Original Investigation

The Role of Parental Cognitive, Behavioral, and Motor Profiles in Clinical Variability in Individuals With Chromosome 16p11.2 Deletions

Andres Moreno-De-Luca, MD; David W. Evans, PhD; K. B. Boomer, PhD; Ellen Hanson, PhD; Raphael Bernier, PhD; Robin P. Goin-Kochel, PhD; Scott M. Myers, MD; Thomas D. Challman, MD; Daniel Moreno-De-Luca, MD; Mylissa M. Slane, MS; Abby E. Hare, PhD; Wendy K. Chung, MD; John E. Spiro, PhD; W. Andrew Faucett, MS; Christa L. Martin, PhD; David H. Ledbetter, PhD

IMPORTANCE Most disorders caused by copy number variants (CNVs) display significant clinical variability, often referred to as incomplete penetrance and variable expressivity. Genetic and environmental sources of this variability are not well understood.

OBJECTIVES To investigate the contributors to phenotypic variability in probands with CNVs involving the same genomic region; to measure the effect size for de novo mutation events; and to explore the contribution of familial background to resulting cognitive, behavioral, and motor performance outcomes in probands with de novo CNVs.

DESIGN, SETTING, AND PARTICIPANTS Family-based study design with a volunteer sample of 56 individuals with de novo 16p11.2 deletions and their noncarrier parents and siblings from the Simons Variation in Individuals Project.

MAIN OUTCOMES AND MEASURES We used linear mixed-model analysis to measure effect size and intraclass correlation to determine the influence of family background for a de novo CNV on quantitative traits representing the following 3 neurodevelopmental domains: cognitive ability (Full-Scale IQ), social behavior (Social Responsiveness Scale), and neuromotor performance (Purdue Pegboard Test). We included an anthropometric trait, body mass index, for comparison.

RESULTS A significant deleterious effect of the 16p11.2 deletion was demonstrated across all domains. Relative to the biparental mean, the effect sizes were −1.7 SD for cognitive ability, 2.2 SD for social behavior, and −1.3 SD for neuromotor performance (P < .001). Despite large deleterious effects, significant positive correlations between parents and probands were preserved for the Full-Scale IQ (0.42 [P = .03]), the verbal IQ (0.53 [P = .004]), and the Social Responsiveness Scale (0.52 [P = .009]) scores. We also observed a 1-SD increase in the body mass index of probands compared with siblings, with an intraclass correlation of 0.40 (P = .07).

CONCLUSIONS AND RELEVANCE Analysis of families with de novo CNVs provides the least confounded estimate of the effect size of the 16p11.2 deletion on heritable, quantitative traits and demonstrates a 1- to 2-SD effect across all neurodevelopmental dimensions. Significant parent-proband correlations indicate that family background contributes to the phenotypic variability seen in this and perhaps other CNV disorders and may have implications for counseling families regarding their children's developmental and psychiatric prognoses. Use of biparental mean scores rather than general population mean scores may be more relevant to examine the effect of a mutation or any other cause of trait variation on a neurodevelopmental outcome and possibly on systems of diagnosis and trait ascertainment for developmental disorders.

Published online December 10, 2014.

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: David H. Ledbetter, PhD, Autism and Developmental Medicine Institute, Geisinger Health System, 100 N Academy Ave, Mail Code 22-01, Danville, PA 17822 (dhledbetter@geisinger.edu).
The recurrent deletion between break points 4 and 5 on chromosome 16p11.2 (chr16: 29.5-30.1) is approximately 600 kilobases long, includes 29 genes, and is generated by nonallelic homologous recombination between flanking segmental duplications. The deletion is one of the most common pathogenic copy number variants (CNVs) and is associated with a broad range of neurodevelopmental and neuropsychiatric diagnoses, including developmental delay, intellectual disability, autism, and schizophrenia, among others.\(^1\)\(^-\)\(^4\) In addition to the broad range of the clinical diagnoses in individuals who carry the deletion (ie, carriers), the 16p11.2 deletion has also been reported in apparently healthy individuals, a finding frequently interpreted as evidence of incomplete penetrance.\(^1\)\(^-\)\(^3\) In a study of more than 100,000 apparently unaffected control participants from the general population of Iceland, 43 individuals with the 16p11.2 deletion were identified. However, the individuals with this CNV exhibited a variety of cognitive and neuropsychological deficits despite the fact that none reached traditional clinical diagnostic thresholds for a neurodevelopmental or a neuropsychiatric disorder.\(^6\)

