Brain Imaging in Neurogenetic Conditions: Realizing the Potential of Behavioral Neurogenetics Research

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Behavioral neurogenetics research is a new method of scientific inquiry that focuses on investigation of neurodevelopmental dysfunction associated with specific genetic conditions. This research method provides a powerful tool for scientific inquiry into human gene–brain–behavior linkages that complements more traditional research approaches. In particular, the use of specific genetic conditions as models of common behavioral and cognitive disorders occurring in the general population can reveal insights into neurodevelopmental pathways that might otherwise be obscured or diluted when investigating more heterogeneous, behaviorally defined subject groups. In this paper, we review five genetic conditions that commonly give rise to identifiable neurodevelopmental and neuropsychiatric disability in children: fragile X syndrome, velo-cardio-facial syndrome, Williams syndrome, Turner syndrome, and Klinefelter syndrome. While emphasis is placed on describing the brain morphology associated with these conditions as revealed by neuroimaging studies, we also include information pertaining to molecular genetic, postmortem, and neurobehavioral investigations to illustrate how behavioral neurogenetics research can contribute to an improved understanding of brain disorders in childhood.
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Research efforts focused on subdividing behaviorally or phenomenologically defined syndromes into etiologically meaningful subgroups are essential to our eventual understanding of the pathogenesis of childhood-onset neurodevelopmental and neuropsychiatric disorders. However, a complementary research strategy that our laboratory has promoted over the past decade focuses on multi-level scientific study of individuals with known or suspected homogenous genetic etiology for neuropsychiatric, cognitive, and developmental dysfunction. The term "behavioral neurogenetics" was coined to represent this novel research approach [Baumgardner et al., 1994; Reiss and Freund, 1998]. A basic premise of behavioral neurogenetics research is the need for multi-level investigation that includes quantitative assessment of genetic factors, brain structure and function, neurobehavioral processes, and environmental influences. As such, behavioral neurogenetics research necessitates the development of expertise, knowledge, and productive collaborations in clinical research design and methodology, molecular, medical, and behavioral genetics, psychoneuroendocrinology, computers and software programming, and

research methods as applied to both anatomical and functional brain imaging.

In this article we review five important genetic conditions that give rise to developmental, cognitive, and neuropsychiatric dysfunction during childhood: fragile X syndrome, velo-cardio-facial syndrome, Williams syndrome, Turner syndrome, and Klinefelter syndrome. Although emphasis is placed on neuroanatomical findings derived from imaging studies, relevant data obtained from molecular genetic, postmortem, and neurobehavioral investigations of individuals with these conditions also are provided. Accordingly, the goal of this review is to illustrate how behavioral neurogenetics investigation can lead to an improved understanding of complex linkages among genetic, neurobiological, and behavioral variables that contribute to neurodevelopmental and neuropsychiatric dysfunction in children.

FRAGILE X SYNDROME

In one of every 2,000 to 4,000 live births [Gustavson et al., 1986; de Vries et al., 1997], a specific single gene mutation alters the course of brain development resulting in the fragile X syndrome, one of the most common inherited causes of developmental disability. The fragile X mutation influences developmental pathways that modulate physical appearance, cognitive ability, and adaptive behavior. Physical manifestations of the syndrome, although variable, include a long and narrow face, large ears, and a prominent jaw [Meryash et al., 1984; Loesch and Hay, 1988; Davids et al., 1990]. These features, combined with macroorchidism, often are observed among postpubertal males [Lachiewicz and Dawson, 1994]. However, physical characteristics are particularly variable among prepubertal children and females and thus are insufficient for making a reliable diagnosis of the condition.

Investigations of cognitive and behavioral features associated with fragile X syndrome demonstrate a predisposition for a particular neurobehavioral profile [Turk, 1992; Freund et al.,

1993; Einfeld et al., 1994; Warren and Ashley, 1995]. This phenotype is different for males and females, potentiated by the fact that the syndrome is X-linked. Females, heterozygous for the fragile X full mutation, typically have either mild mental retardation or normal cognitive functioning accompanied by learning difficulties, particularly math, [Riddle et al., 1998]. Behaviorally, females with fragile X syndrome often exhibit attention deficit, anxiety, and difficulties with socialization [Freund et al., 1993]. Reliant upon a single X chromosome in each cell (i.e., hemizygous), males with the full mutation almost always function cognitively in the range of mental retardation. Their IQ scores usually reflect moderate to severe mental retardation and may decline during middle childhood [Hodapp et al., 1990]. Specific areas of cognitive deficit for males include visual-spatial abilities, visual-motor coordination, and short-term memory [Kemper et al., 1988; Crowe and Hay, 1990; Freund et al., 1993]. Males experience developmental delays in communication and cognition more frequently than in motor and adaptive behaviors [Bailey et al., 1998]. Common behavioral patterns observed among males with fragile X syndrome include hyperactivity, autistic features, difficulties with peer interaction, abnormal social communication, gaze avoidance, and motor stereotypies [Lachiewicz and Dawson, 1994; Baumgardner et al., 1995; Turk and Cornish, 1998]. Although these findings suggest a specific cognitive and behavioral profile, the variability in observations and the shared characteristics with other disorders such as autism [Feinstein and Reiss, 1998] prohibit accurate identification of the presence of the condition based merely upon particular cognitive and behavioral features.

Valid diagnosis of fragile X syndrome is reliant upon genetic testing [Rousseau et al., 1991], and methods for diagnosis have improved considerably over the past 10 years. Initially, early investigations showed that the fragile X phenotype cosegregated with an unusual morphological disruption of the X chromosome [Lubs, 1969]. Karyotyping of cells grown in folate-depleted cell culture media revealed that many patients had a 'fragile' site on one of their X chromosomes that appeared as a constriction on the distal long arm [Lubs, 1969]. In the past decade, knowledge of the molecular genetics of the fragile X syndrome has increased dramatically [Devys et al., 1992; Eichler et al., 1993; Kunst et al., 1997]. In 1991 the most common muta-

tion responsible for the syndrome was identified [Rousseau et al., 1991; Verkerk et al., 1991], spurring an increase in molecular genetic research regarding fragile X syndrome. The syndrome most often results from an expansion of the number of cytosine-guanine-guanine (CGG) triplet repeats occurring within the initial (5′) untranslated portion of FMR1—the Fragile X Mental Retardation gene [Kremer et al., 1991]. Inheritance of an instability in the CGG region causes an increase from the normal number of CGG repeats ($\approx 6-40$) to premutated status (50–200) or from premutation to full mutation (>200 CGG repeat). The stability of the CGG repeat depends primarily on its length (i.e., number of repeats), and probably also on the presence of AGG islets anchoring the region [Zhong et al., 1995]. The gender of the individual who passes the mutation to their offspring can influence CGG stability. When over 200 CGG repeats are present, hyper-methylation of the promoter region of FMR1 is highly probable [Oberle et al., 1991]. Consequently, the transcription and translation of FMR1 is not possible. This "transcriptional silencing" of the gene and the subsequent diminished or absent production of the FMR1 protein results in aberrant brain development and function [Devys et al., 1993; Tamanini et al., 1997].

