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The Cognitive and Behavioral Phenotype of the 16p11.2 Deletion in a Clinically Ascertained Population

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ABSTRACT

BACKGROUND: Deletion of the recurrent ~600 kb BP4-BP5 chromosomal region 16p11.2 has been associated with a wide range of neurodevelopmental outcomes.

METHODS: To clarify the phenotype of 16p11.2 deletion, we examined the psychiatric and developmental presentation of predominantly clinically referred individuals, with a particular emphasis on broader autism phenotype characteristics in individuals with recurrent ~600 kb chromosome 16p11.2 deletions. Using an extensive standardized assessment battery across three clinical sites, 85 individuals with the 16p11.2 deletion and 153 familial control subjects were evaluated for symptom presentation and clinical diagnosis.

RESULTS: Individuals with the 16p11.2 deletion presented with a high frequency of psychiatric and developmental disorders (>90%). The most commonly diagnosed conditions were developmental coordination disorder, phonologic processing disorder, expressive and receptive language disorders (71% of individuals >3 years old with a speech and language–related disorder), and autism spectrum disorder. Individuals with the 16p11.2 deletion not meeting diagnostic criteria for autism spectrum disorder had a significantly higher prevalence of autism-related characteristics compared with the familial noncarrier control group. Individuals with the 16p11.2 deletion had a range of intellectual ability, but IQ scores were 26 points lower than noncarrier family members on average.

CONCLUSIONS: Clinically referred individuals with the 16p11.2 deletion have high rates of psychiatric and developmental disorders and provide a genetically well-defined group to study the emergence of developmental difficulties, particularly associated with the broader autism phenotype.

Keywords: 16p11.2 Deletion, Autism, Autism spectrum disorder, Developmental disability, Genetics, Psychiatric diagnosis

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Deletion of the recurrent ~600 kb BP4-BP5 region on 16p11.2 (chromosome 16 position 29,649,996–30,199,855 in hg19) has been associated with a wide range of neurodevelopmental outcomes with a prevalence of approximately .6% (range, .3%–1% across studies) of all patients with a diagnosis of autism spectrum disorder (ASD), and .4% (range, .3%–.7%) in large series of patients with intellectual disability or birth defects (1–3). These rates are significantly higher than the estimated background population prevalence of .04%–.05% (4,5).

Previous research taking a "genetics first" approach with 16p11.2 copy number variants (CNVs) reported significant heterogeneity in the phenotype of individuals with the 16p11.2 deletion (1–3,6–9) but with consistent findings of increased frequency of ASD, intellectual and learning disabilities, and possible increased frequency of psychiatric disorders. Shinawi *et al.* (3) found that 14 of 16 individuals had speech delays, 3 met criteria for ASD, and 6 had other behavioral difficulties. Even when excluding all psychiatric cases, findings of a cognitive deficit, particularly in verbal ability, persisted in the Icelandic population study by Stefansson *et al.* (5). Hanson *et al.* (6) identified 21 individuals with 16p11.2 deletion who presented with various neurodevelopmental disorders, including developmental delay, variable cognitive presentation, features of ASD, high incidence of language impairment, and a wide range of behavioral and psychiatric conditions. Zufferey *et al.* (8) ascertained 285 16p11.2 deletion carriers through several cohorts, including data on 56 probands from a European consortium gathered from questionnaires completed by referring clinicians, 45

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probands from the Simons Variation in Individuals Project (Simons VIP), and 117 through literature review (which included participants ascertained for developmental/intellectual disabilities, obesity, and from the general population). Results revealed that full-scale IQ (FSIQ) scores were 2 SDs lower in carriers relative to familial control subjects, with verbal IQ (VIQ) being generally lower than nonverbal IQ (NVIQ). Also, 15% of carriers were classified as having ASD, many required speech therapy, and >70% were found to have comorbid psychiatric diagnoses. This heterogeneity in phenotypic presentation is also found in other chromosomal CNVs (e.g., 1q21.1) and gene mutations (e.g., *NLGN4, NRXN1, SHANK2*) associated with ASD and psychiatric disorders (10–15). However, limited phenotypic assessment has been completed in many of these rare genetic disorders, limiting the assessment of the true phenotypic heterogeneity of these disorders.