A report on 101 individuals with the 16p11.2 deletion noted that the Full-Scale IQ (FSIQ) score was 2 SD lower in deletion carriers compared with their relatives who did not carry the deletion (ie, noncarriers).\(^4\) Approximately 15% of the probands met clinical criteria for autism spectrum disorders. In more recent work, Hanson et al\(^7\) studied 80 probands with the 16p11.2 deletion using an extensive battery of assessments. Although only 23% of the probands were diagnosed as having an intellectual disability or borderline intellectual functioning, mean IQ scores were 26 points (1.8 SDs) lower than those of noncarrier family members. Although only 25% of the probands met full clinical criteria for autism, a significant effect on social functioning (as measured by the Social Responsiveness Scale [SRS])\(^8\) was identified as a 1.6-SD shift toward greater impairment in probands compared with noncarrier family members. In addition, individuals with the 16p11.2 deletion showed a high frequency (~95%) of a variety of psychiatric and developmental categorical diagnoses. Altogether, these data indicate high penetrance for the clinically significant cognitive, behavioral, and psychiatric impact of the deletion.

Such findings raise important questions as to what accounts for the clinical heterogeneity of this and other CNV disorders. The clinical manifestations of most genetic disorders are highly variable, even when considering mendelian diseases. For such single-gene disorders, clinical variability may be attributed to variation in (1) the specific mutation type and severity, (2) the expression of the remaining wild-type allele(s), (3) other loci constituting the genetic background, and (4) non-genetic environmental exposures during the life course.

Significant clinical variability is also the rule rather than the exception for classic chromosomal disorders, such as trisomy 21 (Down syndrome) and sex chromosome variations. For disorders involving aneuploidy, in contrast to monogenic mendelian diseases, the mutation itself (an extra or a missing chromosome) is identical across cases, so genetic contributions to clinical variability must be due to variable expression of genes on the involved chromosome(s), must reflect genetic background effects, or both.

Many of the traits that constitute the phenotypes of genetic syndromes are distributed continuously in the general population, and trait variability may be greatly influenced by the parental genetic background. For example, approximately 90% of the trait variability for height and 30% to 70% for cognitive ability are accounted for by the parental genetic background.\(^9\)\(^,\)\(^10\) For some psychometric and anthropometric quantitative traits (cognitive ability, height, head circumference, and body mass index [BMI]), the best predictor of the outcome of an individual from the general population is the birental mean value for such traits, with correlations typically ranging from approximately 0.20 to 0.70.\(^10\) Social behavior, as measured by the SRS, also demonstrates high heritability (an approximate heritability estimate of 0.75), with parent-child correlations of 0.50.\(^11\)

We hypothesize that such parent-child relationships will be preserved in CNV disorders, such as 16p11.2 deletions. Similar to aneuploidy syndromes in which the genetic abnormality is identical for all probands, the functional consequence of recurrent CNVs is essentially identical across cases because the break points lie within repetitive regions of the genome, and the genes included in the intervening deleted or duplicated region are constant. Therefore, for recurrent CNVs, the genetic contribution to clinical variability should be explained by variable expression of the genes in the CNV interval and/or other loci constituting the genetic background.

In this study, we examined the cognitive,\(^10\)\(^,\)\(^12\) social,\(^13\)\(^,\)\(^14\) and motor\(^15\)\(^,\)\(^16\) profiles in 56 individuals with de novo deletions of chromosome 16p11.2 and their noncarrier parents and siblings. We also included BMI, an anthropometric trait that is highly heritable and known to be increased in individuals with 16p11.2 deletions.\(^1,\)\(^7\)\(^,\)\(^18\) We predicted that this quantitative approach would reveal a consistent deleterious impact of 16p11.2 deletions, even in cases in which clinical diagnostic thresholds were not met. Consistent with previous work on individuals with chromosomal aneuploidy\(^19\)\(^-\)\(^21\) and the CNV associated with Prader-Willi syndrome,\(^22\) we predicted that the shared variance observed among first-degree relatives in the general population would be preserved in families of probands with de novo 16p11.2 deletions.

**Methods**

**Participants**

The study was approved by the institutional review boards at each of the following 3 Simons Variations in Individuals Project phenotyping sites: Boston Children’s Hospital, Boston, Massachusetts; Baylor College of Medicine, Houston, Texas; and University of Washington, Seattle. All participants provided written informed consent before data collection.

