodic limb movement index.

Discussion: In this study, children with WS have altered sleep architecture compared to matched controls, with significantly lower sleep efficiency and increased slow wave sleep; for both of these parameters, effect sizes approach the moderate range. It is intriguing to consider that these differences in children with WS may reflect genetic influences on sleep, and may in turn be associated with daytime behavioral features.

Longitudinal Assessment of Receptive Vocabulary in Children and Adolescents with Williams Syndrome: A Multilevel Modeling Analysis

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Statement of Purpose: It is widely accepted that concrete vocabulary and verbal short term memory are relative strengths of children and adolescents with Williams syndrome (WS). Mervis and Becerra (2007) reported an average standard score (SS) of 79.9 (sd = 13.6) on the Peabody Picture Vocabulary Test-III (PPVT-III; a measure of receptive concrete vocabulary) for 238 children (ages 4 – 17 years). PPVT-III SS were uncorrelated (r = -.12) with chronological age (CA), suggesting no developmental change. The purpose of the present study was to examine the relation between CA and receptive vocabulary longitudinally and to document individual differences in the stability of receptive vocabulary in children and adolescents with WS.

Methods: Participants were 63 individuals with WS who had completed the PPVT-III at least 3 times (median = 4 times, range = 3 – 10) and who were 4 – 19 years old at the time of first assessment. Participants also completed the Differential Ability Scales (DAS) Recall of Digits subtest, measuring verbal short-term memory. Each participant's mean Recall of Digits T score was used as a predictor of individual differences in receptive vocabulary. We used multilevel modeling techniques (Raudenbush, Bryk, & Congdon, 2002; Singer & Willet, 2003) to analyze individual change in PPVT-III SS over time periods averaging 5 years (range 2 – 10 years). Since the 63 participants varied in age at the time of their first assessment, we were able to model the developmental trajectories over an age range of 4 to 20 years. The advantage of the multilevel modeling approach is that both within-person and between-person data are analyzed to estimate the average developmental trajectory and the extent to which individual change over time differs from the average trajectory. Multilevel models were fit using HLM 6.0 and full maximum-likelihood estimation. Goodness-of-fit was assessed for each model tested using Chi-Square Deviance tests.

Results: Inspection of individual data suggested that some young children show sharp declines while others show little change or actually improve. However there was less change during adolescence. Consequently the data were modeled by relating PPVT-III SS to log CA (centered at age 10 years). The average trajectory is shown in the figure. The average intercept, which represents the estimate of average performance at age 10 years, was 83.9 and the average slope was -5.9 per log year, resulting in an average decline of 9 points between the ages of 4 and 20 years. There was significant individual variability in

both intercepts (*SD* = 8.8) and slopes (*SD* = 10.0). Digit Recall T score was a significant predictor of individual variability in intercepts (i.e., overall level) but was not a significant predictor of variability in slopes (i.e., change over time). For each 1 point increase in Recall of Digits T score, PPVT-III intercepts increased roughly 1 point.

Discussion: On average, PPVT-III SS for individuals with WS decreased significantly from age 4 – 20 years, showing the most decline between ages 4 and 10. These results underscore the importance of longitudinal data for estimating developmental change and documenting individual differences in language and cognitive abilities.

Relations between Emotion Regulation and Adaptive Functioning in Children and Adolescents with Williams Syndrome

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Background & Purpose: Studies of adaptive functioning in individuals with Williams syndrome have generally found delays across areas, with particular weaknesses noted in daily living skills and motor skills. Although intellectual functioning is related to adaptive behavior, the less than perfect correlation between these constructs, as well as the variability in adaptive functioning warrants investigation of other contributing factors. In particular, few studies have examined relations between adaptive functioning and other behavior in Williams syndrome, and no study to date has evaluated the role of a broad emotional functioning construct, such as emotion regulation, in adaptive functioning. The purpose of the current study is to examine the relation between emotion regulation and adaptive abilities in children and adolescents with Williams syndrome.

Method: Participants included 37 children (17 males, 20 females) with Williams syndrome, ages 8 to 15. Intellectual abilities were measured using the Kaufman Brief Intelligence Test, 2nd Edition (KBIT-II; Kaufman & Kaufman, 2004). Emotion regulation was assessed with two parent-report measures, the Behavior Rating Inventory of Executive Functions (BRIEF; Gioia, Isquith, Guy, & Kenworthy, 2000) and the Emotion Regulation Checklist (ERC; Shields & Cicchetti, 1997). Parents were also interviewed using the Scales of Independent Behavior – Revised (SIB-R; Bruininks, Woodcock, Weatherman, & Hill, 1996), a measure of adaptive abilities. Given the high correlation between the BRIEF Emotional Control and ERC Lability/Negativity scales (r = .71, p < .001), an Emotion Regulation (ER) Composite was created by combining these scales.

