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### Title

Defining the Effect of the 16p11.2 Duplication on Cognition, Behavior, and Medical Comorbidities

### Permalink

<https://escholarship.org/uc/item/0x58q3tq>

### Journal

JAMA Psychiatry, 73(1)

### ISSN

2168-622X

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### Publication Date

2016

### DOI

10.1001/jamapsychiatry.2015.2123

Peer reviewed



# HHS Public Access

Author manuscript

*JAMA Psychiatry*. Author manuscript; available in PMC 2018 April 11.

Published in final edited form as:

*JAMA Psychiatry*. 2016 January ; 73(1): 20–30. doi:10.1001/jamapsychiatry.2015.2123.

## Defining the Effect of the 16p11.2 Duplication on Cognition, Behavior, and Medical Comorbidities

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### Abstract

**IMPORTANCE**—The 16p11.2 BP4-BP5 duplication is the copy number variant most frequently associated with autism spectrum disorder (ASD), schizophrenia, and comorbidities such as decreased body mass index (BMI).

**OBJECTIVES**—To characterize the effects of the 16p11.2 duplication on cognitive, behavioral, medical, and anthropometric traits and to understand the specificity of these effects by systematically comparing results in duplication carriers and reciprocal deletion carriers, who are also at risk for ASD.

**DESIGN, SETTING, AND PARTICIPANTS**—This international cohort study of 1006 study participants compared 270 duplication carriers with their 102 intrafamilial control individuals, 390 reciprocal deletion carriers, and 244 deletion controls from European and North American cohorts. Data were collected from August 1, 2010, to May 31, 2015 and analyzed from January 1 to

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**Author Contributions:** Ms D'Angelo and Drs Lebon and Chen contributed equally to this work, as did senior authors Drs Jacquemont and Chung. Drs Jacquemont and Chung had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Lebon, Snyder, Hanson, Faucett, Bernier, Conus, Martin, Mukherjee, Sherr, Ledbetter, van den Bree, Spiro, Jacquemont, Chung.

**Acquisition, analysis, or interpretation of data:** D'Angelo, Lebon, Chen, Martin-Brevet, Snyder, Hippolyte, Hanson, Maillard, Faucett, Macé, Pain, Bernier, Chawner, Albert, Andrieux, Aylward, Baujat, Caldeira, Conus, Ferrari, Forzano, Gérard, Goin-Kochel, Grant, Hunter, Isidor, Jacqueline, Jønch, Keren, Lacombe, Le Caignec, Martin, Männik, Metspalu, Mignot, Owen, Passeggeri, Rooryck, Rosenfeld, Spence, Steinman, Tjernagel, Van Haelst, Shen, Draganski, Sherr, van den Bree, Beckmann, Reymond, Jacquemont, Chung.

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**Obtained funding:** Hanson, Goin-Kochel, Martin, Metspalu, Owen, van den Bree, Reymond, Jacquemont, Chung.

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**Conflict of Interest Disclosures:** None reported.

**Additional Information:** Approved researchers can obtain the Simons VIP and SSC population data sets described in this study by applying at <https://base.sfari.org>.

August 14, 2015. Linear mixed models were used to estimate the effect of the duplication and deletion on clinical traits by comparison with noncarrier relatives.

**MAIN OUTCOMES AND MEASURES**—Findings on the Full-Scale IQ (FSIQ), Nonverbal IQ, and Verbal IQ; the presence of ASD or other *DSM-IV* diagnoses; BMI; head circumference; and medical data.

**RESULTS**—Among the 1006 study participants, the duplication was associated with a mean FSIQ score that was lower by 26.3 points between proband carriers and noncarrier relatives and a lower mean FSIQ score (16.2-11.4 points) in nonproband carriers. The mean overall effect of the deletion was similar (−22.1 points;  $P < .001$ ). However, broad variation in FSIQ was found, with a 19.4- and 2.0-fold increase in the proportion of FSIQ scores that were very low (< 40) and higher than the mean (>100) compared with the deletion group ( $P < .001$ ). Parental FSIQ predicted part of this variation (approximately 36.0% in hereditary probands). Although the frequency of ASD was similar in deletion and duplication proband carriers (16.0% and 20.0%, respectively), the FSIQ was significantly lower (by 26.3 points) in the duplication probands with ASD. There also were lower head circumference and BMI measurements among duplication carriers, which is consistent with the findings of previous studies.

**CONCLUSIONS AND RELEVANCE**—The mean effect of the duplication on cognition is similar to that of the reciprocal deletion, but the variance in the duplication is significantly higher, with severe and mild subgroups not observed with the deletion. These results suggest that additional genetic and familial factors contribute to this variability. Additional studies will be necessary to characterize the predictors of cognitive deficits.

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The 600-kilobase (kb) break points 4 and 5 (BP4–BP5) 16p11.2 deletion and duplications (chr16; 29.6–30.2 megabase) are among the most frequent genetic causes of autism spectrum disorder (ASD), schizophrenia, and other neurodevelopmental disorders.<sup>1–5</sup> These reciprocal copy number variants (CNVs) are associated with mirror phenotypes of obesity and being underweight and with increased and decreased global and regional brain volumes in deletion and duplication carriers, respectively.<sup>6–8</sup> Previous studies<sup>5,9</sup> have demonstrated that ASD is diagnosed in approximately 18% of deletion carriers and that this CNV affects global cognition by shifting the IQ approximately 2 SDs without altering the variance. To our knowledge, such studies have not been conducted for the reciprocal duplication. Akin to duplications of other genomic regions, case series<sup>10–18</sup> have reported variable expressivity and suggested incomplete penetrance; however, incomplete penetrance was recently ruled out after recalling carriers identified in unselected populations.<sup>19</sup> This phenotypic variability and the limited available data underscore the need to systematically characterize the clinical impact of the duplication with standardized assessments in large numbers of carriers.