We obtained data from the Simons Variation in Individuals Project, which includes a large number of individuals with the same recurrent break point 4 to 5 16p11.2 deletion and their families. This study contains deidentified comprehensive phenotypic data for probands, their parents, and their siblings. Details on recruitment strategy, the inclusion and exclusion criteria, the genotyping and phenotyping tools used, and policies for data...
collection and sharing have been reported previously. The analyses reported herein include 56 probands (≥2 years old) with a de novo 16p11.2 deletion, their noncarrier biological parents, and a noncarrier biological sibling closest in age to the proband. A subset of these families have been described in prior studies. The analyses were limited to de novo cases to avoid potential confounding sources of variance associated with inherited disorders, such as assortative mating, in an effort to accurately measure the effect size of the CNV and the influence of the family background on a range of heritable traits.

Measures
Complete family data varied depending on the measure, resulting in the following sample sizes: 52 dyads for FSIQ and verbal IQ (VIQ); 54 dyads for nonverbal IQ (NVIQ); 44 dyads for the SRS; and 46 dyads for the Purdue Pegboard Test (PPT)47 (47 for the dominant hand). Because BMI is highly age dependent, comparisons of BMI z scores were performed on probands and their siblings who were at least 2 years of age (26 dyads).

We assessed IQ with the Wechsler Abbreviated Scale of Intelligence,28 the Differential Ability Scales,29 or the Mullen Scales of Early Learning,30 depending on age and developmental functioning. We used the FSIQ, VIQ, and NVIQ in the analyses (mean [SD] scores, 100 [15]).

The SRS is a 65-item, quantitative parent-reported or adult self-reported measure that assesses social impairment associated with autism spectrum disorders.8 The SRS is sensitive to subclinical social impairment. Raw scores (mean [SD], 30 [20]) were used to provide greater differentiation of scores at the lower and higher ends of the scales.

The PPT measures fine and gross motor dexterity and hand, finger, and arm coordination. Participants are presented with a board with 4 cups filled with pins across the top and 2 vertical rows of 25 holes down the center. The participants are instructed to place as many pins as possible (in 30 seconds) down the row on the side of their dominant hand, then the side of their nondominant hand, and then the sides of both hands simultaneously, yielding separate scores for the dominant, the nondominant, and both hands and generating standard scores (mean [SD], 50 [10]) for each variable.

We calculated BMI by dividing the weight (in kilograms) by the square of the height (in meters) for each age. The BMI was then converted to a z score.

Statistical Analysis
Analyses were performed using commercially available software (SPSS, version 20; IBM). We performed linear mixed-model (LMM) analyses with unstructured covariance within the family, allowing the variance-covariance to differ among the proband, sibling, and parent within a family. Multiple comparisons were adjusted with Bonferroni methods in the presence of a significant overall family effect within the LMM. We examined the differences between the probands’ observed and expected scores (ie, parent scores) using paired t tests (when only 1 parent was available [13 families], the available parent’s data were used instead of the biparental mean). As recommended, we covaried for the SRS score in the LMM for IQ comparisons, and we covaried for the IQ scores in the LMM for SRS comparisons. Sex was not included as a factor in the LMM because no sex could be assigned to the biparental values. However, independent t tests revealed no significant difference in the mean response (FSIQ, VIQ, NVIQ, SRS, or PPT scores) owing to sex for the probands or the siblings. We used the intraclass correlation (ICC) to examine proband-parent correlations.

Results
FSIQ, VIQ, and NVIQ
We used LMM analysis to examine the mean differences among family members for FSIQ, VIQ, and NVIQ, controlling for the SRS score; we found no significant interaction between the SRS score and the family member for these 3 outcomes. The LMM analysis revealed statistically significant differences in the FSIQ scores among the proband, sibling, and biparental mean scores (F2,55.42 = 22.33 [P < .001]) and an SRS effect (F1,104.11 = 8.26 [P = .005]) (Table 1). The proband mean FSIQ score was significantly lower than the parental and sibling mean FSIQ scores (P < .001). The mean difference in proband-parent FSIQ scores (mean [SD], 25.53 [15.09] for 52 pairs) revealed a 1.7-SD deleterious impact based on standardized IQ norms (Figure 1A). The sibling FSIQ score also differed from the biparental mean score (P = .04), although to a smaller degree than for probands.

