Discontinuity in the genetic and environmental causes of the intellectual disability spectrum

Abraham Reichenberg,a,b,1 Martin Cederlöf,c Andrew McMilland, Maciej Trzaskowski,e Ori Kapara,b, Eyal Fruchter,f
Karen Ginta, Michael Davidsoffb, Mark Weiserd, Henrik Larsson,c Robert Plominb, and Paul Lichtensteinc

*Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY 10029; aDepartment of Preventive Medicine, Icahn School of Medicine at Mount Sinai, New York, NY 10029; bDepartment of Medical Epidemiology and Biostatistics, Karolinska Institutet, SE-17177 Stockholm, Sweden; cMedical Research Council Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology & Neurosciences, King’s College London, London, SE5 9AF London, United Kingdom; cDepartment of Psychiatry, Sheba Medical Center, Tel-Hashomer, 52621 Ramat Gan, Israel; and dDepartment of Mental Health, Israel Medical Corps, 01259 Tel-Hashomer, Israel

Edited by Daniel J. Benjamin, University of Southern California, Los Angeles, CA, and accepted by the Editorial Board November 13, 2015 (received for review April 24, 2015)

Intellectual disability (ID) occurs in almost 3% of newborns. Despite substantial research, a fundamental question about its origin and links to intelligence (IQ) still remains. ID has been shown to be inherited and has been accepted as the extreme low of the normal IQ distribution. However, ID displays a complex pattern of inheritance. Previously, noninherited rare mutations were shown to contribute to severe ID risk in individuals, but in the majority of cases causes remain unknown. Common variants associated with ID risk in the population have not been systematically established. Here we evaluate the hypothesis, originally proposed almost 1 century ago, that most ID is caused by the same genetic and environmental influences responsible for the normal distribution of IQ, but that severe ID is not. We studied more than 1,000,000 sibling pairs and 9,000 twin pairs assessed for IQ and for the presence of ID. We evaluated whether genetic and environmental influences at the extremes of the distribution are different from those operating in the normal range. Here we show that factors influencing mild ID (lowest 3% of IQ distribution) were similar to those influencing IQ in the normal range. In contrast, the factors influencing severe ID (lowest 0.5% of IQ distribution) differ from those influencing mild ID or IQ scores in the normal range. Taken together, our results suggest that most severe ID is a distinct condition, qualitatively different from the preponderance of ID, which, in turn, represents the low extreme of the normal distribution of intelligence.

Intelligence | twins | heritability | intellectual disability | family study

Here, we tested both components of this hypothesis using data from cognitive assessments administered as part of compulsory military service in Sweden 1968–2010 (3 million 18-y-old males) and in Israel 1960–2005 (2.1 million 17-y-old males and females) with 98% male participation in both countries. Diagnoses of severe ID were also available in both countries based on the International Classification of Disease (ICD) (9). From these resources, we identified 400,426 non-twin pairs of brothers and 8,788 male twin pairs from Swedish conscripts and 610,391 sibling pairs of both sexes from Israeli conscripts. From patient records, we identified whether these individuals had a sibling with a diagnosis of severe ID.

From the two cohorts assessed for mandatory military conscription, those who received the lowest possible score (IQ stanine score of 1), and were therefore placed in the bottom 3% (i.e., mild ID) of the distribution, were selected and their siblings compared with the rest of the distribution using IQ as a quantitative trait measure. Importantly, this was repeated for the siblings of individuals diagnosed with severe ID. This study design, combined with DF extremes analysis, a technique named after its developers DeFries and Fulker (10), allows examination of the fundamental issue of the etiologic links between the abnormal and normal. That is, to what extent are the causes of disorders qualitatively different from the influences on normal variation? Specifically, is ID merely the lower tail of the distribution for the same genetic and environmental

Significance

Intellectual disability (ID) is present in almost 3% of children and fundamentally characterized by IQ scores below 70. Genetic research has shown that it is among the most heritable traits, and it has been accepted that ID is the extreme low of the normal IQ distribution. However, we show that, while the genetic and environmental factors influencing mild ID (lowest 3% of IQ distribution) are similar to those influencing IQ in the normal range, factors influencing severe ID (lowest 0.5%) differ from those influencing mild ID or IQ scores in the normal range. Therefore, severe ID is a distinct disorder, qualitatively different from the majority of ID, which in turn represents the low extreme of the normal distribution of intelligence.