To date, few neuropathology research studies have investigated the fragile X mutation's effect on brain development. A small number of autopsy studies have indicated abnormalities in the dendritic arborization in the cerebral cortex of affected males [Rudelli et al., 1985; Hinton et al., 1991; Wisniewski et al., 1991]. Studies investigating the localization of FMR1 mRNA during mammalian development have pointed to neuronal localization and particularly high gene expression in the hippocampus, cerebellum (Purkinje cells), and nucleus basalis [Devys et al., 1993; Tamanini et al., 1997]. Deficits in the expression of the FMR1 protein in neurons appears to result in abnormal dendritic density [Comery et al., 1997; Feng et al., 1997]. The increased density may reflect abnormal development of the organizational process of synapse development and stabilization and decrement in synaptic pruning [Comery et al., 1997]. Observed similarities in cerebral white matter development between typically developing children and children with fragile X [Reiss et al., 1995a] is consistent with the fact that the FMR1 protein is normally expressed only in the neuronal bodies

and not in glial cells, axons, or oligodendrocytes [Feng et al., 1997; Tamanini et al., 1997].

Magnetic resonance imaging (MRI) studies of both children and adults have further localized the neuroanatomical effects of the FMR1 full mutation. Structural MRI studies of the posterior fossa of the brain show that the cerebellar vermis is decreased in size (particularly lobules VI and VII) in both males and females and that the fourth ventricle is enlarged [Reiss et al., 1991a; 1991b; Mostofsky et al., 1998]. The study by Mostofsky et al. [1998] also separately investigated the effect of the FMR1 gene methylation on the development of the vermis in females with fragile X and demonstrated a significant correlation between posterior vermis size and activation ratio. Moreover, decreased size of the vermis is significantly associated with lower scores on verbal and performance IQ scales [Mostofsky et al., 1998] and with increased stereotypic behavior [Mazzocco et al., 1998]. Mostofsky suggested two possible explanations for the correlation between the reduction of posterior vermis with cognitive performance. First, posterior vermis and cerebellum might be directly contributing to deficits since this area is putatively involved in higher order function [Hallett and Grafman, 1997; Parsons and Fox, 1997]. Second, posterior vermis alteration could serve as a temporal marker, indicating a period of time in which the fragile X mutation has the most prominent effect. Dysgenesis of other brain regions, sharing a similar time course with the cerebellar vermis, would explain the cognitive deficits associated with this condition. In investigations of mesiotemporal structures, our lab has reported that volumes of the hippocampus, a structure known for its role in learning and memory, are increased among individuals with fragile X syndrome [Reiss et al., 1994; Kates et al., 1997]. However, Jakala et al. [1997] found no differences in hippocampal volumes but subjectively assessed atypical appearance of hippocampal morphology. Relatively small sample sizes in both these studies remains a serious limitation. Further replication to measure the magnitude of volumetric change in the hippocampus in fragile X syndrome is necessary. Volumetric aberrations have been detected in other important brain regions, including the caudate nucleus [Reiss et al., 1995a]. Increased lateral ventricular volumes have been observed among males with the full mutation, and enlargement of the

thalamus has been noted among females [Reiss et al., 1995a].

Collectively, these studies have utilized advanced methodology and have provided important initial findings concerning the FMR1 gene, brain development, and neurobehavioral phenotype among persons with fragile X syndrome. These findings will ultimately help define better and more targeted treatment. However, more definitive conclusions regarding the association between molecular changes and structural anomalies await advances of future research. A comprehensive model of the developmental impact of the fragile X mutation requires research on four levels: (1) intracellular changes relating to protein expression and function; (2) changes in individual cell functioning and morphology; (3) subregional brain tissue development and cytology; and (4) the effects of tissue organization on brain volume and function. Recent efforts have advanced our knowledge of the first [Comery et al., 1997; Feng et al., 1997; Tamanini et al., 1997], and fourth levels [Reiss et al., 1994; Kates et al., 1997; Mostofsky et al., 1998], whereas the mediating pathways between these stages has yet to be elucidated.

VELO-CARDIO-FACIAL SYNDROME (VCFS)

As a subject of scientific interest and investigation, velo-cardio-facial syndrome (VCFS) has received increased attention in the recent genetic and psychiatric literature. For example, 20% of the total number of publications on VCFS were published in the past year alone. This phenomenon is partially due to the acknowledgement of the high frequency of VCFS, making it one of the most common identifiable causes of cognitive disability. However, this rapid acceleration in VCFS research is likely attributable to the fact that this condition is associated with an increased risk for manifestation of specific neuropsychiatric symptoms and may represent a genetically-mediated subtype of schizophrenia [Bassett and Chow, 1999]. Additionally, the recent genetic breakthrough of the complete sequencing of chromosome 22 [Dunham et al., 1999] will undoubtedly motivate additional interest in VCFS.

Velo-cardio-facial syndrome, a congenital, autosomal dominant condition first defined by Shprintzen [Shprintzen et al., 1978], is estimated to occur in at least one per 2,000 to 4,500 live births [Tezenas Du Montcel et al., 1996]. In most affected individuals, a de novo 3 Mb deletion at chromosome 22q11.2 is responsible for the syndrome [Scambler]

et al., 1992; Driscoll et al., 1993; Lindsay et al., 1995; Carlson et al., 1997]. The major features of VCFS include cardiac malformations, cleft palate or velopharyngal insufficiency, a characteristic facial appearance, and learning disabilities. More than 40 physical anomalies have been observed in association with VCFS [Goldberg et al., 1993; Ryan et al., 1997].