Differences emerged among family members on the VIQ scores (F2,52.53 = 19.91 [P < .001]; SRS effect, F1,102.86 = 6.52 [P = .01]). Mean scores for the probands differed significantly from those for the parents and siblings (P < .001). The mean difference between the proband and the parent VIQ scores (mean [SD], −24.63 [15.77] for 52 pairs) showed a 1.6-SD effect size for the deletion.

The analysis for the NVIQ score (F2,50.65 = 19.97 [P < .001]) also revealed the cognitive impact of de novo 16p11.2 deletions, with the scores for the probands differing significantly from those for the parents (P < .001) and siblings (P = .01); furthermore, the scores for the siblings were different from those for the parents (P = .001), but to a lesser extent than the scores for the probands. Accounting for the SRS score revealed an overall linear effect of the SRS on the NVIQ score (P = .01). The mean difference between the scores for the probands and parents (mean [SD], −25.08 [18.55] for 54 pairs) indicated a deleterious effect size of 1.7 SD in the NVIQ.

As noted above, in typical families, parent-child IQ correlations range from approximately 0.30 to approximately 0.70. For the parent-proband dyads, the ICC for the mean FSIQ approached that observed in the general population (ICC0.5 = 0.42 [P = .03]); similar results were observed for the VIQ score (ICC0.5 = 0.53; [P = .004]). The NVIQ score correlation did not reach statistical significance (ICC0.5 = 0.20 [21]) (Table 1).

Despite the shift in the mean IQ of the probands relative to the parents, the typical parent-child IQ correlation that is observed in the general population is largely preserved, indicating a significant role for parental background in determining the cognitive performance of a child with the 16p11.2 deletion. The exception was the NVIQ, which is less heritable than the VIQ or the FSIQ in the typical population.
Table 1. Descriptive Statistics for Probands, Siblings, and Biparental Mean Scores on 4 Quantitative Traits

<table>
<thead>
<tr>
<th>Domain</th>
<th>Mean (SD)</th>
<th>No. of Participants</th>
<th>Mean (SD)</th>
<th>No. of Participants</th>
<th>Mean (SD)</th>
<th>No. of Participants</th>
<th>ICC</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cognitive</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FSIQ score</td>
<td>86 (15)</td>
<td>54</td>
<td>106 (10)</td>
<td>38</td>
<td>112 (10)</td>
<td>54</td>
<td>0.42</td>
<td>.03</td>
</tr>
<tr>
<td>VIQ score</td>
<td>83 (17)</td>
<td>54</td>
<td>106 (11)</td>
<td>38</td>
<td>108 (9)</td>
<td>54</td>
<td>0.33</td>
<td>.004</td>
</tr>
<tr>
<td>NVIQ score</td>
<td>88 (17)</td>
<td>54</td>
<td>105 (11)</td>
<td>38</td>
<td>114 (10)</td>
<td>54</td>
<td>0.20</td>
<td>.21</td>
</tr>
<tr>
<td><strong>Behavioral</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SRS score</td>
<td>75 (33)</td>
<td>47</td>
<td>24 (25)</td>
<td>33</td>
<td>30 (18)</td>
<td>51</td>
<td>0.52</td>
<td>.009</td>
</tr>
<tr>
<td>Neuromotor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPT score, DH</td>
<td>30 (16)</td>
<td>48</td>
<td>39 (12)</td>
<td>33</td>
<td>43 (9)</td>
<td>53</td>
<td>0.17</td>
<td>.27</td>
</tr>
<tr>
<td>PPT score, NDH</td>
<td>29 (16)</td>
<td>47</td>
<td>40 (12)</td>
<td>33</td>
<td>41 (10)</td>
<td>53</td>
<td>0.01</td>
<td>.81</td>
</tr>
<tr>
<td>PPT score, BH</td>
<td>30 (16)</td>
<td>47</td>
<td>43 (10)</td>
<td>33</td>
<td>42 (9)</td>
<td>53</td>
<td>0.21</td>
<td>.22</td>
</tr>
<tr>
<td><strong>Anthropometric</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI z score</td>
<td>1.22 (1.16)</td>
<td>56</td>
<td>0.26 (0.97)</td>
<td>36</td>
<td>NA</td>
<td>NA</td>
<td>0.40</td>
<td>.07</td>
</tr>
</tbody>
</table>

Abbreviations: BH, both hands; BMI, body mass index (calculated as the weight in kilograms divided by the square of the height in meters); DH, dominant hand; FSIQ, Full-Scale IQ; ICC, intraclass correlation; NA, not applicable; NDH, nondominant hand; NVIQ, nonverbal IQ; PPT, Purdue Pegboard Test; SRS, Social Responsiveness Scale; VIQ, verbal IQ.
* These sample sizes are based on total participants for each group. The linear mixed-model comparisons and ICC in the results reflect only those data for which matched samples of probands and first-degree relatives are available.