The goal of this study was to characterize and elucidate the effects of the 16p11.2 duplication on cognitive, behavioral, medical, and anthropometric traits and to understand the specificity of these effects by systematically comparing results in duplication carriers and reciprocal deletion carriers, who are also at risk for ASD. To this end, we established, to our knowledge, the largest cohort of duplication ( $n = 270$ ) and deletion ( $n = 390$ ) carriers to date from the 16p11.2 European and Simons Variation in Individuals Project (Simons VIP) consortia and the Cardiff University Experiences of Children With Copy Number Variants

(ECHO) Study. We present here the natural history and phenotypic variation among the 16p11.2 duplication carriers and compare their results with those of their intrafamilial control individuals (n = 102) and of individuals with the reciprocal 16p11.2 deletion ascertained by similar methods.

## Methods

### Patients

This study was reviewed and approved by the ethical committee or institutional review board for the European consortium (<http://www.cer-vd.ch/>). Written informed consent and, when appropriate, assent were obtained from the participants who underwent full clinical assessments.

### Inclusion and Exclusion Criteria

This study describes only the proximal 600-kb recurrent 16p11.2 CNV delineated by BP4 and BP5 (29.6–30.2–Hg19).<sup>5</sup> Carriers have the same BP4–BP5 duplication (or deletion). Control participants were family members of the carriers who do not carry the 16p11.2 duplication or deletion. Individuals with an additional deleterious CNV were excluded. Deleterious CNVs were defined as (1) a known recurrent genomic disorder, (2) a CNV encompassing a published critical genomic region or disrupting a gene that is a known cause of neurodevelopmental disorders, or (3) rare (<1 of 1000) and large (>500 kb) CNVs. The percentages of additional deleterious CNVs were compared between duplication probands and deletion probands similarly ascertained on the basis of a neurodevelopmental disorder (eMethods in the Supplement). Ascertainment is detailed in eTable 1 and the eMethods in the Supplement. Data were collected from August 1, 2010, to May 31, 2015.

### Cognitive Functioning, Psychiatric, and Behavioral Assessments

Phenotypic evaluations for the Simons VIP participants and the 16p11.2 European Consortium were performed as previously reported.<sup>5</sup> The Wechsler Abbreviated Scales of Intelligence was used to assess IQ for the ECHO Study participants.

### Statistical Analysis

Data were analyzed from January 1 to August 14, 2015. We examined differences in the Full Scale (FSIQ), Verbal (VIQ), and Nonverbal (NVIQ) IQs and *z* scores for body mass index (BMI) (calculated on height and weight) and head circumference (HC) between 16p11.2 duplication carriers and their noncarrier familial controls. The IQ values were derived from age and developmentally appropriate standardized measures (*Differential Ability Scales*,<sup>20</sup> *Mullen Scales for Early Learning–AGS Edition*,<sup>21</sup> and *Wechsler Abbreviated Scales of Intelligence*<sup>22</sup>). Cognitive measures are standardized to a mean (SD) of 100 (15), with higher scores indicating more developed cognitive abilities. For participants performing out of normative range on instruments, we generated ratio IQ scores based on subtest raw score age equivalencies (mental age/chronological age × 100) so that an accurate IQ estimate was established for each participant. The BMI *z* scores were estimated based on age and sex norms, and HC *z* scores were estimated based on age- and sex-normed orbitofrontal HC measurements obtained during laboratory visits.

Carriers were stratified into the following 3 groups: probands, pediatric carrier relatives (<18 years of age), and adult carrier relatives (>18 years of age). These groups were compared with noncarriers. We also compared differences in phenotypes between probands whose inheritance status (de novo and inherited) was documented and their noncarrier familial controls. The same analyses were performed with the deletion carriers and their noncarrier familial controls.

We used linear mixed models to compare differences in phenotypes between carrier or inheritance groups while accounting for correlated measures within families (familial clustering) to estimate the effect of the 16p11.2 duplication or deletion on the phenotype. The group differences were controlled for by study cohort (European vs United States), age, and sex. Additional contrasts were included for multilevel categorical variables to allow for pairwise comparison among all levels of the variable. To examine whether the group differences were driven by other diagnostic factors, additional linear mixed models were fitted by adding ASD, seizure diagnosis, and, when applicable, NVIQ to the existing models as covariates.

We used the Levene test<sup>23</sup> to assess equality of variance and the Fisher exact test to assess the association between binary variables. To study the longitudinal trend of BMI and HC values among deletion and duplication groups, we grouped the data points into age windows. We used linear mixed models to compare the mean values of BMI and HC of carriers to the population means or familial controls (if available) at each time window. All statistical analyses were conducted using SAS (version 9.4; SAS Institute Inc) and R (R Core Team) software.

## Results

Descriptive statistics for our 1006 study participants are shown in Table 1 and Table 2. We first compared duplication carriers with their familial controls for cognition, neurologic findings, psychiatric symptoms, BMI, and HC and then performed similar comparisons between deletion carriers and their familial controls.

### Global Cognitive Functioning

The mean FSIQ across the 270 duplication carriers was 78.8. Forty-seven of 154 carriers (30.5%) met criteria for intellectual disability. When controlling for cohort, age, and sex, the FSIQ was significantly lower in duplication carriers compared with intrafamilial controls (18.0 points;  $P < .001$ ; Table 3). The largest effect was observed in probands (decrease in mean FSIQ, 26.3 points) followed by pediatric and adult carrier relatives (decreases, approximately 16.2 and 11.4 points, respectively) relative to intrafamilial controls. When controlling for the same covariates, the effect of the reciprocal deletion was similar, with a mean decrease in carriers of 22.1 points ( $P < .001$ ; eTable 2 in the Supplement) in FSIQ compared with intrafamilial controls.