Author contributions: A.R., R.P., and P.L. designed research; A.R. performed research; A.R., M.C., A.M., M.T., O.K., M.W., and H.L. analyzed data; M.T., E.F., K.G., M.W., M.D., and H.L. contributed to revisions of the paper; E.F., M.D., and M.W. obtained data, administrative approvals, and revisions of the manuscript; R.P. obtained funding; and A.R., M.C., E.F., K.G., M.D., M.W., H.L., R.P., and P.L. wrote the paper.

The authors declare no conflict of interest.

This article is a PNAS Direct Submission. D.J.B. is a guest editor invited by the Editorial Board.

Freely available online through the PNAS open access option.

1To whom correspondence should be addressed. Email: avi.reichenberg@msm.edu.

This article contains supporting information online at www.pnas.org/lookup/suppl/doi:10.1073/pnas.1508093112/-/DCSupplemental.

Edited by Daniel J. Benjamin, University of Southern California, Los Angeles, CA, and accepted by the Editorial Board November 13, 2015 (received for review April 24, 2015)

Intellectual disability (ID) occurs in almost 3% of newborns. Despite substantial research, a fundamental question about its origin and links to intelligence (IQ) still remains. ID has been shown to be inherited and has been accepted as the extreme low of the normal IQ distribution. However, ID displays a complex pattern of inheritance. Previously, noninherited rare mutations were shown to contribute to severe ID risk in individual families, but in the majority of cases causes remain unknown. Common variants associated with ID risk in the population have not been systematically established. Here we evaluate the hypothesis, originally proposed almost 1 century ago, that most ID is caused by the same genetic and environmental influences responsible for the normal distribution of IQ, but that severe ID is not. We studied more than 1,000,000 sibling pairs and 9,000 twin pairs assessed for IQ and for the presence of ID. We evaluated whether genetic and environmental influences at the extremes of the distribution are different from those operating in the normal range. Here we show that factors influencing mild ID (lowest 3% of IQ distribution) were similar to those influencing IQ in the normal range. In contrast, the factors influencing severe ID (lowest 0.5% of IQ distribution) differ from those influencing mild ID or IQ scores in the normal range. Taken together, our results suggest that most severe ID is a distinct condition, qualitatively different from the preponderance of ID, which, in turn, represents the low extreme of the normal distribution of intelligence.
Mild ID (lowest possible IQ stanine scale score of 1 equals lowest 3% IQ scores) is familial. Siblings of persons with mild ID have significantly and substantially lower IQs than the population. (A) Swedish results for male siblings of persons with IQ stanine score of 1 (mean = 3.31, SD = 1.80, n = 12,431 male pairs) and for the entire sibling population (mean = 5.10, SD = 1.95, n = 382,122 pairs). (B) Israeli results for male siblings of persons with IQ stanine score of 1 (mean = 3.36, SD = 2.46, n = 6,800 male pairs) and for the entire sibling population (mean = 5.49, SD = 1.94, n = 239,117 pairs). Note: individuals with severe ID are not included in the stanine IQ score distributions presented.

Factors that affect individual differences throughout the normal range of variation in IQ? Indeed, individuals with the lowest IQ could reflect a mixture of those at the lower tail of the population distribution, as well as those whose low performance represents a qualitatively different impairment. This fundamental question has not been directly tested before.