Genes deleted in the critical region of chromosome 22 are likely to influence neurodevelopment in humans. At least 30 genes are encoded in the commonly deleted segment [Dunham et al., 1999], a few of which are highly expressed in brain tissue and are likely to be essential for normal brain development [Gottlieb et al., 1997; Yamagishi et al., 1999]. For example, the UFD1L gene probably plays a key role in the embryonic development of the heart and brain [Yamagishi et al., 1999]. Ufd1 (the mouse homologue gene) is expressed specifically in palatal precursors, fronto-nasal regions, and neural crest-derived cells forming the conotrocal part of the heart. In the brain, Ufd1 is expressed with marked specificity in the medial telencephalon that forms the hippocampus. Another gene, GSCL is expressed in the anterior portion of the embryo and, in the brain, it is most expressed in the pons and dorsal thalamus [Gottlieb et al., 1997; 1998] and thus is likely to be involved in the abnormal development of the inferior brain and posterior fossa that is observed in VCFS.

Although several studies have delineated the physical phenotype associated with VCFS, fewer have investigated the neurobehavioral and psychiatric phenotype. Cognitive ability, learning, and speech and language are clearly affected by the 22q11.2 deletion [Golding-Kushner et al., 1985; Scherer et al., 1999]. Learning disorders are prevalent among the VCFS population and have been documented in nearly all neurobehavioral investigations of the syndrome [Goldberg et al., 1993; Ryan et al., 1997; Swillen et al., 1997; Moss et al., 1999]. In an early clinical study, learning disabilities were observed in 99% of a sample of 75 cases, making this the most prevalent of the identified physical and neurodevelopmental features [Goldberg et al., 1993]. Potentially underlying these learning problems, significant deficits in overall cognitive ability resulting in decreased educational achievement have been commonly observed [Golding-Kushner et al., 1985; Swillen et al., 1997; Bassett and Chow, 1999]. Children with VCFS have IQ scores that are lower than the population average, and many per-

form in the range of mild to moderate mental retardation [Golding-Kushner et al., 1985; Goldberg et al., 1993; Ryan et al., 1997; Moss et al., 1999]. Moreover, an affected child will frequently have a Verbal IQ score that exceeds Performance IQ, a profile suggestive of a nonverbal learning disability [Swillen et al., 1997; 1999; Moss et al., 1999].

The behavioral deficits of the VCFS phenotype have been observed with relative consistency and are possibly related to the deficits in cognitive ability described above. In a recent study utilizing a preschool pediatric sample, behaviors of 9 out of 12 affected children were rated as highly active, impulsive, highly emotional, or disorganized [Gerdes et al., 1999]. Prior studies also have documented difficulties with social interactions [Golding-Kushner et al., 1985; Swillen et al., 1997], as well as labile behavior ranging from disinhibition to shyness [Golding-Kushner et al., 1985]. Compared to normative data, behavioral ratings of children with VCFS on the Child Behavioral Checklist have indicated significant behavioral problems, primarily in the domains of social interaction and attention, but also in areas of thought problems and withdrawn behaviors [Swillen et al., 1997; 1999]. It is possible that these behavioral features are premorbid indicators of severe psychiatric disorders in adulthood. Indeed, children with VCFS are at an increased risk for psychoses including schizophrenia [Shprintzen et al., 1992; Chow et al., 1994; Pulver et al., 1994; Bassett and Chow, 1999; Gothelf et al., 1999; Murphy et al., 1999] and perhaps bipolar disorders as well [Papolos et al., 1996]. One of the first investigations of VCFS and risk for psychopathology noted an elevated incidence of schizophrenia and schizoaffective disorders among adults with this genetic disorder [Shprintzen et al., 1992]. A subsequent investigation [Papolos et al., 1996] asserted an etiological link with bipolar rather than schizophrenic disorders; 64% of subjects with velo-cardio-facial syndrome met the DSM-III-R criteria for bipolar disorders, while only 6% were diagnosed with schizoaffective disorder. Recently, evidence has pointed again towards a predisposition for schizophrenia within the VCFS population [Gothelf et al., 1997; Bassett et al., 1998; Murphy et al., 1999]. A study of 46 patients with childhood-onset schizophrenia found that 6.4% had the 22q11.2 deletion [Nicolson and Rapoport, 1999]. Another study detected the 22q11.2 deletion among 2% of subjects

in a random sample of 100 patients with schizophrenia [Karayiorgou et al., 1995].

Despite the observation of serious neurocognitive and psychiatric symptoms associated with VCFS, little information exists concerning the neurobiology and brain development of persons with the syndrome. Most of the studies and reported cases rely on qualitative methods and, for this reason, are restricted to an anecdotal level of analysis. A qualitative analysis of MRI data [Mitnick et al. 1994], however, concluded that 9 of 11 study participants with VCFS (mean age = 9.5 years) had visible brain abnormalities. The most common finding in five patients was a small cerebellar vermis. Additionally, reduced volume of the posterior fossa was found in four cases, and cysts adjacent to the anterior horns of the ventricles were found in three. In another study, Chow [Chow et al., 1999b] described 11 adults (mean age = 28.4, SD = 6.5) with VCFS and schizophrenia. The most common finding (≈90% of the cases) was the presence of bilateral white matter hyperintensities, distributed mainly within the frontal lobes. Forty-five percent of the cases had either cavum septum pellucidum or cavum vergae suggesting midline developmental defects and 36% had cerebellar hypoplasia. A number of additional case studies [Altman et al., 1995; Lynch et al., 1995; Devriendt et al., 1996] also are consistent with results from these two investigations.