The effect of cohort on FSIQ was the same in both CNV groups, with significantly lower FSIQ in the European vs the US cohort (by 13.3 points in the duplication group and 13.9 points in the deletion group;  $P < .001$ ). The effects of both CNVs on FSIQ, VIQ, and NVIQ

remained similar after additionally controlling for ASD and seizures (eTables 3–8 in the Supplement), which were associated with IQ in the duplication but not the deletion groups (see the Neurologic Findings and Psychiatric Symptoms subsections in this Results section).

### Variability of the Effect on Global Cognition

The variance of FSIQ in duplication carriers was significantly higher than observed in deletion carriers (Levene test,  $P < .001$ ). We found a 19.4-fold excess (Fisher exact test,  $P < .001$ ) of very low FSIQ ( $< 40$ ; 15 of 154 [9.7%]) in the duplication compared with the deletion carriers (1 of 200 [0.5%]) and a 2.0-fold enrichment (Fisher exact test,  $P = .01$ ) of the duplication carriers greater than the population mean FSIQ compared with deletion carriers ( $> 100$ ; 30 of 154 [19.5%] vs 20 of 200 [10.0%]) who were ascertained by the same investigators using the same methods (Figure 1). The European and US duplication cohorts contributed (albeit not equally) to the lower- and higher-functioning participants (eFigures 1 and 2 in the Supplement). The large variance of FSIQ among duplication probands was not driven by cohort, the presence of ASD, seizure status, or HC (eFigure 2 in the Supplement).

Another factor underlying increased variation in IQ may have been additional undetected genetic variants. When we combined the European, Simons VIP, and Signature Genomics Laboratories data sets (described in eMethods in the Supplement), the odds of an additional deleterious CNV were 2.5-fold higher in duplication compared with deletion carriers ascertained for neurodevelopmental disorders ( $P = .006$ ) (eMethods and eTable 9 in the Supplement). The median size and the mean number of genes included in additional CNVs are similar for 16p11.2 deletion and duplication carriers (eFigure 3 in the Supplement).

### Global Cognition of De Novo and Inherited Duplication Carriers

The FSIQ, NVIQ, and VIQ were not significantly different in probands with de novo vs inherited duplications but were significantly greater in probands with de novo vs inherited deletions (eTables 10 and 11 in the Supplement). In families with inherited duplications, approximately 36.0% of the IQ variance in probands was accounted for by the IQ of the transmitting parent (eFigure 4 in the Supplement). Too few de novo carriers were available for this analysis ( $n = 13$ ). For deletion carriers, less of the variability was explained by parental IQ (11.0% for inherited and de novo cases; eFigure 4 in the Supplement).

### Neurologic Findings

Epilepsy was reported in 35 of 180 of duplication probands (19.4%) and 2 of 90 of their carrier relatives (2.2%) (eTable 12 in the Supplement). We found a broad spectrum of severity ranging from benign focal epilepsy to severe epileptic syndromes, with focal epilepsies being the most frequent type (16 of 37 [43.2%]). In the reciprocal deletion group, the frequency of epilepsy was similar, with 69 of 317 probands (21.8%) and 4 of 73 relatives (5.5%) ( $P = .56$  and  $P = .39$ , respectively). The clinical spectrum was broad, with a predominance of generalized seizures (eTable 13 in the Supplement).

In a subset of 86 duplication carriers with a magnetic resonance image of the brain, enlarged ventricles and cerebellar hypoplasia were the most frequent findings (13 [15.1%] and 10 [11.6%], respectively). In deletion carriers, posterior fossa abnormalities were observed

most frequently (36 of 108 [33.3%]), along with Chiari type I malformations (11 of 36 [30.6%]) (eResults and eTables 12 and 13 in the Supplement).

The median age at first walking was delayed in 82 duplication proband carriers compared with 164 reciprocal deletion proband carriers (18 vs 16 months; Wilcoxon rank sum test,  $P = .009$ ). This difference was mainly driven by the increased proportion (2.6-fold) of very-late-onset walking (>24 months) among the duplication probands compared with the deletion probands ( $P = .02$ ) (eFigure 5 in the Supplement).

### Psychiatric Symptoms

Diagnostic criteria for ASD were met in 36 of 180 duplication probands (20.0%) and 2 of 90 of their carrier relatives (2.2%). In the deletion group, the proportion of probands with a diagnosis of ASD was similar (51 of 317 [16.1%];  $P = .27$ ). However, among those with an ASD diagnosis, duplication probands were significantly more impaired in cognition than deletion probands by 26.3 points (2-sided unpaired  $t$  test,  $P < .001$ ). Duplication probands with ASD also had significantly lower cognition than those without an ASD diagnosis (mean FSIQ, 52.8 vs 75.4;  $t$  test,  $P < .001$ ; Figure 1E). Other *DSM-IV* diagnoses were reported in 25 of 38 of duplication carriers with ASD (65.8%), 71 of 143 probands (49.7%), and 38 of 86 of their carrier relatives without a diagnosis of ASD (44.2%). Among deletion carriers, other *DSM-IV-TR* diagnoses were reported in 45 of 55 with ASD (81.8%), 157 of 266 probands (59.0%), and 31 of 69 of their carrier relatives without ASD (44.9%) (eTables 14 and 15 in the Supplement). We did not identify cases of schizophrenia beyond the 4 duplication carriers ascertained from a schizophrenia cohort.

