Letter to the Editor

Williams Syndrome Cognitive Profile Also Characterizes Velocardiofacial/DiGeorge Syndrome

To the Editor:

Williams-Beuren Syndrome (WBS) is a contiguous gene deletion disorder characterized by a distinctive facies, supravalvar aortic stenosis and other vascular abnormalities, hypercalcemia, mild to moderate mental retardation, a unique personality, and a specific cognitive profile [Jones and Smith, 1975; Bellugi et al., 1997; Mervis et al., 1999a]. This syndrome has been the subject of extensive neuropsychological investigation, due to its notable pattern of neurocognitive “peaks and valleys,” involving relative strengths in language and facial processing, and profound impairment in spatial cognition [Bellugi et al., 1994; Mervis et al., 1999b]. WBS is caused by a hemizygous deletion of ~1.5 megabases at chromosome 7q11.23 (Fig. 1), which includes LIM-kinase1, a gene which is strongly expressed in the brain, particularly in the cerebral cortex [Frangiskakis et al., 1996]. Mervis et al. [1999b] propose that 1) WBS is associated with an identifiable and very distinctive cognitive profile, and 2) there is a specific genetic basis for the extreme difficulties with visuospatial construction evidenced by most individuals with this syndrome. They cite evidence from neuropsychological comparisons of patients with small deletions in the WBS critical region to those with more standard deletions, in order to support the claim that “LIM-kinase1 hemizygosity contributes to the difficulties individuals with Williams Syndrome evidence in visuospatial construction”. Specifically, they find that those individuals with smaller deletions that include Elastin, but not LIMK1, do not evidence any cognitive or personality aspects of the WBS phenotype. Mervis et al. [1999b] conclude from these findings that “hemizygous deletion of LIMK1 on chromosome 7 forms a foundation for the deficit in visuospatial constructive cognition evidenced in WBS.” The generality of this observation has been questioned by other investigators [Tassabehji et al., 1999], who found that three subjects with small deletions did not fit the criteria for the characteristic Williams Syndrome Cognitive Profile (WSCP, see Appendix) despite their LIMK1 deletions, leading them to conclude that LIMK1 deletion may be a “necessary but not sufficient” condition for the WSCP.

We have noted a strikingly similar cognitive and neuroanatomic profile in a large proportion of patients with another, more common microdeletion syndrome, Velocardiofacial/DiGeorge Syndrome (22q11.2 Deletion Syndrome). This multiple-malformation syndrome is characterized by structural and functional palate anomalies, conotruncal cardiac malformations, immunodeficiency, hypercalcemia, and typical facial anomalies [Shprintzen et al., 1981; McDonald-McGinn et al., 1997]. Similar to WBS, the disorder is also characterized by low IQ (with average full-scale IQ in the borderline range), learning disabilities, and a characteristic cognitive and behavioral phenotype [Moss et al., 1999; Bearden et al., 2001]. In the majority of cases (~90%), the syndrome results from a common three-Mb deletion at chromosome 22q11.2 (Fig. 2) [Carlson et al., 1997]. Applying the Wechsler [1991] equivalents of the psychometric criteria for the WSCP outlined by Mervis et al. [2000] to a group of 97 patients with the 22q Deletion Syndrome (22q DS), we found that 61 of these patients meet all criteria for the WSCP, yielding a sensitivity of .63 (Bearden and Wang, manuscript in preparation). While this is somewhat lower than the sensitivity of .88 for individuals with molecularly defined WBS, as reported by Mervis et al. [2000], it is notable that the profile characterizes almost 2/3 of subjects with 22q11.2 deletions, despite the fact that these criteria were specifically tailored to best fit the putatively unique cognitive profile of WBS. Mervis and colleagues [2000] found that only four of 56 subjects in an IQ-matched contrast group of mixed etiology met the WSCP criteria (specificity = .93), leading them to conclude that these combined criteria depict a profile that is “rare for individuals who do not have WBS.” In comparison to a contrast group of individuals with 22q DS, however, the specificity of the WSCP criteria is quite poor (.37). Thus, while this cognitive profile may be unusual, our findings demonstrate that it is not unique to WBS.