Investigations using quantitative methods are necessary to more accurately gauge the strength of associations between abnormal brain morphology and components of the VCFS neurobehavioral phenotype. Only two abstracts and one regular publication thus far have reported quantitative data in children [Eliez et al., 2000] or adults [Chow et al., 1999a; van Amelsvoort et al., 1999] with VCFS. Chow et al. [1999a] reported an overall decrease of gray but not white matter in 11 subjects with VCFS and schizophrenia, even after covarying for total brain size. Van Amelsvoort et al. [1999] described smaller total and left temporal lobe size and loss of ventricular asymmetry among seven adults with VCFS compared to eight matched controls. Eliez et al. [2000] compared 15 children and adolescents with VCFS with 15 individually age- and gender-matched controls. Total brain volume was approximately 11% smaller in the VCFS group due to a significant decrease in both gray and white matter volume. Investigation of lobar morphology indicated a distinct pattern of regional varia-

tion among persons with VCFS. Specifically, frontal lobe tissue tended to be enlarged relative to overall reduction in brain volume. Normal symmetry of parietal lobe tissue observed in the comparison group was not evident in the VCFS group. This loss of symmetry was attributable to a significant reduction of gray matter in the left parietal lobe. The authors also observed a decrease in right cerebellar tissue volume due to a disproportionate reduction in white matter for this area. The crucial role of the parietal lobe in memory processes has been demonstrated in many functional imaging studies [Ungerleider, 1995]. Eliez et al. hypothesized that, because of the involvement of parietal lobe in episodic memory retrieval [Shallice et al., 1994], working memory tasks, implicit or explicit recognition memory [Rugg et al., 1998], and long-term memory consolidation [Shadmehr and Holcomb, 1997], alteration of this structure may result in aberrant information storage and retrieval and contribute to learning difficulties observed in VCFS. Since functional imaging studies have demonstrated the role of the parietal lobe in the semantic processing of words [Vandenberghe et al., 1996; Schlosser et al., 1998], the specific language deficits observed in VCFS could be partially explained by the reduced parietal lobe volumes found in this syndrome.

Recent investigations of the genotype, and the neuroanatomic and neurobehavioral phenotype of VCFS have led to a better understanding of the pathways leading to the cognitive and psychiatric profile observed in this population. Nevertheless, there is a great need for continued research that targets the impact of the VCFS deletion on brain development and function. Ideally, refined imaging techniques might provide biological markers for increased risk of cognitive impairment or psychiatric disorder among affected children and adults.

WILLIAMS SYNDROME

Williams syndrome (WMS) is a relatively rare (one in approximately 20,000 live births) [Grimm and Wesselhoeft, 1980] neurogenetic disorder caused by a hemizygous microdeletion on chromosome 7 (7q11.23). The physical characteristics of the syndrome include distinct facies, cardiac malformations, particularly supravalvular aortic stenosis (SVAS), hyperacusis, delayed development, short stature, hypercalcemia, and a failure to thrive in infancy [Morris et al., 1988; Einfeld et al., 1997; Bellugi et al, 1999]. Many physical problems oc-

curring in WMS are attributable to the hemizygous deletion of ELN, a gene that codes for the structural protein elastin [Ewart et al., 1993]. Elastin is highly expressed in skin, connective and cardiovascular tissue, and is the most common target gene for florescent in situ hybridization (FISH) tests used to confirm the presence of WMS [Oxlund et al., 1988; Lowery et al., 1995].

The extent of the deletion in WMS is highly consistent from one affected individual to another [Brondum-Nielsen et al., 1997; Wu et al., 1998]. This "critical" deletion usually is associated with mild to moderate mental retardation, with a mean IQ of 60 and ranging from 40–100 [Bellugi et al., 1994; 1999]. Studies by Bellugi and others have revealed that individuals with WMS have a characteristically uneven neurocognitive profile, with severe deficits in visual-spatial ability but with relative preservation of linguistic competence, particularly in semantics, vocabulary, and affective prosody [Udwin et al., 1987; Wang and Bellugi, 1994; Bellugi et al., 2000]. It is this rare combination of a relatively small genetic deletion (approximately 25 genes spanning a genetic distance of only 2 cM), and a strong dissociation between visual and linguistic abilities that has prompted some researchers to consider WMS a putative genetic model of cognitive modularity [Pinker, 1991; Paterson et al., 1999].

However, the neurobehavioral phenotype associated with WMS is more complex than a simple verbal/visual contrast. Though visual-spatial ability is profoundly impaired, individuals with WMS perform facial processing tasks at or above the level of typically developing controls [Wang and Bellugi, 1994]. Such a large disparity between visual-spatial perception and facial recognition suggests a dissociation between the dorsal ("where") and the ventral ("what") visual pathways in this syndrome [Wang et al., 1995]. The ability to recognize faces may be related to the strong attraction to people and social situations that individuals with WMS typically show [Reilly et al., 1990; Jones et al., 2000], though unusual social behaviors accompanying this hypersociality often interfere with the ability to successfully interact with other people [Einfeld et al., 1997]. Perhaps the most unique cognitive characteristic found in WMS is a profound love of music, sound, and rhythm [Sacks, 1995; Levitin and Bellugi, 1998].

Individuals with WMS are at risk for a variety of psychiatric and neurological problems. In particular, anxiety is

commonly found in WMS [Einfeld et al., 1997]. Problems with distractability and impulsivity also are frequently reported [Chapman et al, 1996; Bawden et al., 1997; Power et al., 1997]. Indeed, attention deficit hyperactivity disorder (ADHD) was diagnosed in 84% of children with WMS in an initial study by Morris [Morris et al., 1988] and at a rate that was four times that of a control group in a study by Finegan [Finegan et al., 1994].

Significant advances recently have been made in identifying and characterizing the genes found in the critical WMS deletion region. As expected, many genes are expressed in human brain tissue. Of these, several (STX1A, FZD3, and LIM-1, among others) have well-documented roles in brain development and synaptic transmission and are therefore possible contributors to the neurocognitive and neuroanatomic phenotype of WMS. STX1A, for example, codes for syntaxin 1A, a docking protein for synaptic vesicle exocytosis [Nakayama et al., 1998]. The mouse homolog of FZD3 has a known function in rostrocaudal neurodevelopment and cell differentiation [Chapman et al., 1996; Bawden et al., 1997; Power et al., 1997; Wang et al., 1997; 1999]. Finally, LIM-1 kinase plays a role in axon guidance, and its partial expression has been linked to the visual–spatial problems observed in WMS [Frangiskakis et al., 1996; Wang et al., 1998].