### Body Mass Index

The mean BMI  $z$  score was approximately 0.6 points lower ( $P = .003$ ) in duplication carriers compared with intrafamilial controls (Table 3 and Figure 2A); this decrease was consistent across all carrier groups, including probands, pediatric carrier relatives, and adult carrier relatives ( $P = .004$ ,  $P = .09$ , and  $P = .01$ , respectively). The relative risk for obesity (BMI  $z$  score  $\geq 2$  SDs above the 98th percentile in children; BMI raw score [calculated as weight in kilograms divided by height in meters squared]  $\geq 30$  in adults) decreased 3-fold in pediatric and adult duplication carriers when compared with the control group (Fisher exact test,  $P < .001$ ). In the reciprocal deletion carriers, BMI  $z$  score increased by 0.7 points in carriers compared with intrafamilial controls (eTable 2 in the Supplement). Body mass index was not associated with ASD, seizures, or NVIQ in duplications or deletions (eTables 16 and 17 in the Supplement). In the longitudinal analysis, BMI increased with age in deletion carriers, whereas it remained relatively stable from 0 to  $-1$  SD in duplication carriers (Figure 2B).

### Head Circumference

The HC  $z$  score was a mean of 1.1 points lower in duplication carriers ( $P < .001$ ; Table 3 and Figure 2C) and 0.5 points higher ( $P = .002$ ) in deletion carriers compared with noncarriers (eTable 2 in the Supplement). Similar to BMI and in contrast to IQ, this effect on HC  $z$  score was consistent across probands and relatives. Forty-eight of 215 duplication carriers (22.3%) were microcephalic (HC  $z$  score, less than  $-2$  SDs below the 2th percentile). Head circumference was significantly associated with NVIQ in duplications ( $P = .03$ ) but not



deletions ( $P = .28$ ), and we found a marginal association between HC and ASD in deletions ( $P = .07$ ) but no association in duplications ( $P = .16$ ). Seizures were not associated with HC in duplications or deletions (eTables 18 and 19 in the Supplement). Head circumference and BMI  $z$  scores were correlated within the deletion and duplication probands (for both groups,  $r = 0.4$ ;  $P < .001$ ). In the longitudinal analysis, the significant decrease in HC  $z$  scores during the first 2 years of life mirrored the increasing HC  $z$  scores during the same period observed in deletion carriers (Figure 2D). Malformations, medical problems, and sex differences are detailed in the eResults and eTables 20 to 23 in the Supplement.

## Discussion

We present here a comprehensive phenotypic characterization of the 16p11.2 BP4–BP5 duplication and deletion ascertained in US and European cohorts to understand their specific effects on neurocognitive, behavioral, and anthropometric phenotypes. The large variance in FSIQ is an important feature of the duplication, with increased proportions of individuals at both extremes of the FSIQ distribution when compared with the deletion group. Unlike the deletion group, which showed a consistent effect of 16p11.2 deletion on FSIQ across carrier groups and a normal distribution consistent with what is observed in the general population, the duplication was associated with a multimodal distribution in FSIQ and different effect sizes for probands and other carriers in the family. The mean IQ decrement in duplication probands (26.3 points) was likely influenced by the clinical ascertainment for neurodevelopmental disorders. In contrast, the 11.4-point mean decrease observed in adult carriers was most likely an underestimate of the duplication effect because most of these adults are transmitting parents ascertained for higher functional status. The mean effect of the duplication may therefore lie between these 2 estimates. Differences in IQ observed in the European and US cohorts did not influence these estimates. This finding was also in agreement with that of a recent adult population-based study from Iceland<sup>25</sup> that reported a 15- to 19-point decrease in VIQ and NVIQ in 7 duplication carriers ( $P = .006$  and  $P < .001$ , respectively). We suspect that the subpopulation of low-functioning duplication carriers with FSIQ of 40 or less harbors additional factors that are not tolerated and possibly lethal before birth in deletion carriers, who almost never present such severe cognitive impairment.

Participants with second pathogenic CNVs, other identified monogenic disorders, prematurity, fetal alcohol syndrome, and neonatal hypoxia were intentionally excluded from the main analyses, but other undetected factors may have influenced the severity of the clinical presentation in the probands. The 2- to 3-fold increase of additional deleterious CNVs in duplication compared with deletion probands ascertained for neurodevelopmental disorders suggests that the duplication requires additional factors to reach the threshold for clinical evaluation compared with the deletion. Some of these unknown genetic factors may be inherited from parents as suggested by the correlation between FSIQ in probands and their parents ( $r = 0.4$ , similar to previously published studies estimating the heritability of IQ in the general population<sup>26,27</sup>). The remaining unexplained variation was substantial, making the use of parental IQ alone as a predictor insufficient (eFigure 4 in the Supplement). The significant decrease in IQ in probands with an inherited vs a de novo deletion confirmed our hypothesis that families with an inherited deletion may be enriched in additional genetic or



environmental factors that affect cognition. We did not observe this phenomenon for inherited duplications.

Differences in the European vs US cohorts may be the consequence of access to clinical chromosome microarrays that differ by health care system. Recruitment methods also differed in both cohorts. Probands from the European cohort were directly referred from genetic units to the research center, whereas the Simons VIP participants required active participation of the proband's family. Nonetheless, these differences between cohorts did not influence the effect of the duplication on IQ.

The frequency of ASD was similar in deletion and duplication probands and was consistent with previous case-control association studies<sup>28-30</sup> that have demonstrated that both reciprocal CNVs equally predispose to ASD. However, our study suggests that the duplication is associated with a form of low-functioning ASD, whereas cognition in deletion carriers with ASD is mostly within the normal range. This finding also applies in epilepsy, equally frequent in duplication and deletion probands but only associated with lower FSIQ in the duplication group. This finding suggests that these neuropsychiatric diagnoses may occur in the presence of additional factors with a negative effect on IQ. Similar to ASD cohorts, an excess of male participants and lower IQ in female participants were observed in the duplication and deletion carriers ascertained for neurodevelopmental disorders.

The low frequency of schizophrenia in the duplication cohort is discordant with the association reported in prior studies.<sup>4</sup> This discordance is likely in part owing to the youth of our participants (mean ages, 18.2 years in the US and 26.7 years in the European cohorts) and the fact that adults were ascertained as parents. Following up our probands is required to estimate the risk for schizophrenia accurately.

