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Genotype-first analysis of the 16p11.2 deletion defines a new type of “autism”

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Hanson and colleagues report one of the most comprehensive neurodevelopmental and psychiatric evaluations of the BP4-BP5 16p11.2 deletion to date (1). The scope of this study was impressive: 85 carriers compared to 153 noncarriers. Studying the phenotype within the context of the family provided a means for genetically matched comparisons as well as 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.

While 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 the DSM-IV-TR (autistic disorder, PDD-NOS and Asperger’s) 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 (ADOS) and the autism diagnostic interview (ADI). Many of the patients, however, had features akin to autism. Of the 16p11.2 deletion carriers, for example, 71% (60/85 carriers) showed a speech or language-related disorder such as expressive/mixed

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FINANCIAL DISCLOSURE AND POTENTIAL CONFLICTS OF INTEREST:

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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 when compared to controls (88% of the deletion carriers versus 33% of controls showed more than two types of these behaviors). As expected (5), a remarkable decrement in full-scale IQ (FSIQ) of 26.8 points or 1.8 SD was observed when comparing carriers and noncarriers. The decrement was slightly greater for verbal IQ (VIQ), 27.6 points or 1.5 SD, when compared to nonverbal IQ (NVIQ), 23.5 points or 1.6 SD. A population-based study also found a significant decrement in VIQ in carriers vs. controls ($p=5.90\times 10^{-16}$) as well as 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. Developmental coordination disorder marked by impaired motor skills (i.e., clumsiness) and failure to achieve milestones such as crawling, walking or sitting was the most common phenotypic feature identified in 16p deletion carriers (53%). Diagnoses of attention-deficit hyperactive disorder (ADHD) or enuresis (bedwetting) were almost as common (18% and 19%) as a diagnosis of autism. Almost half of deletion carriers (48%) reported either left-hand or mixed-hand dominance when compared to 14% of noncarrier family members. The authors speculate that this may reflect differences during brain development leading to cerebral asymmetry (7). While 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. The FSIQ, for example, shows a significant difference between *de novo* and inherited carriers with inherited carriers having an FSIQ of 8.33 points less than *de novo* carriers ($p = 0.0468$). Female patients also tend to have fewer DSM diagnoses than males ($p = 0.0065$). Larger sample sizes and more extensive longitudinal assessments will be necessary to determine the significance of these and other trends highlighted in this study.

It is clear that the 16p11.2 phenotype eludes simple classification spanning more than 20 different disorders as described by the defunct DSM-IV-TR (Figure 1). Although the majority of 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 the DSM-IV-TR, it is clear that there are a variety of diagnoses 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 actually showing an increase in IQ when compared to their parents (Figure 1B). Likely explanations include genetic, stochastic and/or environmental factors. Of these, the former is 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. While website recruitment introduces a level of 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 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). While the focus of the Simons VIP Connect remains the 16p11.2 deletion (10), 28 genes associated with autism along with the 1q21 CNV have recently been added to their website as targets for future investigation. Efforts to network families with specific mutations and researchers/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.

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 in order 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 latter will ultimately lead to the design of clinical trials and the large number of patients assembled will speed their implementation. 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.

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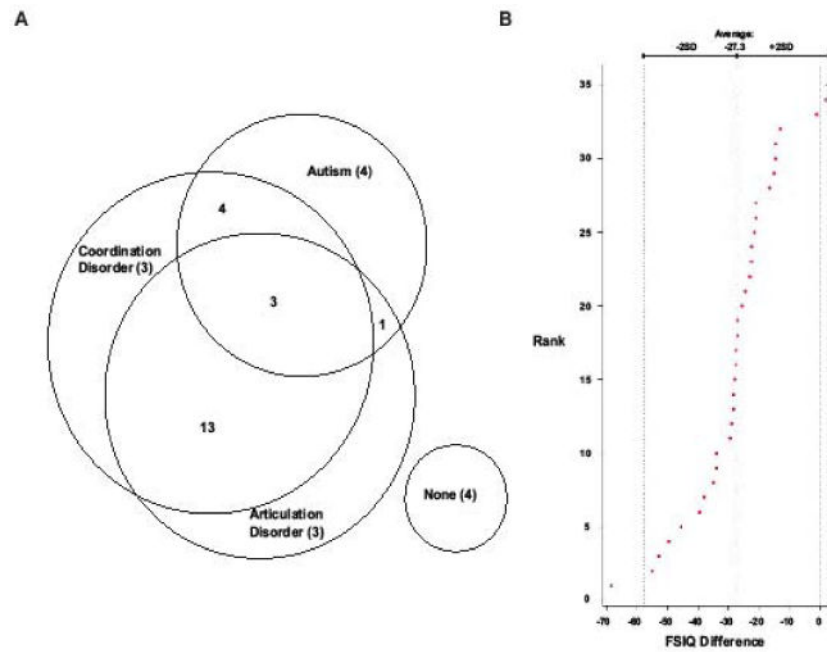


Figure 1. Phenotypic heterogeneity of 16p11.2 deletion cases

A) Overlap of three disorders in the 35 patients of 3 years or older 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 designation predominates although more than 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. The range is, however, considerable with some patients being more significantly impaired (e.g., 5 have a >40-point decrement) while others show almost no change (3 have a decrement or increment within 5 points of zero).