While over 30 genetics papers have been published on WMS in the last two years alone, only a handful of neuropathological and neuroimaging studies exist. Nevertheless, these studies reveal a unique neuroanatomy that appears consistent with the cognitive profile of WMS and with what is known about human brain function. Initial imaging studies comparing small numbers of subjects with WMS to subjects with Down syndrome (DS) showed global cerebral tissue reduction in subjects with WMS, but with preservation of temporal-limbic structures [Jernigan et al., 1993] and the cerebellum [Bellugi et al., 1990; Jernigan and Bellugi, 1990; Jernigan et al., 1993]. Both the DS and WMS groups had brain tissue reductions that were significantly smaller than the typically developing control group. Subjects with DS appeared to have a more even reduction in cerebral brain volume (including significantly reduced cerebellar volumes), while subjects with WMS appeared to have volume reductions centered in posterior cerebral regions. Further investigation of the cerebellum revealed preservation of
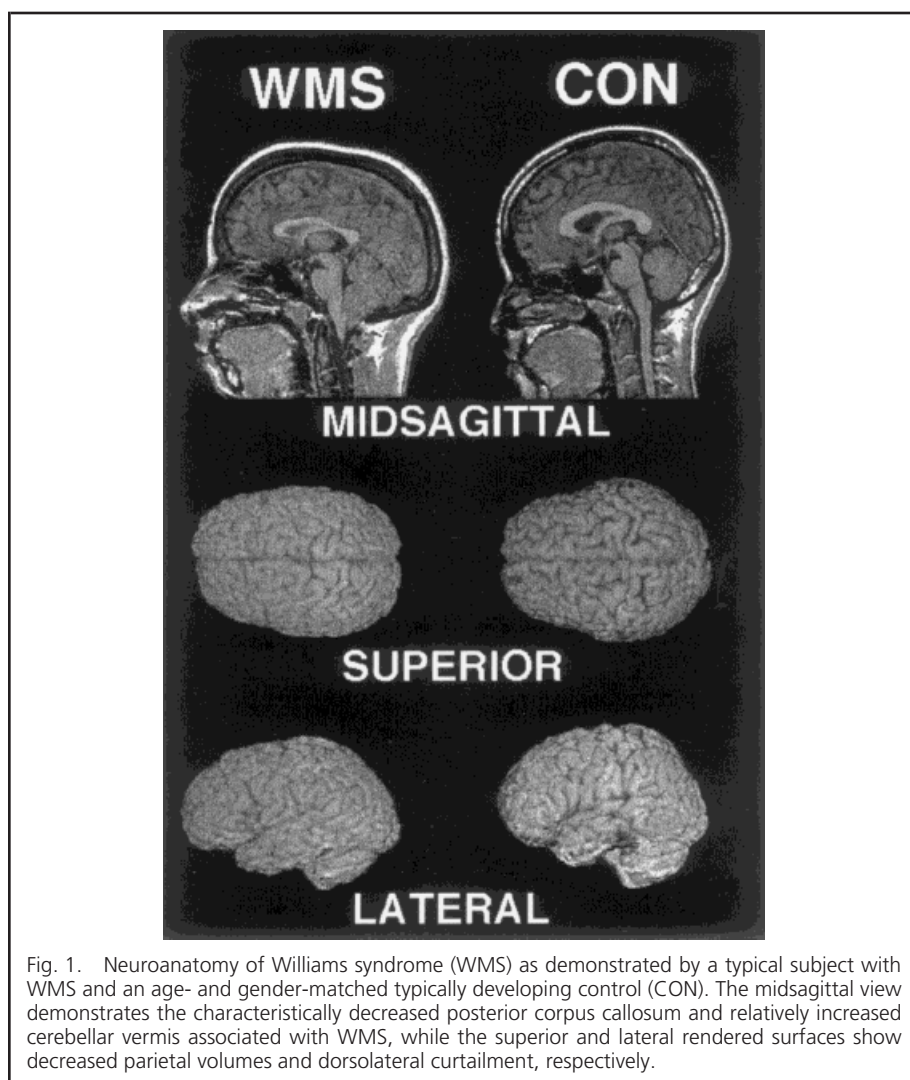

Fig. 1. Neuroanatomy of Williams syndrome (WMS) as demonstrated by a typical subject with WMS and an age- and gender-matched typically developing control (CON). The midsagittal view demonstrates the characteristically decreased posterior corpus callosum and relatively increased cerebellar vermis associated with WMS, while the superior and lateral rendered surfaces show decreased parietal volumes and dorsolateral curtailment, respectively.

vermal lobules VI-VII [Bellugi et al., 1990; Jernigan and Bellugi, 1990], and preservation of the neocerebellar tonsils in WMS [Wang et al., 1992b].

More recent imaging studies using high-resolution scanning techniques, larger samples, and advanced tissue segmentation and parcellation protocols have helped to further quantify the shape and structure of the WMS brain [Reiss et al., 2000] (Fig. 1). In addition to confirming earlier findings of decreased cerebral and preserved cerebellar volumes (13%), these studies also have found specific reductions in the right occipital lobe and brainstem, and bilateral preservation of the superior temporal gyrus (STG) in WMS when compared to typically developing controls. Overall, white matter is more significantly reduced in volume in WMS when compared to gray matter. Supporting evidence for white matter differences in WMS also comes from reports of decreased size of the corpus callosum in 11 subjects with WMS compared to typically developing controls [Wang et al., 1992a].

The posterior cerebrum (parietal and occipital lobes) in WMS is significantly more reduced than frontal and temporal regions [Reiss et al., 2000]. This posterior reduction is undoubtedly related to brain shape differences in WMS that have been described recently [Schmitt et al., 2000]. Specifically, both cerebral hemispheres and the corpus callosum show reduced curvature in individuals with WMS compared to age- and gender-matched typically developing controls, seemingly owed to truncated posterior cerebral development ($P > 0.001$). Gross anatomical studies by Galaburda and Bellugi [2000] also show evidence of posterior cerebral hypoplasia, particularly in the superior-inferior (dorsal/ventral) dimension (see Fig. 1).

It is intriguing to speculate on how neuroanatomical variations in WMS may be associated with the neurocognitive and neurobehavioral profiles that have been described. For example, neuroana-

tomic reductions in posterior cerebral and callosal regions may be related to visual-spatial deficits in WMS. Findings of preserved volume of the superior temporal gyrus appears to correlate well with preserved linguistic functions, face recognition, and musical abilities found in WMS. Other brain regions also are of interest. The cerebellum, consistently preserved in WMS, is enjoying new attention as a structure that performs higher cognitive functions in addition to balance and motor coordination [Leiner et al., 1993; Ackermann et al., 1998; Dolan, 1998]. In particular, lesion and functional imaging studies have found evidence for a cerebellar role in verbal working memory and social function [Desmond et al., 1997; Schmahmann and Sherman, 1998]. It is possible that cerebellar hyperplasia is at least partially responsible for hypersocial behavior and linguistic preservation in WMS. This hypothesis is further supported by reports of cerebellar hypoplasia in VCFS, fragile X syndrome, and autism, all which typically result in withdrawn, hyposocial behaviors [Courchesne et al., 1988; Reiss et al., 1988; Saitoh and Courchesne, 1998; Eliez et al., 2000].