Although the penetrance of obesity is higher in the deletion group compared with being underweight in the duplication group, the effect sizes of both variants appear to be similar when compared with intrafamilial controls. The effect of the duplication mirrors that of the deletion with the exception of the age-related effect.<sup>5</sup> As expected, geographic location influences BMI, but the effect of the duplication is similar in both cohorts.

The 1-point decrease in mean HC *z* score in duplication carriers occurs during the first two years of life and mirrors the early increased growth observed in the deletion carriers (Figure 2D). Head circumference, which is highly correlated with brain volume,<sup>7,8</sup> is associated with NVIQ in the duplication carriers (albeit with a small effect size) and a trend was observed for ASD in deletion carriers. The main limitation of this study is the ascertainment bias in the probands who came to clinical attention and underwent clinical testing with a chromosome microarray. We attempted to minimize this bias by performing cascade genetic testing within families to identify additional duplication carriers and include all duplications carriers within the study.

## Conclusions

The 16p11.2 duplication has a consistent effect on some traits, such as HC and BMI. The duplication may interact with additional factors that lead to different severities of

neurobehavioral phenotypes, including a subgroup of low-functioning duplication carriers with ASD, which is absent in the deletion group. The estimated effect size of the duplication on IQ suggests that this CNV contributes to approximately half of the cognitive deficit in carriers with mild to moderate intellectual disability. Additional factors may contribute to the neurodevelopmental outcome in some individuals. Future studies will aim to quantify the contribution of additional genetic and environmental factors to the phenotype.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Acknowledgments

**Funding/Support:** This study was supported by the Center of Excellence in Genomics; by grant SPIGVARENG (University of Tartu); by grant IUT20-60 from the Estonian Research Council; by a fellowship from the Swiss Scientific Exchange NMS Program (Dr Männik); by a Bursary Professor fellowship of the Swiss National Science Foundation (SNSF) (Dr Jacquemont); by grant SFARI274424 from the Simons Foundation (Dr Reymond); by grant 31003A160203 from the SNSF (Dr Reymond); by Sinergia grant CRSII33-133044 from the SNSF (Dr Reymond); and by a Medical Research Council (MRC) doctoral training grant at the MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University (Mr Chawner). Dr Dragaski is supported by project grants 320030\_135679 and SPUM 33CM30\_140332/1 from the Swiss National Science Foundation (NCCR Synapsy), Foundation Parkinson Switzerland, Foundation Synapsis and the European Union Seventh Framework Program (FP7/2007–2013) under grant agreement 604102 (Human Brain Projects). LREN receives financial support from the Roger de Spoelberch and Partridge Foundations. The Simons VIP work is supported by the Simons Foundation Autism Research Initiative (SFARI).

**Role of the Funder/Sponsor:** The funding sources 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.

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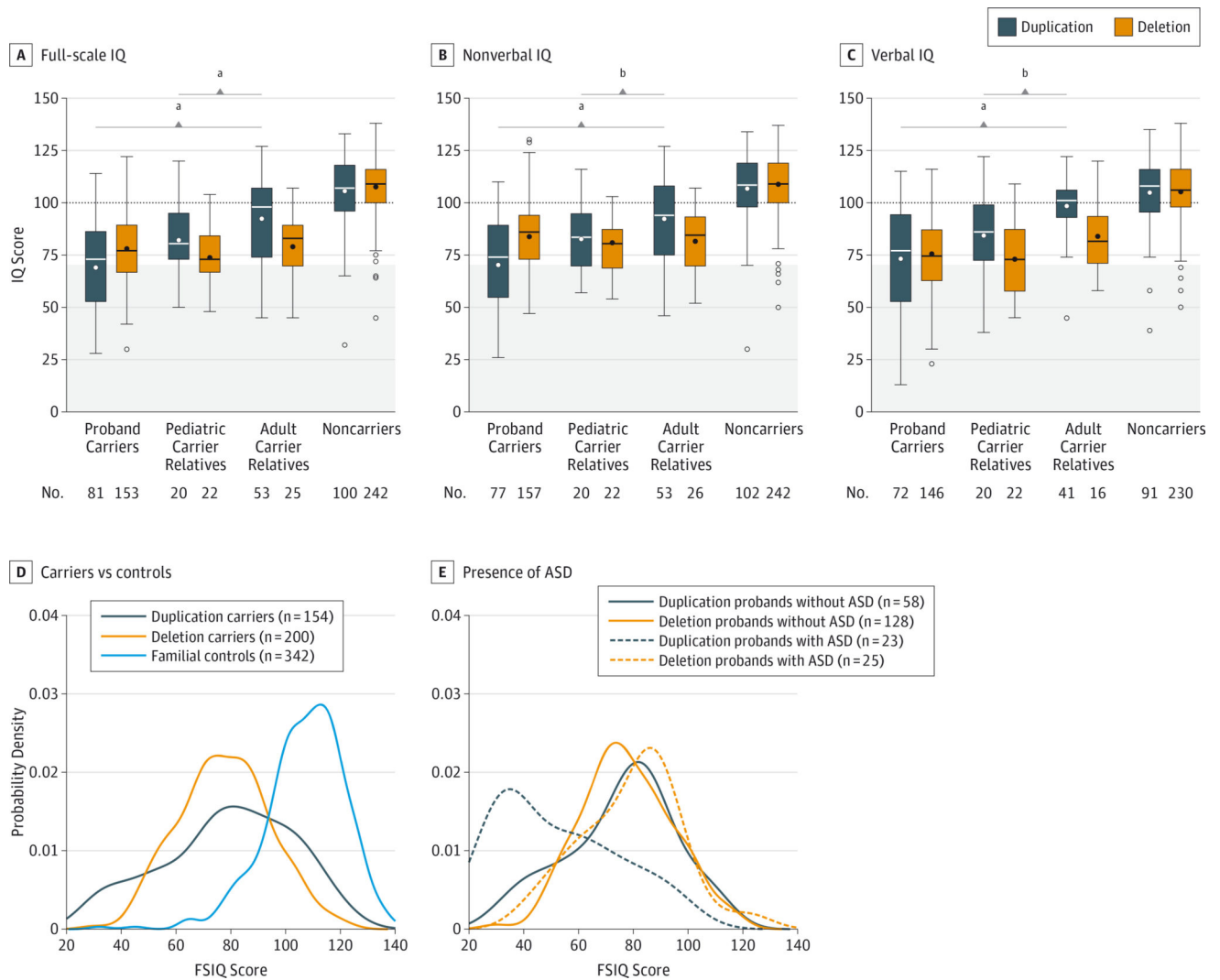
**Additional Contributions:** We are grateful to all of the families who participated in the Simons Variation in Individuals Project (VIP) and the Simons VIP Consortium (data from Simons VIP are available through SFARI Base). We thank the coordinators and staff at the Simons VIP and SCC sites. We are grateful to all of the families at the participating SSC sites and the principal investigators (A. Beaudet, MD, R. Bernier, PhD, J. Constantino, MD, E. Cook, MD, E. Fombonne, MD, D. Geschwind, MD, PhD, R. Goin-Kochel, PhD, E. Hanson, PhD, D. Grice, MD, A. Klin, PhD, D. Ledbetter, PhD, C. Lord, PhD, C. Martin, PhD, D. Martin, MD, PhD, R. Maxim, MD, J. Miles, MD, PhD, O. Ousley, PhD, K. Pelphrey, PhD, B. Peterson, MD, J. Piggot, MD, C. Saulnier, PhD, M. State, MD, PhD, W. Stone, PhD, J. Sutcliffe, PhD, C. Walsh, MD, PhD, Z. Warren, PhD, E. Wijsman, PhD). We appreciate obtaining access to phenotypic data on SFARI base. The Galliera Genetic Bank member of the Telethon Network of Genetic Biobanks (project No. GTB12001; funded by Telethon Italy) provided us with specimens. We thank participants and families in the Experiences of Children with Copy Number Variants (ECHO) Study. The National Health Service medical genetics clinics, Unique–The Rare Chromosome Disorder Support Group, a UK-registered charity, and UK-based 16p11.2 online support groups advertised the study and referred participants. Hayley Moss, BSc, Maria Niarchou, PhD, and Aimée Davies, BSc, Medical Research Council Centre for Neuropsychiatric Genetics and Genomics, Institute of Psychological Medicine and Clinical Neurosciences, Cardiff University, contributed to recruitment and assessment of the participants. They did not receive compensation for this role.