Social Responsiveness Scale
Significant differences emerged among first-degree relatives on social behavior, measured by the SRS (F1,350 = 24.17 [P < .001]), controlling for the FSIQ score (F1,112.32 = 4.39 [P = .04]). The mean SRS score for probands differed from the scores for parents and siblings (P < .001), but those for parents and siblings did not differ from each other. The proband-parent difference (mean [SD], 43.90 [29.44] for 44 pairs) indicates a 2.2-SD effect size for the deletion (Figure 1B). As with the IQ scores, the SRS scores were also highly and positively correlated between the probands and their parents ( ICCp = 0.52 [P = .009]), indicating an important contribution of parental social functioning to a proband’s performance level. Although not part of our primary analysis for this report, significant parent-proband correlations were also observed for other adaptive and maladaptive behaviors as indicated by components of the Vineland Adaptive Behavior Scales34 and the Child Behavior Checklist35 (eTable in the Supplement).

Purdue Pegboard Test
For the PPT score on the dominant hand, the LMM analysis revealed differences among family members (F2,46.47 = 12.43 [P < .001]), the proband-parent (P < .001) and proband-sibling (P = .01) differences were significant. The proband-parent difference (mean [SD], −13.34 [18.05]) was significantly greater than the sibling-parent difference and revealed a 1.3-SD effect size. For the PPT score on the nondominant hand, the LMM finding was also significant (F2,49.32 = 10.79 [P < .001]), with differences between the proband and the biparental and sibling means (P < .001 for both), revealing a 1.3-SD effect size. The PPT scores for both hands also revealed significant differences among probands, siblings, and biparental means (F2,49.05 = 15.43 [P < .001]), with a 1.3-SD effect size relative to those of the parents (for 46 pairs) (Figure 1C). The correlation comparing parent-proband scores for both hands was in the expected direction but did not reach statistical significance (ICC45 = 0.21 [P = .22]) (Table 1).

Body Mass Index
Proband and sibling BMI z scores differed significantly (F1,137.21 = 19.25 [P < .001]), controlling for a significant interaction of age by family member (F1,65.51 = 0.85 [P = .36]). The mean paired difference between the proband (mean [SD], 1.22 [1.16]) and the sibling (mean [SD], 0.26 [0.97]) BMI z score was 0.98 (SD, 1.36) or a 1-SD effect size toward a higher BMI (for 36 proband-sibling pairs). The correlation of the proband and sibling BMI z score approached significance (ICC35 = 0.40 [P = .07]) (Figure 1D).

Discussion
The recurrent 16p11.2 deletion is one of the most common pathogenic CNVs and is associated with a broad range of neurodevelopmental and neuropsychiatric disorders.1-4 In this study, we investigated the effect size of the 16p11.2 deletion in de novo cases from a subset of the Simons Variations in Individuals Project cohort.7 We examined quantitative trait measures for cognitive, social, motor, and anthropometric traits with known heritability to understand the contribution of family background to the phenotypic variability of this CNV.

Relative to first-degree family members, the effect size of the de novo 16p11.2 deletion ranged from 1.0 to 2.2 SD on measures of cognitive, social, and motor performance and on BMI (Figure 1 and eTable in the Supplement). The largest effect was...
on behavioral and cognitive domains, followed by motor performance and BMI. In all domains, probands showed deleterious effects relative to expected outcomes given the biparental mean values.

Evidence of the parental influence on the phenotype resulting from a de novo 16p11.2 deletion is represented by significant ICCs between the parents (or the siblings) and the probands on key phenotypic features of this syndrome (Table 1 and eTable in the Supplement). These correlations indicate that the observed shifts from the expected phenotype are not random but rather are tied closely to familial background and influenced by parental traits, as is the case in the general population. For most of the traits, the parent-proband correlations were nearly identical to those observed in the general population. Given the high heritability for each of these traits, a significant portion of the parental influence is likely owing to genetic background. The nature of the associations between the biparental (or sibling in the case of BMI) and the proband mean scores was found to be linear, with slope values ranging from 0.3844x (IQ) to 0.6656x (SRS) (eFigure in the Supplement). As seen in the general population, a marked phenotypic variability still exists for each individual, and parental cognitive, behavioral, and motor performances are not perfect predictors of the child’s status. However, these findings raise the possibility that when the effect of a CNV on various aspects of brain function is known, assessment of parental phenotype may allow more accurate prediction of the expected range of performance or the risk for particular clinical diagnoses in their offspring with the CNV.