TURNER SYNDROME

Turner syndrome (TS), a genetic disorder characterized by partial or complete absence of one of the two X chromosomes in a phenotypic female, occurs in approximately one in 2,500 to 5,000 live births [Nyborg and Nielsen, 1977; Hook and Warburton, 1983]. Atypical physical and neurocognitive characteristics result from the expression of one copy of a selected number of X-chromosome genes rather than the two copies required for normal development. Affected females share common physical characteristics including short stature, webbed neck, low-set ears, shield chest, infertility, gonadal dysgenesis, and the absence of estrogen, progesterone and secondary sexual production. More variable than the associated physical features, the cognitive phenotype is often marked by deficits in visual-spatial/perceptual skills and attention [Pennington et al., 1985; Romans et al., 1998].

A number of neuropsychological studies have addressed visual-spatial information processing in females with TS. Results indicate that individuals with TS are particularly impaired in the coding and transforming of visual-spatial information. Individuals with TS typically show relative neurocognitive weakness for tests assessing roadmap skills, mental rotation, line orientation, and arithmetic

ability [Waber, 1979; Downey et al., 1989; Reiss et al., 1995b; Romans et al., 1998]. Difficulties with visual-motor drawing and visual memory have been demonstrated using the Rey-Osterreith Complex Figure Test [Netley and Rovet, 1982a; Downey et al., 1989; Romans et al., 1998]. Researchers also have shown that children with TS perform relatively poorly on cognitive tasks that are linked to executive function such as the Wisconsin Card Sorting Test, Tower of Hanoi, and tests of verbal fluency [Waber, 1979; Romans et al., 1998].

Previous investigations have assessed hypotheses proposing cerebral lateralization of cognitive impairments in TS. While several studies have found atypical cortical organization in TS compared to controls, the neuroanatomical localization of cognitive impairments to either the left or right hemisphere has been inconsistent. A spectrum of cerebral specialization has been reported, ranging from focal right parietal dysfunction [Money, 1973] to bilateral hemispheric deficits in the frontal and parietal lobes [Waber, 1979]. The variability of cerebral lateralization in TS may be explained by a neurodevelopmental hypothesis proposed by Rovet [1990]. This model suggests that TS individuals undergo aberrant neural development that results in altered cerebral specialization. Many factors that regulate neuronal migration or cellular organization may influence the mature neurocognitive phenotype in TS and may explain in part the inter-individual variability in cerebral and hemispheric specialization.

Despite manifesting relative deficits in the visual-spatial domain of cognition, individuals with TS generally possess intact verbal skills. Reports of standardized cognitive tests indicate that average verbal IQ is in the low normal to normal range, whereas average performance IQ is almost one standard deviation below the population mean [Garron, 1977; Rovet, 1990; Reiss et al., 1995b].

In addition to impairment in nonverbal cognitive processing, many studies have focused on psychosocial behavior in the TS population. These investigations have shown that individuals with TS may be more prone to attention deficits and hyperactivity [Rovet, 1986] as well as decreased facial affect recognition and social flexibility [McCauley et al., 1987]. Problems with social cognition may result in maladaptive behavior in school and poor peer relations [Rovet, 1990].

Phenotypic variability in spatial cognition and social function within the TS population was addressed in a recent

investigation that inquired whether imprinting of a genetic locus on the X chromosome may influence outcome in TS [Skuse et al., 1999]. Skuse et al. reported that individuals with TS and a paternally retained X chromosome possess better verbal, executive, and social skills when compared to individuals with a maternal X chromosome. The authors postulated that these skills together mediate improved social interaction in the subgroup of patients with a paternal X chromosome and may account for phenotypic variability in social cognition in TS.

Abnormalities in cognitive and psychosocial abilities in TS subjects likely reflect underlying aberrant brain development and function in this disorder. Neuropathological information collected from a small number of postmortem examinations of the brain has revealed variable results although it suggests overall decreased cortical organization. More specifically, changes in the posterior fossa and possible neuronal migration deficits were observed [Gullotta and Rehder, 1974; Molland and Purcell, 1975; Urich, 1979; Reske-Nielsen et al., 1982; Della Giustina et al., 1985].

With the advent of neuroimaging, structural studies have been used to characterize the neuroanatomical basis of executive and visual-spatial cognition in TS. An early volumetric MRI study showed decreased size of the right parietal lobe as well as a number of other structures including the caudate, hippocampus, and cerebellum [Murphy et al., 1993]. In a case study of 10-year-old prepubertal monozygotic twins discordant for X monosomy and TS, there were decreased gray matter volumes in the right prefrontal, right and left posterior parietal and right occipital cortices [Reiss et al., 1993] in the affected twin. Furthermore, the affected twin had increased overall CSF and fourth ventricular volume, and decreased size of the cerebellar vermis, medulla, and pons. Subsequently, Reiss et al. [1995b] examined a group of 30 girls with TS for volumetric differences in brain structures that are known to be linked to executive and spatial impairments. Consistent with earlier studies, decreased relative volumes were observed primarily in the region of the parietal lobe (Fig. 2). These three volumetric studies reveal proportionally smaller volumes in the parietal lobe but variable structural differences in frontal and subcortical structures. An early functional imaging study using positron emission tomography (PET) measured cerebral glucose metabolism in five subjects with TS. Consistent with the aforemen-

tioned structural studies, this pilot investigation showed decreased glucose metabolism in the right parietal and occipital lobes but not in the frontal lobes [Clark et al., 1990].

KLINEFELTER SYNDROME

Occurring in an estimated one in 800 newborn male infants [Abramsky and Chapple, 1997], the 47,XXY karyotype is the most common form of sexchromosomal aneuploidy. The supernumerary X-chromosome in individuals with 47,XXY is acquired either through an error of nondisjunction during parental gametogenesis or, less frequently, from an error in division during mitosis in the zygote [Jacobs et al., 1989]. The resulting extra X-chromosome material in phenotypic males is often associated with a collection of atypical physical features commonly referred to as Klinefelter syndrome (KS).