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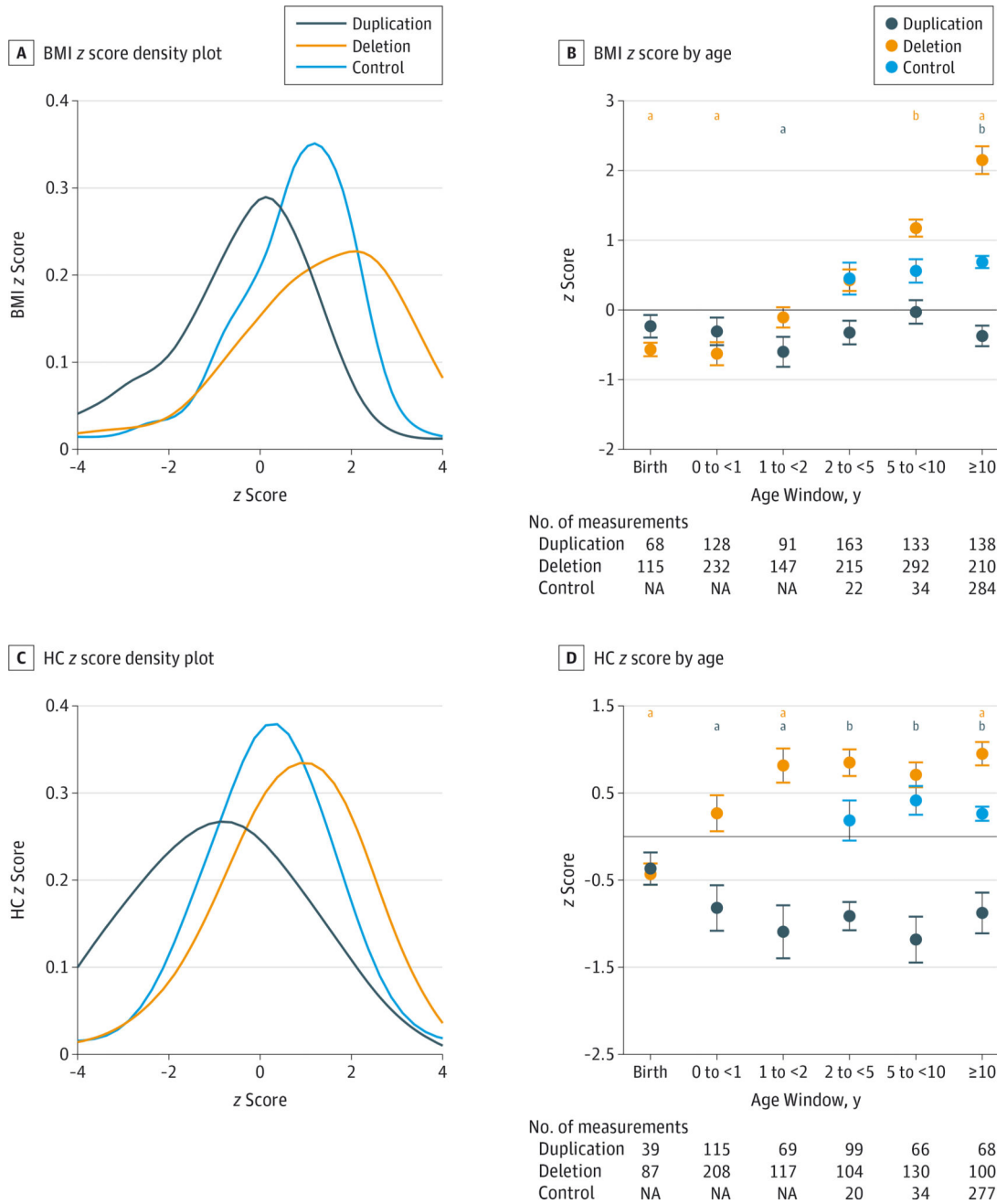


