Commentary

Biological Psychiatry

Genotype-First Analysis of the 16p11.2 Deletion Defines a New Type of "Autism"

Michael H. Duyzend and Evan E. Eichler

Hanson *et al.* (1) report one of the most comprehensive neurodevelopmental and psychiatric evaluations of the BP4-BP5 16p11.2 deletion to date. The scope of this study was impressive: 85 carriers compared with 153 noncarriers. Studying the phenotype within the context of the family provided a means for genetically matched comparisons and some control for differences in socioeconomic status. Phenotypic evaluations were performed primarily at three centers with careful attention to standardization and center bias in addition to recognition of the potential issues associated with ascertainment.

Although patients carrying the 16p11.2 deletion have been known to show extensive variability in their phenotype (2,3), the size of this study allowed for specific aspects of the phenotype to be defined and quantified for the first time. An important conclusion is that the 16p11.2 deletion is not primarily associated with a standard diagnosis of autism confirming earlier reports (4,5). The assessment included three behavioral subtypes according to DSM-IV-TR (autistic disorder, pervasive development disorder, not otherwise specified, and Asperger's disorder) meeting clinical criteria. Only 20 (24%) of the carriers in this study could be classified as having a clinical diagnosis of autism spectrum disorder, and only 15 (18%) met strict criteria based on the Autism Diagnostic Observation Schedule and the Autism Diagnostic Interview. However, many of the patients had features akin to autism. Of the 16p11.2 deletion carriers, for example, 71% (60 of 85 carriers) showed a speech or language-related disorder such as expressive/mixed receptive-expressive language deficits or a phonological processing (articulation) disorder. Carriers were also 2.7 times more likely to show restricted or repetitive behavior patterns compared with control subjects (88% of the deletion carriers vs. 33% of control subjects showed more than two types of these behaviors). As expected (5), a remarkable decrement in full-scale IQ of 26.8 points or 1.8 SD was observed when comparing carriers and noncarriers. The decrement was slightly greater for verbal IQ, 27.6 points or 1.5 SD, compared with nonverbal IQ, 23.5 points or 1.6 SD. A population-based study also found a significant decrement in verbal IQ in carriers versus control subjects ($p = 5.90 \times 10^{-16}$) and a reduction in fecundity ($p = 1.6 \times 10^{-12}$) (6).

There were surprises in the phenotypic analysis, with other features occurring frequently in this particular cohort. The most common phenotypic feature identified in 16p deletion carriers (53%) was developmental coordination disorder marked by impaired motor skills (i.e., clumsiness) and failure to achieve milestones such as crawling, walking, or sitting. Diagnoses of attention-deficit/hyperactivity disorder and enuresis (bed-wetting) were almost as common (18% and 19%, respectively) as a diagnosis of autism. Almost half of deletion carriers (48%) reported either left-hand or mixed-hand dominance compared with 14% of noncarrier family members. The authors speculate that this finding may reflect differences during brain development leading to cerebral asymmetry (7). Although deletion carriers share similar clinical characteristics, the data suggest that there may be phenotypic differences between de novo versus inherited and male versus female carriers. For example, full-scale IQ shows a significant difference between de novo and inherited carriers with inherited carriers having a full-scale IQ of 8.33 points less than de novo carriers ($p = .0468$). Female patients also tend to have fewer DSM diagnoses than male patients ($p = .0065$). Larger sample sizes and more extensive longitudinal assessments are necessary to determine the significance of these and other trends highlighted in this study.

The 16p11.2 phenotype eludes simple classification, spanning >20 different disorders as described by the defunct DSM-IV-TR (Figure 1). Although most patients would not qualify as autistic by this strict definition, some aspects of the 16p11.2 deletion phenotype are remarkably consistent and reminiscent of a "type of autism" not yet recognized by the DSM. These conclusions highlight the power of the genotype-first–based approach (8) to studying autism and neuropsychiatric disease more generally. Similar to reports for other autism genes (9), the findings presented suggest that "autism" phenotypes conditioned on a common genetic etiology may be superior and more meaningful diagnostically than the strict DSM nosology.