Clinical recognition of KS during childhood remains unusual [Ratcliffe et al., 1982], with most overt features being identified during later sexual maturation and early adulthood. As originally described by Klinefelter et al. [1942], hypogonadism and infertility due to reduced or absent spermatogenesis continue to be the hallmark features of this disorder. Individuals with KS also are described as having a generally typical appearance, with taller stature [Stewart et al., 1986], smaller head circumference [Ratcliffe et al., 1994], and an increased incidence of gynecomastia. Men with KS have low basal testosterone levels, and increased follicle stimulating hormone (FSH), leutinizing hormone (LH), and prolactin levels [Schiavi et al., 1984] compared to euploidic men. Peripubertal increases in estrogen levels [Salbenblatt et al., 1985] also have been documented.

Although the behavioral and cognitive features associated with KS are variable and often subtle, results from several large-scale prospective studies of newborns screened for aneuploidy of the sex chromosome [Sergovich et al., 1969; Lubs and Ruddle, 1970; Bell and Corey, 1974; Jacobs et al., 1974; Nielsen and Sillesen, 1975; Goad et al., 1976; Walzer and Gerald, 1977; Buckton et al., 1980] have helped produce a comprehensive phenotypic description. These studies provide evidence that men with KS perform normally on tests of nonverbal abilities and general intelligence but are specifically impaired on measures of language skills [Funderburk and Ferjo, 1978; Graham et al., 1988]. These deficits seem to be most apparent in areas of verbal fluency and expression [Walzer et al., 1978; Netley and Rovet,
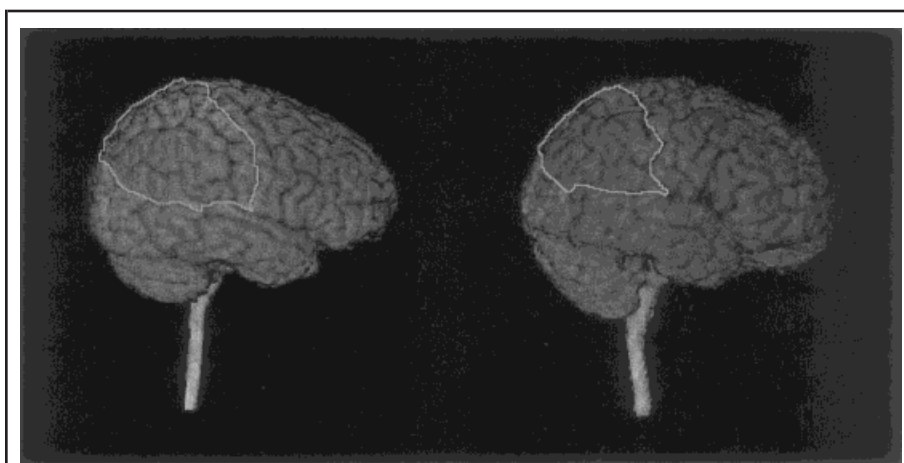

Fig. 2. The images illustrate the relative decreased proportion of the parietal lobe (outlined in white) in a typically developing 13-year-old girl (*left*) and an age- and gender-matched girl with Turner syndrome (*right*). Cortical surfaces were rendered from high-resolution 3D SPGR MRI scans using BrainImage 4.x.
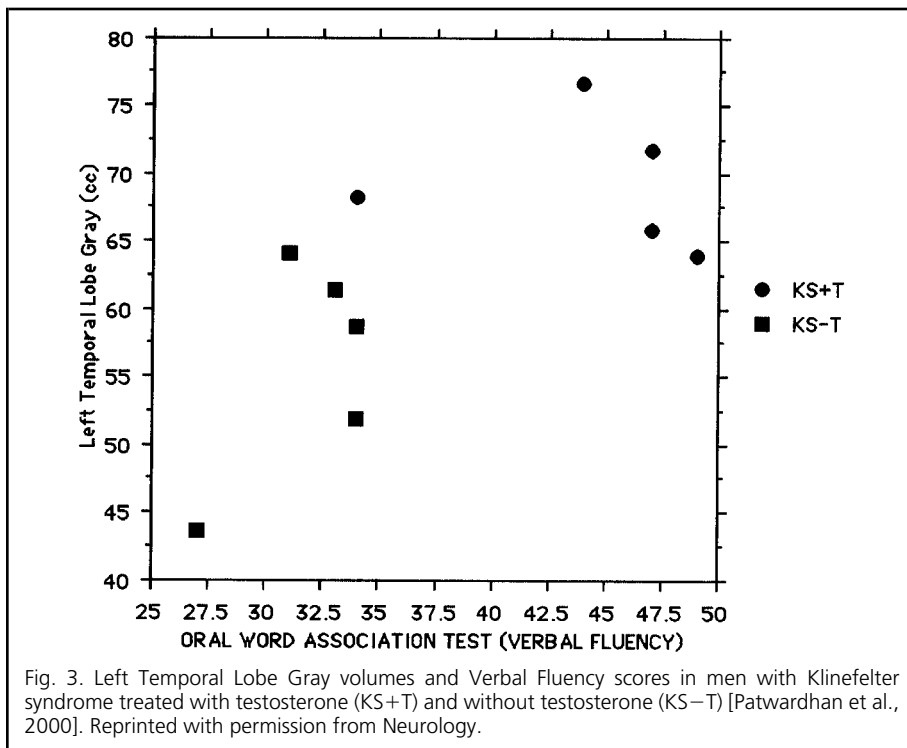
1982b; Ratcliffe et al., 1994] and are consistent with the high incidence of reading disabilities diagnosed in children with KS [Bender et al., 1986]. Specific deficits in KS include impairments of verbal memory and verbal processing speed [Bender et al., 1989] and reduced performance on tests of retrieval, reading skill, and verbal IQ [Netley and Rovet, 1982b]. Delayed speech development also is common in children with KS [Ratcliffe, 1999] as well as demonstrated deficits of auditory processing and auditory short-term memory [Graham et al., 1988].