In these prior studies characterizing 16p11.2 deletion carriers, diagnostic characterization was established through multiple methods, including clinical assessment, questionnaires, and medical history reviews in some cases; this process often lacked a standardization of the clinical assessment. Finally, several of these studies included multiple modes of ascertainment. These limitations stress the need for large sample sizes ascertained uniformly for the presence of the 16p11.2 deletion and assessed with a standardized neuropsychological battery to assess the diversity of difficulties previously found to be common in the disorder as well as standardized assessments of nondeletion relatives to serve as familial control subjects.

Familial comparisons offer a valid design (16–18) as well as an efficient way to overcome potential confounding problems inherent to unrelated case-control designs, including differing genetic backgrounds and socioeconomic statuses (19,20). To characterize in detail psychiatric and developmental problems such as ASD in a genetically well-defined CNV, we performed cognitive, adaptive, language, psychiatric, behavioral, and diagnostic testing, including standardized ASD assessment, on a large number of individuals with 16p11.2 deletions and noncarrier siblings and parents. Because of the high likelihood of ASD in this population, we also explored whether differences between the carriers and familial control subjects were associated with the deficits inherent to this diagnosis or if these deficits were seen even when controlling for ASD-related difficulties.

METHODS AND MATERIALS

Subjects

Subjects included individuals with the same recurrent 600 kb BP4-BP5 16p11.2 deletion without other pathogenic CNVs or known genetic diagnoses, the biological siblings of the individual with the deletion, and the biological parents of the individual with the deletion (Table 1). Siblings were selected for participation based on closeness in age to the carrier. One half-sibling was included. Adoptive parents were not used as control subjects but were interviewed for information about their carrier child. Most individuals with the 16p11.2 deletion were clinically identified, but cascade genetic testing within the families (see later) identified some additional carriers.

Biological or adoptive families that included an individual with the recurrent ~600 kb 16p11.2 BP4-BP5 deletion mediated by segmental duplications (chromosome 16 position 29,652,999–30,199,351 in hg19) identified through clinical diagnostic evaluations and who expressed interest in participating in research on the Simons VIP Connect website were invited to participate. All deletion carriers had the same recurrent deletion and no additional pathogenic CNVs or known monogenic disorders. Recruitment included directing traffic to the Simons VIP Connect website (SimonsVIPConnect.org) from Google Ads, links from patient advocacy websites and social media sites, collaborations with clinical molecular cytogenetics laboratories that informed treating physicians of the study, and direct mailings to medical professionals. [See Simons VIP Consortium (21) for more details on recruitment and inclusion and exclusion criteria.] Cascade genetic testing was conducted for all family members using a custom-designed oligonucleotide array containing genome-wide coverage at a resolution of ~400 kb and targeting known disease gene coverage at a resolution of ~50 kb (OGT 60K; Oxford Gene Technologies, Tarrytown, New York), according to previously published methods of analysis (22), to determine if the deletion was de novo or inherited and to identify other deletion carriers within the family.

Following screening, families participated in data collection at one of three Simons VIP phenotyping sites (Boston, Houston, and Seattle) for a comprehensive and standardized multiday evaluation. The study was approved by the institutional review board at each participating institution; all participants provided informed consent before data collection. All diagnostic interviewing and cognitive testing of children <5 years old was videotaped for later review. Standardization of measurement across sites included mandatory formalized, standardized training on all measures through in-person training sessions and webinars for all clinicians, cross-site reliability and maintenance through monthly clinician conference calls and periodic videotape review, and validation and diagnostic confirmation through data review and observation of video recorded sessions by independent consultants.

The current analyses were limited to individuals ≥3 years old because of lack of complete data sets in very young children and infants; to control for the possible instability of IQ measurement in very young children, particularly children with ASD and developmental disability (23–28); and to control for changes in presentation and rates of DSM diagnoses over time in very young children (29–31).

Phenotypic Assessment

Psychiatric Diagnosis. Experienced, licensed clinicians gave best-estimate, clinical DSM-IV-TR (32) diagnoses using all information obtained during the research evaluation. Information was based on the standardized interview, questionnaire, and observation processes described subsequently as well as results from standardized administration of the Diagnostic Interview Schedule for Children (33) and symptom checklist 90 (34) and review of available medical records and prior testing. To capture the range of psychiatric presentation, exclusionary criteria for diagnoses were not considered (e.g., if a child met criteria for both attention-deficit/hyperactivity