**Figure 1. Distribution of IQ Measures in BP4-BP5 16p11.2 Duplication and Deletion Carriers and Intrafamilial Noncarrier Control Individuals**

A-C, Box plots. Bold line indicates median; circles, outliers; dot inside the box, mean; top of each box, the 75th percentile (Q3); bottom of each box, 25th percentile (Q1); upper end of the error bar, the highest observed data value within the span from Q3 to Q3 + 1.5 times the interquartile range (IQR) (calculated as Q3 - Q1); the lower end, the lowest observed data value within the span from Q1 to Q1 - 1.5 times the IQR; shading, intellectual disability range (IQ < 70); and dotted line, population mean (IQ = 100). The numbers below the graphs represent the number of duplication and deletion carriers in each group. D and E, Density plots. Increased variance is seen in the duplication group with a significant excess of low- and high-functioning duplication carriers compared with the deletion group, which was ascertained with the same method. The Full-Scale IQ (FSIQ) of probands with autism spectrum disorder (ASD) is significantly lower in duplication compared with deletion carriers.

<sup>a</sup>  $P < .05$ .

<sup>b</sup>  $P < .1$ .



**Figure 2. Body Mass Index (BMI) and Head Circumference (HC) z Scores in Deletion and Duplication Carriers and Intrafamilial Control Individuals**

Density plots depict cross-sectional data. Only data from probands were used for deletion and duplication density plots. Stratification of z scores by 6 age windows used the combined longitudinal and cross-sectional data. In the 3 youngest age windows, we compared the mean z scores (data markers; error bars indicate SEs of the estimates in linear mixed models) of deletions and duplications in each individual age window with the population mean (z score, 0). In the 3 oldest age windows where familial controls were available, we compared the mean z score for deletions and duplications in each individual age window with their familial controls. Deletion and duplication carriers demonstrate low BMI during

infancy. After 2 years of age, the BMI *z* score of deletion carriers increases and remains low in duplication carriers. NA indicates not available.

<sup>a</sup>  $P < .05$ , carriers vs normative data, using the method of Gao et al<sup>24</sup> for the *P* value calculation to account for the multiple tests across multiple age windows.

<sup>b</sup>  $P < .05$ , carriers vs controls, using the method of Gao et al<sup>24</sup> for the *P* value calculation to account for the multiple tests across multiple age windows.

Table 1

Sex, Age, and Inheritance Status by 16p11.2, Cohort, and Carrier Group

Cohort by Carrier Group	No. of Participants	Male, No. (%)	Age, Mean (SD), y	16p11.2 Inheritance, No. (%) <sup>a,b</sup>	
				De Novo	Inherited
<b>16p11.2 Duplication</b>					
European					
Proband carrier	97	54 (55.7)	24.2 (21.9)	14 (14.4)	31 (32.0)
Pediatric carrier relative	6	3 (50.0)	5.7 (3.4)	0	6 (100)
Adult carrier relative	24	13 (54.2)	41.9 (12.0)	0	6 (25.0)
Noncarrier	12	5 (41.7)	28.8 (14.8)	7 (58.3)	4 (33.3)
United States					
Proband carrier	83	50 (60.2)	9.1 (8.8)	17 (20.5)	44 (53.0)
Pediatric carrier relative	17	8 (47.1)	7.3 (4.4)	0	17 (100)
Adult carrier relative	43	21 (48.8)	40.3 (10.2)	3 (7.0)	13 (30.2)
Noncarrier	90	38 (42.2)	28.9 (17.8)	28 (31.1)	57 (63.3)
<b>16p11.2 Deletion</b>					
European					
Proband carrier	170	101 (59.4)	16.5 (15.9)	57 (33.5)	49 (28.8)
Pediatric carrier relative	21	13 (61.9)	10.6 (3.5)	0	19 (90.5)
Adult carrier relative	31	11 (35.5)	38.1 (8.9)	0	6 (19.4)
Noncarrier	33	15 (45.5)	30.5 (16.2)	21 (63.6)	6 (18.2)
United States					
Proband carrier	147	86 (58.5)	7.6 (4.9)	87 (59.2)	18 (12.2)
Pediatric carrier relative	11	6 (54.5)	8.6 (3.9)	2 (18.2)	9 (81.8)
Adult carrier relative	10	5 (50.0)	39.0 (5.0)	1 (10.0)	0
Noncarrier	211	90 (42.7)	28.9 (14.9)	183 (86.7)	12 (5.7)

<sup>a</sup>For noncarriers, the value represents the number from families with proband carriers having de novo, inherited, or unknown status.<sup>b</sup>Inheritance status was unknown for some carriers. Percentages are based on the total number of carriers and not only those with known inheritance status.