Despite these unifying features of the 16p11.2 deletion phenotype, the big unanswered question remains: why is there so much variability in disease manifestation even within the context of a family (Figure 1A)? Notwithstanding the limitations of DSM-IV-TR, it is clear that various diagnoses are associated with the 16p11.2 deletion, with the number of distinct diagnoses ranging from zero to more than a dozen. There is also wide variance in terms of the IQ difference with some cases showing an increase in IQ compared with their parents (Figure 1B). Likely explanations include genetic, stochastic, and environmental factors. Of these, genetic factors are perhaps the most tractable. With large numbers of samples of known inheritance and detailed phenotypes, the presence of additional modifiers and differences in the genetic background can be systematically explored through genome sequencing.

The study design provides an important blueprint for going forward on a much grander scale. The rapid recruitment of such a large number of participants was achieved via the Simons VIP Connect (https://simonsvipconnect.org/). The Simons VIP Connect specifically leverages the Internet and serves as a portal for clinicians, genetic counselors, and families with a 16p11.2 copy number variant (CNV) diagnosis to network and become involved in specific research studies. Although website recruitment introduces a level of

SEE CORRESPONDING ARTICLE ON PAGE 785

http://dx.doi.org/10.1016/j.biopsych.2015.02.032
ISSN: 0006-3223

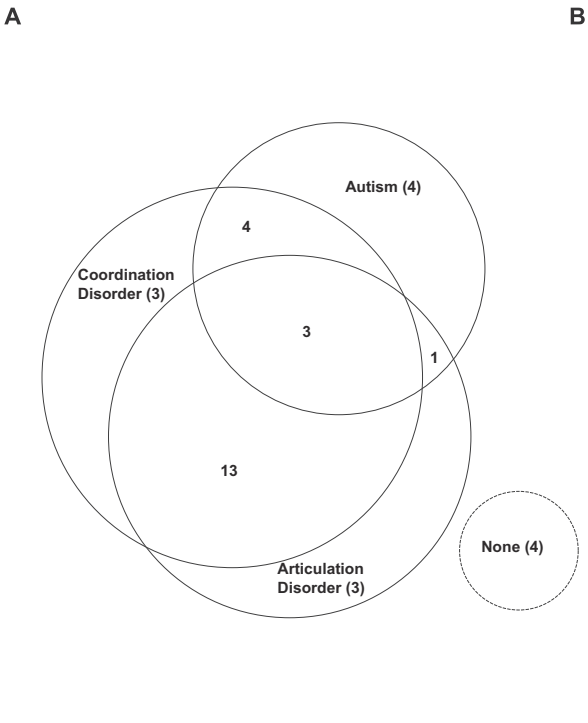

Figure 1. Phenotypic heterogeneity of 16p11.2 deletion cases. **(A)** Overlap of three disorders in 35 patients ≥3 years old with phenotype information from both parents and a de novo deletion (only). Four patients did not have one of these three diagnoses. No single DSM-IV-TR diagnosis predominates, although >50% carry two or more diagnoses. **(B)** The full-scale IQ (FSIQ) difference measures the change in FSIQ between parents and child carrying a de novo 16p11.2 deletion. We define the FSIQ difference as the average of the FSIQ of the parents subtracted from the FSIQ of the child. De novo deletion carriers show, on average, a 27-point decrement of FSIQ. However, the range is considerable with some patients being more significantly impaired (five have a >40-point decrement), whereas others show almost no change (three have a decrement or increment within 5 points of zero).

ascertainment bias, the fact that participants were flown (at no expense to the family) to a site where standardized testing could be performed provided not only sufficient numbers but also a more rigorous phenotypic assessment. Standardization involved formalized training of clinicians through in-person meetings and webinars as well as cross-center reliability checks. Independent consultants reviewed tape-recorded meetings with patients to confirm diagnoses. Similar efforts are being piloted for other CNVs and genes for which recurrent de novo, likely gene-disruptive mutations have been identified (9). Although the focus of the Simons VIP Connect remains the 16p11.2 deletion (10), 28 genes associated with autism along with the 1q21 CNV have been added to their website as targets for future investigation. Efforts to network families with specific mutations and researchers and clinicians are also occurring in Europe often for the same genes or CNVs (http://www.rarechromo.org/, www.humandiseasegenes.com). The 16p11.2 deletion project provides a powerful roadmap on how to balance the interests of patients, researchers, and clinicians.