There also is an increased incidence of psychiatric disorders in KS, ranging from anxiety and depression to psychosis [Mandoki et al., 1991; Bender et al., 1995]. Adolescents and young men with KS have reduced activity levels, self-esteem, and sexual interest compared to euploidic peer groups [Bancroft et al., 1982; Ratcliffe et al., 1982] and often describe themselves as being more sensitive, introspective, and insecure [Ratcliffe et al., 1982; Mandoki et al., 1991]. A tendency for passivity and social reluctance [Walzer et al., 1978, Theilgaard, 1984; Stewart et al., 1986] also is seen in men with KS, although the behavioral phenotype is highly variable. Testosterone supplementation, a common therapy for young adolescents and adults with KS, seems to mitigate these behavioral problems [Mandoki and Sumner, 1991]. Elevated mood and energy, increased sexual drive, and better interpersonal relations [Myhre et al., 1970; Nielsen et al., 1988] during testosterone treatment have been reported even when initiation of treatment is delayed into adulthood.

Although the clinical features of the 47,XXY karyotype are now well-established, most evidence offering support for the effects of KS on brain development and anatomy has been inferential. Reduced scores on tests of language skills [Netley and Rovet, 1984] and the diagnosis of reading disabilities [Bender et al., 1986] in KS have led to speculation that a left-hemisphere dysfunction is involved. Autopsy studies [Galaburda, 1993] of dyslexic brains, whose cognitive phenotype is similar to that of KS men, reveal a loss of the typical leftward asymmetry seen in control brains, particularly in the area of the planum temporale. Men with KS also seem to be predisposed to the development of cerebral germ cell tumors although the pathogenic relevance of a supernumerary X-chromosome is still unclear [Arens et al., 1988; Prall et al., 1995].

Despite the high incidence of the 47,XXY karyotype compared to other forms of chromosomal aneuploidy, only two imaging investigations on this disorder have been conducted to date and they have produced conflicting results. Both of these studies involve adult men with KS recruited from unselected birthcohort populations, resulting in clinically unbiased yet relatively small samples. In a high-resolution MR imaging study, Warwick et al. [1999] first reported reduced whole brain volumes and enlarged lateral ventricles in a group of young adults with 47,XXY compared to matched controls. A weak correlation between whole brain volumes and IQ, as measured by the New Adult Reading Test (NART) [Nelson and O'Connell, 1978] and Quick IQ test [Ammons and Ammons, 1962], was seen in these subjects. The neurodevelopmental significance of these findings remains unclear;

Fig. 3. Left Temporal Lobe Gray volumes and Verbal Fluency scores in men with Klinefelter syndrome treated with testosterone (KS+T) and without testosterone (KS−T) [Patwardhan et al., 2000]. Reprinted with permission from Neurology.

however, it does demonstrate that a supernumerary X chromosome seems to have an adverse effect on brain development. Given the apparent excess of the 47,XXY genotypes in people with schizophrenia [DeLisi et al., 1994], Warwick discusses these findings in comparison to similar neuroanatomical features found in schizophrenia [Ward et al., 1996; Lawrie and Abukmeil, 1998]. Although their significance remains unclear, areas of high intensity signal (HIS) foci also were increased in 47,XXY subjects compared to matched controls. Warwick suggests that their presence may reflect the susceptibility of a developmentally abnormal brain to brain injury or an increased rate of head trauma in 47,XXY individuals.

In a second high-resolution MR study, Patwardhan et al. [2000] investigated the neuroanatomical consequences of the 47,XXY karyotype in the presence and absence of testosterone supplementation. In contrast to previously published findings [Warwick et al., 1999], Patwardhan and colleagues measured segmented areas of the entire brain and found that whole brain and lateral ventricular volumes were not significantly different between men with 47,XXY and matched controls. Additionally, subjects involved in this cohort study were subdivided into two groups: men with KS who received testosterone therapy (KS+T) and those that did not (KS−T). There was a significant reduction in left temporal lobe gray matter tissue in KS−T men compared to controls. Conversely KS+T men were not significantly different for any areas of the brain compared to controls, including the left temporal lobe. Results from this study show that the 47,XXY karyotype is associated with reductions of left temporal lobe gray matter—an area of the brain thought to be responsible for the verbal and language impairments often seen in men with KS. Moreover, testosterone supplementation was associated with preservation of the left temporal lobe volumes to within control values. The superior temporal gyrus (STG), an area thought to be essential for reading, was not found to be principally responsible for the temporal gray matter reductions in KS−T subjects. Reduced scores on a test for verbal fluency also were seen in KS−T subjects yet were preserved in KS+T men, indicating diminished verbal abilities in untreated men. Scores of verbal fluency and left temporal lobe volumes are shown in Fig. 3.

CONCLUSIONS

Several decades of research on behaviorally defined syndromes such as autism, attention deficit hyperactivity disorder (ADHD), mental retardation, and learning disabilities suggest that rapid progress toward understanding underlying contributory factors may be impeded by the etiological heterogeneity of individuals meeting the widely accepted DSM or ICD diagnostic criteria that define these important disorders. Accordingly, as a field, we are in great need of biological markers and new methodology to improve our understanding of etiologically meaningful subgroups and the pathophysiology of childhood onset brain disorders.

As an important complement to ongoing scientific inquiry into the etiologies of behaviorally defined syndromes, behavioral neurogenetics research provides a powerful tool for investigation into human gene–brain–behavior linkages. This approach, which combines genetic, neurobiological, and neurobehavioral investigation, is designed to improve our knowledge of neural mechanisms underlying human neurodevelopmental and neuropsychiatric dysfunction. In addition to providing critical information about individuals affected with specific genetic conditions, behavioral neurogenetics research has potentially wider applicability as these conditions are looked upon as models of behavioral and cognitive conditions occurring in the general population; for example, fragile X syndrome as a model for autism, social anxiety disorder and math disability, VCFS as a model for psychosis, and Klinefelter syndrome as a model for specific language disability and dyslexia.

Our research, and that of others, demonstrates that neuropsychology, neuropsychiatry, genetics, and neuroanatomy are all merely different perspectives on the same intriguing biological puzzle. The vast and growing body of knowledge about the etiology of these conditions is providing explanations for the unique behaviors and the cognitive strengths and weaknesses that affected individuals manifest. Imaging and other techniques that elucidate neuroanatomical structure and function will, undoubtedly, continue to be key components in obtaining a more complete understanding of how genetic variations contribute to the complex human intellect. ■

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