Results: Emotion regulation difficulties were observed in the majority (73%) of participants based on ratings on the BRIEF EC scale, which is norm-referenced (M=66.62, SD = 11.78). Negative correlations were found between the ER Composite and all five SIB-R domain standard scores, including Broad Independence (r = -.59, p < .001), Motor Skills (r = -.52, p < .01), Social/Communication Skills (r = -.43, p < .01), Personal Living Skills (r = -.64, p < .001), and Community Living Skills (r = -.49, p < .01). These findings indicated that higher levels of emotion regulation difficulties were associated with poorer adaptive functioning. As intellectual abilities and adaptive behavior were correlated, partial correlations were then conducted, to control for the role of intellectual functioning. Significant negative correlations remained between the ER Composite and Broad Independence (r = -.51, p = .005), Motor Skills (r = -.44, p = .007), and Personal Living Skills (r = -.60, p < .001), once intellectual functioning was taken into account. Finally, partial correlations, controlling for intellectual functioning, were conducted between the ER Composite and specific scale raw scores of the SIB-R. The ER

composite was significantly related to Gross Motor Skills (r = -.44, p = .007), Toileting (r = -.43, p = .008), Personal Self-Care (r = -.45, p = .005), and Domestic Skills (r = -.54, p = .001).

Discussion: Findings revealed that greater emotion regulation difficulties were related to poorer adaptive functioning in some domains even when intellectual abilities were taken into account. Research about the potential role of emotion regulation in acquisition of daily living skills is warranted. Further implications of these findings for the understanding of the behavioral phenotype in Williams Syndrome will be discussed.

Association between Cerebral Shape and Social Use of Language in Williams Syndrome

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Williams syndrome is a neurogenetic disorder resulting from a hemizygous microdeletion at band 7q11.23. It is characterized by aberrant development of the brain and a unique profile of cognitive and behavioral features. We sought to identify the neuroanatomical abnormalities that are most strongly associated with Williams syndrome employing signal detection methodology. Once identified with a Quality Receiver Operating Characteristic Curve, we hypothesized that brain regions distinguishing subjects with Williams syndrome from controls would be linked to the social phenotype of individuals with this disorder. Forty-one adolescents and young adults with Williams syndrome and 40 typically developing controls matched for age and gender were studied. The Quality Receiver Operating Characteristic Curve identified a combination of an enlarged ventral anterior prefrontal cortex and large bending angle of the corpus callosum to distinguish between Williams syndrome and controls with a sensitivity of 85.4% and specificity of 75.0%. Within the Williams syndrome group, bending angle significantly correlated with ventral anterior prefrontal cortex size but not with other morphometric brain measures. Ventral anterior prefrontal size in subjects with Williams syndrome was positively associated with the use of social engagement devices in a narrative task assessing the use of social and affective language. Our findings suggest that aberrant morphology of the ventral anterior prefrontal cortex is a pivotal contributing factor to the abnormal size and shape of the cerebral cortex and to the social-linguistic phenotype of individuals with Williams syndrome.

Growth Pattern in Japanese Children with Williams Syndrome. Does it Relate to the Neurobehavioral Phenotype?

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Background and Objective:
There are several genetic conditions where physical growth patterns are diagnostic and perhaps represent the specific brain and endocrine maturation, which also play a role in developing unique neurobehavioral phenotypes. In Williams syndrome (WS) following characters were pointed out in the previous western studies, failure to thrive in early infancy associated with irritability, short stature, early pubertal growth spurt and obesity in adolescence often with mental health problems. The purpose of this study is to know whether Japanese children with WS

show similar growth pattern and to make standard growth curves of height, weight, and head circumference for health assessment and for a future study on growth pattern and neurobehavioral phenotypic correlations.

Methods:
Subjects: Eighty eight WS individuals (41female and 47 male) were enrolled from Nero-genetic clinic in Osaka City General Hospital. They were diagnosed WS based on their clinical manifestations as well as by Fluorescence *in situ* hybridization□FISH□. The numbers of measurements by sex (female/male) were as follows: weight 429/590, height 326/494 and head circumference 137/193. The study was approved by the Ethics Committee. Analysis: Mean weight, height and head circumference were calculated from data obtained from hospital notes and compared to standardized growth data of Japanese children. All data were presented as mean and standard deviation. The ranges of BMI were illustrated by sex and age.

Results:
Mean weight, height and head circumference at birth of WS are lower than those of typical development children, corresponding to -1- -1.5SD. During first 2 years, significant growth deficiency was revealed, more clearly in girls than boys and more in height than weight. Thinness was a specific problem in female infants and obesity occurs in school-age youngsters of both sexes. After eight years of age, deviation from the mean weight was more significant in boys than in girls. Pubertal growth spurt reached it's peak at 10years in both sexes (earlier than the standards, 1 year in girls and 3 years in boys). A mid-growth spurt was noted in girls around 6 years of age.