Our findings emphasize the quantitative nature of clinical expression in neurodevelopmental disorders and support the recent proposal by Cuthbert and Insel36 to develop and apply dimensional approaches to mental health research. A dichotomous all-or-none approach to diagnosis has long dominated the fields of medical genetics, psychiatry, and psychology, in which the penetrance of a disorder in a population is determined by dichotomizing a quantitative trait and applying somewhat arbitrary thresholds to classify individuals as affected or unaffected. Although such approaches may appeal to our tendency to adopt simplified heuristics, they fail to recognize the complexity of a more nuanced, quantitative underlying biological reality. Determining the relative deleterious impact of genetic variants requires an estimate of expected outcome, a benchmark representing the actual potential phenotype, were it not for the genetic variant in question.37

The deleterious impact of the deletion and the intraclass correlation (ICC) between probands and their first-degree relatives is indicated for each measure. The arrows represent the direction of the shift of the proband’s distributions relative to biparental and sibling distributions. A, Full-Scale IQ (FSIQ). B, Social Responsiveness Scale (SRS). C, Purdue Pegboard Test (PPT). D, Body mass index (BMI; calculated as the weight in kilograms divided by the square of the height in meters). We transformed the FSIQ, SRS, PPT, and BMI data into a normal distribution using commercially available software (NORMDIST function [x, mean, SD, and cumulative] in Microsoft Excel, version 14.3.9; Microsoft Corporation). The cumulative was set to false to obtain the height of the probability density curve.

Figure 1. Distribution of 4 Core Traits in Probands With the De Novo 16p11.2 Deletion and Their Noncarrier Family Members
In a recent report, 37 parental scores on quantitative measures were used in a model as an estimate of a child’s expected performance or as a starting point from which the deleterious impact of a CNV is subtracted when evaluating the contribution of that CNV to developmental brain dysfunction. Herein, we tested this model and provided familial data that illustrate that the variability associated with a given CNV must be considered in relation to the biparental mean whenever heritable quantitative traits are involved. As shown in Figure 2, probands with the identical CNV all show a deleterious effect compared with parents and siblings but may have different combinations of clinical diagnoses. In Family 14718 (Figure 2A), the deleterious effect of the deletion on quantitative cognitive and motor traits results in FSIQ and PPT scores below the diagnostic threshold line, whereas the behavioral domain performance is still within the reference range. This patient has clinical diagnoses of intellectual disability and developmental coordination disorder but not autism. In Family 14747 (Figure 2B), the proband’s cognitive performance is decreased compared with that of the parents but still within the reference range, whereas the behavioral score is within the impaired range, consistent with this patient’s clinical diagnosis of autism. In Family 14795 (Figure 2C), the proband has a quantitative neurodevelopmental profile suggestive of isolated motor deficiency without cognitive or behavioral impairments, which matches this individual’s diagnosis of developmental coordination disorder without intellectual disability or autism. The variability of clinical diagnoses in part depends on the parental cognitive, social, and motor performance levels. This dependence indicates that the biparental mean values rather than the general population mean values may be more appropriate in measuring the effect size on neurodevelopmental outcomes for a given CNV and for predicting the potential range of outcomes for any individual child. 37

Estimating the deleterious impact of genetic mutations through the assessment of quantitative traits in the context of familial background has been considered for at least 50 years (Table 2). At least 6 studies report that, although individuals with Turner syndrome exhibited the expected shorter stature, the parent-proband correlation for height was conserved (r range, 0.42-0.84). 19-22 Similarly, in Klinefelter syndrome, investigators have reported the increased height associated with the XXY chromosomal complement while also noting that the correlation between biparental and child height that is observed in typical families was preserved (r = 0.62). 19 Moreover, a recent study on 118 individuals with Klinefelter syndrome 23 showed a significant effect of familial learning disabilities on the proband’s neurodevelopmental outcomes.