**Table 2**  
Mean IQ and Anthropometric Measures by 16p11.2 Status, Cohort, and Carrier Group

Cohort by Carrier Group	z Score															
	FSIQ	No. of Participants	Mean (SD)	NVIQ	No. of Participants	Mean (SD)	VIQ	No. of Participants	Mean (SD)	BMI	No. of Participants	Mean (SD)	HC	No. of Participants	Mean (SD)	
<b>16p11.2 Duplication</b>																
European																
Proband carrier	30	63.9 (25.5)	27	65.1 (23.4)	24	69.0 (28.5)	90	-0.5 (1.7)	59	-1.2 (1.7)						
Pediatric carrier relative	4	69.8 (17.0)	4	70.3 (10.7)	4	75.3 (24.5)	6	-1.5 (1.7)	5	-1.8 (1.3)						
Adult carrier relative	14	71.8 (19.7)	13	70.5 (15.7)	2	80.5 (50.2)	24	-0.3 (1.3)	19	-0.9 (1.4)						
Noncarrier	12	98.6 (14.6)	12	100.0 (15.7)	3	119.0 (3.0)	12	0.3 (1.5)	10	-0.3 (0.8)						
United States																
Proband carrier	51	72.0 (21.1)	50	73.2 (21.0)	48	75.3 (25.8)	76	-0.02 (1.3)	76	-0.7 (1.6)						
Pediatric carrier relative	16	85.3 (18.5)	16	85.8 (16.0)	16	86.7 (22.8)	15	0.3 (0.9)	17	-0.6 (1.5)						
Adult carrier relative	39	99.7 (14.7)	40	99.4 (16.3)	39	99.4 (13.1)	42	0.6 (1.1)	42	-0.8 (1.5)						
Noncarrier	88	106.5 (16.4)	90	107.6 (17.3)	88	104.5 (15.6)	86	0.8 (1.2)	87	0.3 (1.2)						
<b>16p11.2 Deletion</b>																
European																
Proband carrier	47	69.4 (15.1)	47	77.9 (13.7)	40	70.4 (15.2)	162	1.8 (2.4)	119	0.6 (1.5)						
Pediatric carrier relative	15	69.8 (13.6)	15	77.9 (13.2)	15	69.7 (15.6)	19	1.4 (1.6)	14	0.03 (1.1)						
Adult carrier relative	15	73.9 (17.2)	17	74.8 (14.2)	7	78.4 (15.1)	30	2.2 (1.8)	24	1.0 (1.4)						
Noncarrier	31	94.7 (17.3)	31	96.9 (16.8)	19	91.2 (21.8)	32	0.5 (1.0)	30	-0.5 (1.2)						

Cohort by Carrier Group	FSIQ				NVIQ				VIQ				BMI				HC			
	No. of Participants	Mean (SD)	No. of Participants	Mean (SD)	No. of Participants	Mean (SD)	No. of Participants	Mean (SD)	No. of Participants	Mean (SD)	No. of Participants	Mean (SD)	No. of Participants	Mean (SD)	No. of Participants	Mean (SD)	No. of Participants	Mean (SD)		
United States																				
Proband carrier	106	81.8 (16.1)	110	86.5 (16.8)	106	77.6 (19.1)	129	1.0 (1.4)	140	1.0 (1.5)										
Pediatric carrier relative	7	82.9 (13.6)	7	87.3 (12.7)	7	80.6 (17.7)	11	1.1 (1.1)	10	1.6 (1.6)										
Adult carrier relative	10	86.8 (15.9)	9	94.3 (8.5)	9	88.3 (18.7)	10	2.1 (1.1)	10	0.5 (0.8)										
Noncarrier	211	109.5 (12.3)	211	110.6 (13.0)	211	106.6 (12.4)	203	1.0 (1.0)	209	0.4 (1.3)										

Abbreviations: BMI, body mass index; FSIQ, Full-Scale IQ; HC, head circumference; NVIQ, Nonverbal IQ; VIQ, Verbal IQ.

Table 3

Effect of the Duplication on Global Intelligence and Anthropometric Measures

Comparison <sup>a</sup>	z Score									
	FSIQ (n = 253)	NVIQ (n = 251)	VIQ (n = 223)	BMI (n = 351)	HC (n = 314)					
	Estimate	Value <sup>b</sup>	P	Estimate	Value <sup>b</sup>	P				
Fixed effects parameters										
Intercept	97.5	<.001	99.9	<.001	98.3	<.001	0.4	.07	0.5	.06
Proband carrier vs noncarrier	-26.3	<.001	-26.7	<.001	-24.4	<.001	-0.6	.004	-1.2	<.001
Pediatric carrier relative vs noncarrier	-16.2	.001	-16.6	<.001	-15.6	.005	-0.6	.09	-1.1	.002
Adult carrier relative vs noncarrier	-11.4	<.001	-14.8	<.001	-6.0	.13	-0.5	.01	-1.2	<.001
European vs US cohort	-13.3	.001	-14.0	<.001	-8.4	.11	-0.7	<.001	-0.4	.06
Age, y	0.3	<.001	0.3	<.001	0.1	.05	0.02	.001	-0.001	.86
Female vs male	-1.5	.42	-4.1	.04	0.6	.78	-0.1	.69	-0.2	.25
Additional contrasts										
Carrier vs noncarrier	-18.0	<.001	-19.3	<.001	-15.3	<.001	-0.6	.003	-1.1	<.001
Proband carrier vs pediatric carrier relative	-10.1	.02	-10.1	.01	-8.8	.08	-0.01	.98	-0.1	.73
Proband carrier vs adult carrier relative	-14.9	<.001	-11.9	.001	-18.4	<.001	-0.03	.87	0.1	.75
Pediatric vs adult carrier relative	-4.8	.33	-1.8	.71	-9.6	.11	-0.03	.94	0.02	.96

Abbreviations: BMI, body mass index; FSIQ, Full-Scale IQ; HC, head circumference; NVIQ, Nonverbal IQ; VIQ, Verbal IQ.

<sup>a</sup>Carriers include proband carriers (individuals ascertained for a neurodevelopmental disorder), pediatric carrier relatives (mostly siblings of the probands), and adult carrier relatives (mostly transmitting parents).<sup>b</sup>Linear mixed model analysis was used to estimate the effect of duplication on FSIQ, NVIQ, VIQ, BMI z score, and HC z score.