Discussion:
Characteristic features of growth in WS described in previous studies were confirmed among Japanese children with WS. Therefore these features seem to be culture or race related but genetically determined. It is to be discussed whether these are related to the neurobehavioral phenotypes.

Face Processing Strength in Williams Syndrome Extends to Memory for Faces

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Williams syndrome (WS) is characterized by profound impairments in visuo-spatial abilities, but relatively spared face recognition skills. Individuals with WS tend to display "hyper-social' behavior, the hallmark of which is a preference for, and increased attention to, human faces relative to other visual stimuli. While previous studies have assessed short- and long- term auditory and visuo-spatial memory in WS, memory for faces has not been explored. Participants completed the immediate and delayed (30 minutes) recall tasks on three subtests of the Wechsler Memory Scale - 3rd Edition, including one auditory memory (Logical Memory) and two visual memory (Faces & Family Pictures) subtests. Performance of the WS group was compared to that of age-, gender-, and IQ-matched individuals with general developmental delay (DD), as well as age- and gender- matched typically developed controls (TD). While in the visual domain, results revealed no significant differences between WS and DD groups on memory for Family Pictures, the WS group performed significantly better than the DD group on memory for Faces. These results suggest that the relative strength in face processing in WS extends to memory for faces.

INDEX

Asada, K 37
Allen, CL **28**
Appelbaum, M 45
Arens, R 57
Atkinson, J **55**
Attias, J **27**

Bayle, JH 7
Becerra, AM 18, 37, 39,
40, 51
Bellugi, U 5, 14, 15, **26**,
34, 49, 53, 60
Berman, K **13**, 14
Bradshaw, JL 47
Breckenridge, K **27**

Carracedo, A 43
Cashon, CH **28**, 41
Ciciolla, L 33, 44, 52, 54
Chen, XN 45, 53
Cole, TJ 57
Crawford, NA 42
Currier, A 18

Dai, L 5, 45, 53
Deisseroth, K 7
Ding, F 7
Dodd, H **27**, 42
Dykens, EM 21

Eis, PS 53
Estes, KG 28

Fine, A 44
Francke, U 7
Freckmann, ML 3

Galaburda, A 14, 49, 60
Gallo, FJ **23**
Gao, MC 5, 45
Gothelf, D **23**, 60
Gowans, G 18
Gregg, RG 3
Greis, SM 46
Grichanik, M 61
Gulbronson, M 18

Ha, OR 28
Haas, BW 14, **15**
Halm, B 7
Harrison, KC 7
Hill, KJ 49, 61
Hobart, HH 3, 18
Hocking, DR 47
Hoeft, F **14**, 14

Itakura, S 37

Janke, KM 48
Järvinen-Pasley, A 49 53
John, AE 18, 32,, 39, 40,
41, 42, 50, 51, 58
Joseph, R 44

Kaplan, P 3, 57
Karchemskiy, A 14
Kennedy, M 52
Kimberley, K 18
Kistler, DJ 29, 58
Klein-Tasman, B **23, 26**,
48, 59
Koch, K 3
Kondo, L 3
Korenberg, J **3**, 5, 14, 45, 49, 53, 60
Kwak, EE 54
Kuscuoglu, U 7

Lacassie, Y 3
Lanre-Amos, T 60
Lens, M 43
Leonard, MK 49
Leyfer, O 21
Li, HH **7**
Lindeke, M **33**, 52, 54

Manguoglu, E 3
Marler, JA **25**
Martens, MA 55, 56
Martin, NDT 57
Marshall, CR 3
Mason, T 57
McGinley, J 47
Meltzer, LA 7
Mervis, CB 3, 18, **21**, **28, 29**, 32, **37**, 39, 40, 41, 42, 50, 51, 58
Mills, DL 5, 14, 15, 49, 53, 60
Morimoto, M 3
Morris, C.A. 3, **18**
Murashima, K 60

Ogrodnik, K 33
Okada, M 37, 60
Okazaki, S 60
O'Leary, J 8
Osborne, LR **3**, **7**, 8

Pack, A 57
Pani, AM 3
Pulst-Korenberg, AM 53
Paylor, R 7

Peippo, M 3
Peregrine, E 18, 40, 51, 58
Peters, GL 42
Phillips, KD 48, 59

Plesa-Skwerer, D **33**, 44, 52, 54
Pober, B **11**
Porter, MA **27**, 42
Preece, MA 57
Priolo, M 3

Rapee, RM 42
Reilly, J **34**, 60
Reiss, AL 5, **13**, 14, 15, 49, 53, 60
Reutens, DC 55, 56
Rinehart, NJ 47
Rios, C 18
Roe, K 13
Weiss, R 5
Wightman, FL **29**
Wijesuriya, H 45
Wilson, SJ 55, 56
Woodruff-Borden, J **21**, 44
Wright, E 7

Yam, A 15, 49, 61
Young, EJ 3, **8**

Zarchi, O **23**
Zitzer-Comfort, C 34
Zuffardi, O 3