Such findings also hold true for other traits. Children with Down syndrome exhibited significant IQ deficits, and yet a strong correlation with parental IQ was preserved. 24 Studies on Prader-Willi syndrome also showed that significant parent-child correlations are retained for IQ (r = 0.33), height (r = 0.52), and BMI (r = 0.53). Altogether, the data given in the present study combined with previous reports indicate that, despite the significant deleterious impact associated with chromosomal aneuploidy or CNVs, a proband’s performance levels on
Clinical Variability in 16p11.2 Deletions

ORIGINAL INVESTIGATION Research

Department of Psychiatry, Harvard Medical School, Hospital Boston, Boston, Massachusetts (Hanson); Division of Developmental Medicine, Children's University, Lewisburg, Pennsylvania (Boomer); (Evans); Department of Mathematics, Bucknell University, Lewisburg, Pennsylvania (Challman, Ledbetter); Department of Psychology, Pennsylvania (A. Moreno-De-Luca); Program in Neuroscience, Bucknell University, Lewisburg, Pennsylvania (Myers, Challman); Department of Mathematics, Bucknell University, Lewisburg, Pennsylvania (Evans); Department of Psychiatry, Bucknell University, Lewisburg, Pennsylvania (Chung); Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle (Bernier); Department of Pediatrics, Baylor College of Medicine, Houston, Texas (Goin-Kochel); Department of Pediatrics, Geisinger Health System, Danville, Pennsylvania (Myers, Challman); Department of Psychiatry, Yale University, New Haven, Connecticut (D. Moreno-De-Luca); Simons Foundation, New York, New York (Chung, Spiro); Department of Pediatrics, Columbia University, New York, New York (Chung); Department of Medicine, Columbia University, New York, New York (Chung).

ARTICLE INFORMATION

Submitted for Publication: May 12, 2014; final revision received July 28, 2014; accepted August 5, 2014.


Author Affiliations: Autism and Developmental Medicine Institute, Geisinger Health System, Lewisburg, Pennsylvania (A. Moreno-De-Luca, Evans, Myers, Challman, Slane, Hare, Faucett, Martin, Ledbetter); Genomic Medicine Institute, Geisinger Health System, Danville, Pennsylvania (A. Moreno-De-Luca, Faucett, Martin, Ledbetter); Department of Radiology, Geisinger Health System, Danville, Pennsylvania (A. Moreno-De-Luca); Program in Neuroscience, Bucknell University, Lewisburg, Pennsylvania (A. Moreno-De-Luca, Evans, Myers, Challman, Ledbetter); Department of Psychology, Bucknell University, Lewisburg, Pennsylvania (Evans); Department of Mathematics, Bucknell University, Lewisburg, Pennsylvania (Evans); Division of Developmental Medicine, Children's Hospital Boston, Boston, Massachusetts (Hanson); Department of Psychiatry, Harvard Medical School, Boston, Massachusetts (Hanson); Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle (Bernier); Department of Pediatrics, Baylor College of Medicine, Houston, Texas (Goin-Kochel); Department of Pediatrics, Geisinger Health System, Danville, Pennsylvania (Myers, Challman); Department of Psychiatry, Yale University, New Haven, Connecticut (D. Moreno-De-Luca); Simons Foundation, New York, New York (Chung, Spiro); Department of Pediatrics, Columbia University, New York, New York (Chung); Department of Medicine, Columbia University, New York, New York (Chung).

Author Contributions: Drs A. Moreno-De-Luca and Evans contributed equally to this work. Dr Ledbetter had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: A. Moreno-De-Luca, Evans, Hanson, Myers, Challman, D. Moreno-De-Luca, Chung, Spiro, Martin, Ledbetter.

Acquisition, analysis, or interpretation of data: A. Moreno-De-Luca, Evans, Boomer, Chung, Martin, Bernier, Goin-Kochel, Myers, Slane, Hare, Chung, Faucett, Martin, Ledbetter.

Drafting of the manuscript: A. Moreno-De-Luca, Evans, Boomer, Chung, Martin, Ledbetter.

Critical review of the manuscript for important intellectual content: All authors.

Statistical analysis: A. Moreno-De-Luca, Evans, Boomer, Slane, Hare.

Obtained funding: Hanson, Goin-Kochel, Chung, Faucett, Martin, Ledbetter.