In conclusion, with exome and genome sequencing becoming routine clinical practice, the genotype-first approach will likely soon spread beyond autism and developmental delay to include genes and CNVs associated with other psychiatric disorders. There are three immediate benefits: 1) establishing or rejecting phenotype-genotype correlations with statistical rigor, 2) networking families with other families to provide real-life solutions to often idiosyncratic problems associated with a specific genetic disorder, and 3) linking patients and their families with clinical and basic researchers specifically focused on understanding the biology of a gene or gene network. The last-mentioned will ultimately lead to the design of clinical trials, and the large number of patients assembled will speed the implementation of the trials. The pioneering families recruited through these networks will likely be the most informed by research advances and have the benefit of being at the head of the line when such clinical trials are implemented for their specific genetic subtype of autism.

Acknowledgments and Disclosures

This work was supported by the Simons Foundation Autism Research Initiative Grant No. 303241 (EEE), National Institutes of Health Grant No. R01MH101221 (EEE), and National Institutes of Health Fellowship Grant No. 1F30MH105055-01 (MHD). EEE is an Investigator of the Howard Hughes Medical Institute.

We thank Raphael Bernier for helpful discussion and Tonia Brown for review of the manuscript.

EEE is on the scientific advisory board of DNAnexus, Inc., and is a consultant for Kunming University of Science and Technology as part of the 1000 China Talent Program. MHD reports no biomedical financial interests or potential conflicts of interest.

Article Information

From the Department of Genome Sciences (MHD, EEE) and Howard Hughes Medical Institute (EEE), University of Washington School of Medicine, Seattle, Washington.

Address correspondence to Evan E. Eichler, Ph.D., Howard Hughes Medical Institute, University of Washington School of Medicine, Foege S413C, 3720 15th Avenue NE, Box 355065, Seattle, WA 98195-5065; E-mail: eee@gs.washington.edu.

Received Feb 23, 2015; accepted Feb 25, 2015.

References

1. Hanson E, Bernier R, Porche K, Jackson FI, Goin-Kochel RP, Snyder LG, *et al*. (2015): The cognitive and behavioral phenotype of the 16p11.2 deletion in a clinically ascertained population. Biol Psychiatry 77:785–793.

2. Weiss LA, Shen Y, Korn JM, Arking DE, Miller DT, Fossdal R, *et al*. (2008): Association between microdeletion and microduplication at 16p11.2 and autism. N Engl J Med 358:667–675.
3. Kumar RA, KaraMohamed S, Sudi J, Conrad DF, Brune C, Badner JA, *et al*. (2008): Recurrent 16p11.2 microdeletions in autism. Hum Mol Genet 17:628–638.
4. Shinawi M, Liu P, Kang S-HL, Shen J, Belmont JW, Scott DA, *et al*. (2010): Recurrent reciprocal 16p11.2 rearrangements associated with global developmental delay, behavioural problems, dysmorphism, epilepsy, and abnormal head size. J Med Genet 47:332–341.
5. Zufferey F, Sherr EH, Beckmann ND, Hanson E, Maillard AM, Hippolyte L, *et al*. (2012): A 600 kb deletion syndrome at 16p11.2 leads to energy imbalance and neuropsychiatric disorders. J Med Genet 49:660–668.
6. Stefansson H, Meyer-Lindenberg A, Steinberg S, Magnusdottir B, Morgen K, Arnarsdottir S, *et al*. (2014): CNVs conferring risk of autism or schizophrenia affect cognition in controls. Nature 505: 361–366.
7. White LE, Lucas G, Richards A, Purves D (1994): Cerebral asymmetry and handedness. Nature 368:197–198.
8. Stessman HA, Bernier R, Eichler EE (2014): A genotype-first approach to defining the subtypes of a complex disease. Cell 156:872–877.
9. Bernier R, Golzio C, Xiong B, Stessman HA, Coe BP, Penn O, *et al*. (2014): Disruptive CHD8 mutations define a subtype of autism early in development. Cell 158:263–276.
10. Simons VIP Consortium (2012): Simons Variation in Individuals Project (Simons VIP): A genetics-first approach to studying autism spectrum and related neurodevelopmental disorders. Neuron 73:1063–1067.