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Other neurogenetic disorders (e.g., Turner syndrome, Fragile X) have a similar pattern of cognitive abilities, involving deficits in arithmetic and visuospatial abilities, with a relative strength in rote verbal memory [Reiss et al., 2000a; Kwon et al., 2001]. This pattern is commonly referred to as a “Nonverbal Learning Disorder” [Rourke, 1995]. In the case of Fragile X syndrome, the characteristic cognitive impairments have been attributed to the absence of the FMR1 gene product (FMRP) in neurons, resulting in abnormal morphology of dendritic spines and a reduction in the length of synapses in the cortex [Rudelli et al., 1985; Hinton et al., 1991]. Turner syndrome, a genetic disorder characterized by partial or complete absence of one of the two X chromosomes in a phenotypic female, is also characterized neuropsychologically by deficits in visual-spatial/perceptual skills and attention [Pennington et al., 1985; Olney and Schaefer, 1998]. While the molecular etiology of these cognitive deficits is incompletely understood in Turner syndrome, an MRI study of females with this disorder found decreased proportional volumes primarily in the region of the parietal lobe, an area known to be linked to visuospatial function [Reiss et al., 1995].

Several studies have described a characteristic neuroanatomy of WBS, suggesting a possible underlying pathophysiology for the cognitive deficits. Gross anatomical findings in WBS consist mainly of overall volume reduction, with curtailment in the posterior-parietal and occipital regions [Galaburda and Bellugi, 2000; Reiss et al., 2000b]. Notably, similar volumetric reductions in parietal and occipital brain regions have been noted in the 22q DS population [Eliez et al., 2000; Kates et al., 2001]. Thus, it is important to examine candidate neurodevelopmental genes in the 22q11.2 region that might have similar effects. Goosecoid-like (GSCL) is one potential candidate; this gene in the 22q11 region is expressed early during embryogenesis in a limited number of tissues [Gottlieb et al., 1997], and has been hypothesized to be responsible for abnormal development of posterior brain regions in 22q DS [Eliez et al., 2001]. However, one notable difference between the characteristic neuroanatomy of WBS as compared to 22q DS is that subjects with Williams syndrome have been reported to have significant increases in the volume of the posterior vermis and the neocerebellar hemispheres relative to normal controls [Jernigan et al., 1993; Wang and Bellugi, 1993], while 22q DS subjects show decreased volumes in cerebellar regions concomitant with parietal—occipital reduction [Eliez et al., 2000]. While subjects with WBS tend to be unusually socially outgoing and overly friendly [Jones et al., 2000], subjects with 22q DS are often described as withdrawn [Swillen et al., 1999] or as having flat affect [Bassett et al., 1998], and have an elevated incidence of autistic-spectrum diagnoses [Niklasson et al., 2001]. In addition, subjects with both Fragile X and Joubert syndrome also typically possess social and communication problems resembling autistic behavior [Cohen et al., 1991; Holroyd et al., 1991], and these disorders have both have been shown to have decreased cerebellar vermal areas [Holroyd et al., 1991; Guerreiro et al., 1998]. Thus, comparison of neurogenetic disorders with prominent affective components suggests that there may be a possible relationship between posterior vermis size and level of social drive.

In summary, while the cognitive and neuroanatomic profiles of WBS do indeed make it a compelling model for elucidating complex gene-brain-behavior relationships, cross-syndrome comparisons can isolate candidate genes which may have similar distal effects on brain development, resulting in similar neurocognitive patterns. Thus, we argue that 1) the “Williams syndrome cognitive profile” is not unique, and 2) the putative effects of hemizygous LIM-kinase1 deletion on cognition and neuroanatomy are non-specific. Rather, LIMK1 may have similar effects on neural development as other candidate neurodevelopmental genes, and hemizygosity for any of these genes may result in a final common pathway of anomalous brain development, which is the underlying basis of this characteristic cognitive profile. While we fully agree with Mervis et al. [2000] in their conclusion that “this research demonstrates the importance of systematic phenotypic methods . . . to the efficient search for associations between behavior and genotype,” we would like to highlight the additional point that comparison not only across domains, but across syndromes, is
critical to determine both the unique and shared effects of particular genes on brain and cognition.

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APPENDIX

Criteria for WSCP [from Mervis et al., 2000]1

1. Pattern-Construction T score < mean T score for core subtests
2. Pattern-Construction T score < Digit-recall T score
3. Pattern-Construction T score < 20th percentile
4. T-score for either Digit Recall, Naming/Definitions, or Similarities, > 1st percentile

Additional Criteria

1. Digit Recall T score > mean T score
2. Naming/Definitions T score > Pattern-Construction T score
3. Similarities T score > Pattern-Construction T score

REFERENCES


1Mervis et al. [2000] employed the Differential Abilities Scale (DAS) as their primary cognitive assessment measure, whereas we administered the Wechsler Intelligence Scale for Children (WISC-III, 3rd edition). The DAS subtests (Pattern-Construction, Digit Recall, Naming/Definitions, and Similarities) were designed to be analogous to the Wechsler tests, and are highly correlated with the respective WISC-III measures (Block Design, Digit Span, Vocabulary, and Similarities, respectively).


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