Administrative, technical, or material support: Evans, Hanson, Goin-Kochel, D. Moreno-De-Luca, Hare, Chung, Spiro, Faucett, Martin, Ledbetter.

Study supervision: A. Moreno-De-Luca, Evans, Chung, Martin, Ledbetter.

Conflict of Interest Disclosures: Drs Chung and Spiro are part-time or full-time employees of the Simons Foundation. No other disclosures were reported.

Funding/Support: This study was supported by Simons Foundation Autism Research Initiative (SFARI) awards 216845 and 313100 from the Simons Foundation (Mr Faucett and Drs Martin and Ledbetter) and by grants RO1MH074090 (Drs Martin and Ledbetter), SR25MH071584-07 (Dr D. Moreno-De-Luca), and 5T32MH19961-14 (Dr D. Moreno-De-Luca) from the National Institute of Mental Health.

Copyright 2015 American Medical Association. All rights reserved.

Table 2. Summary of Studies Assessing Parental Influence on Height and IQ for Selected Genetic Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Height</th>
<th></th>
<th>IQ</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Effect Size, SD</td>
<td>Correlation, r Valuea</td>
<td>Effect Size, SD</td>
<td>Correlation, r Valuea</td>
</tr>
<tr>
<td>45,X</td>
<td>NA</td>
<td>0.84</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>45,X</td>
<td>−3.07</td>
<td>0.84</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>45,X</td>
<td>−4.44</td>
<td>0.61</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>45,X</td>
<td>&gt;−2.00</td>
<td>0.49</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>45,X</td>
<td>−4.08</td>
<td>0.69</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>45,X</td>
<td>−4.07</td>
<td>0.50 (F), 0.42 (M)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>47,XX+21</td>
<td>−1.87 (F), −4.86 (M)</td>
<td>0.29 (F), 0.21 (M)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>47,XX+21</td>
<td>NA</td>
<td>NA</td>
<td>−3.17b</td>
<td>0.50 (F), 0.42 (M)</td>
</tr>
<tr>
<td>47,XX+21</td>
<td>NA</td>
<td>NA</td>
<td>−5.27b</td>
<td>0.29 (F), 0.69 (M)</td>
</tr>
<tr>
<td>47,XXX</td>
<td>+2.15</td>
<td>0.62</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Prader-Willi</td>
<td>−0.9 (F), −1.3 (M)</td>
<td>0.46 (F), 0.24 (M)</td>
<td>−2.9 (F), −2.8 (M)</td>
<td>0.58 (female), 0.12 (male)</td>
</tr>
</tbody>
</table>

Abbreviations: F, fathers; M, mothers; NA, not available.

a Indicates proband-parent correlation.

b Includes home-reared probands.

c Indicates institutionalized probands.

d Includes IQ data on mothers only.

A variety of quantitative traits is significantly influenced by familial background.40

The argument that the 16p11.2 deletion represents a variant with incomplete penetrance is not supported by the quantitative approach reported herein and previously.3,37 Simply because arbitrary diagnostic thresholds are not met does not indicate that a particular proband is unaffected or that a given mutation confers no deleterious impact in some individuals. Our findings highlight the importance of studying genetically distinct subgroups of individuals with neuropsychiatric disorders relative to their own familial/genetic background to determine, in a quantitative manner, the extent to which a given genetic mutation affects all aspects of development. Limiting the analyses to de novo cases provides the clearest test of the effect of a CNV on heritable traits because including inherited cases may introduce other sources of variance, such as assortative mating and likely the deleterious effect of the ability of the carrier parent to raise the child and provide a nurturing environment.

Conclusions

Understanding the developmental profiles of populations with CNVs and single gene mutations relative to family background requires a multidimensional, quantitative approach. The resulting information may have important clinical utility in guiding clinical geneticists, neurodevelopmental pediatricians, genetic counselors, and others as they work with families to better understand the developmental implications of a variety of specific genetic mutations.
Role of the Funder/Sponsor: The Simons Foundation is a private not-for-profit research and education organization that funds and participates in research related to autism through cooperative agreements, such as the Simons Variation in Individuals Project. The funding source had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Information: Approved researchers can obtain the Simons VIP population dataset described in this study by applying at https://base.sfari.org.

Additional Contributions: We thank all of the families at the participating Simons Variation in Individuals Project (VIP) sites and the Simons VIP working group. We appreciate obtaining access to phenotypic data on the SFARI Base.

REFERENCES

Copyright 2015 American Medical Association. All rights reserved.