Results
In both countries, results strongly supported the hypothesis that most ID is the lowest end of the normal distribution of IQ, but severe ID is etiologically distinct. As shown in Fig. 1, mild ID (the lowest 3% IQ scores; lowest possible IQ stanine score of 1) is highly familial. Siblings of persons with mild ID have an IQ distribution shifted sharply to the left of the population with a mean (IQ stanine score of 3) halfway between mild ID and the total sibling population average (IQ stanine score of 5).

Application of DF extremes analyses (Materials and Methods) to these data showed a significant estimate of 0.43 for Sweden [95% confidence interval (CI): 0.40–0.46] and of 0.47 for Israel (95% CI: 0.41–0.53) for group-differences familiality for male siblings, indicating that about half of the difference between mild ID and average IQ is familial in origin. This is called “group-differences familiality” to distinguish it from the usual estimate of familiality, which refers to differences among individuals, rather than to mean differences between an extreme group and the population.

Familial effects could be due to genetic or shared environmental factors (i.e., nongenetic factors that make twins similar, such as socioeconomic background or similar in-utero environment). The twin data in Fig. 2 show that this familial effect for mild ID is largely genetic in origin. The results for dizygotic (DZ) co-twins (mean = 2.78) in Fig. 2 are highly similar to those for non-twin siblings in Fig. 1 and much lower than the population [mean = 13.19, P < 0.0000001]. In contrast, monozygotic (MZ) co-twins (mean = 1.96) have much lower IQs than DZ co-twins [mean = 3.88, P = 0.00013]. In other words, MZ co-twins regress only 0.96 points to the sample mean, whereas same-sex DZ co-twins regress 1.78 points, suggesting that genetics contribute substantially to the mean difference between the probands and the population. Applying the DF extremes analysis (Materials and Methods) to these data yields a significant estimate of 0.46 (95% CI: 0.32–0.60) for group-differences heritability, indicating that a large proportion of the mean difference between the probands and the population can be ascribed to genetic factors.

The estimate of group shared environment is 0.30 (95% CI: 0.19–0.41) for same-sex twins, suggesting that about one-third of the mean difference between the probands and the population may be due to environmental factors involved in growing up in the same environment. The remaining 24% (95% CI: 0.18–0.29) of the difference is due to error of measurement and nonshared environmental influences.

Twin analyses of individual differences in the entire sample yielded similar results, which suggests that the factors influencing the lowest 3% of IQ scores are similar to those influencing IQ in the normal range. For the entire sample, intraclass correlations were 0.83 for MZ twins (n = 3,039 pairs) and 0.57 for same-sex DZ twins (n = 3,196 pairs). Model-fitting analysis (Materials and Methods) for the unselected sample of twins yields an individual differences heritability estimate of 0.55 (95% CI: 0.39–0.72) for same-sex twins. In other words, about half of the variance in IQ scores throughout the entire distribution can be attributed to genetic factors. Shared environment accounts for 28% (95% CI:...
0.13–0.43) of the individual differences in IQ scores, and error of measurement and nonshared environment accounts for an additional 16% (95% CI: 0.13–0.21).

Fig. 3 shows strikingly different results for siblings of individuals with severe ID. In both countries, these individuals had normal IQ scores indistinguishable from the population distribution. Application of DF extremes analyses (Materials and Methods) to these data estimated group-differences familiality to be negligible (upper limit estimate: −0.01 for Sweden and 0.13 for Israel). Comparison with the results above supports the hypothesis that the factors influencing severe ID differ from those influencing mild ID or IQ scores in the normal range.

We examined the effects of sex as a moderator of the group-differences familiality estimates. The Israeli data (available for both male and females) yielded similar results for male, female, and opposite-sex sibling pairs (Figs. S1 and S2). These findings suggest that sex does not importantly affect estimates of group-differences familiality. The proportion of men drafted to the military in Sweden fell sharply during the 1990s (following the end of the Cold War). As the draft data may therefore be less representative for recent cohorts, we conducted a sensitivity analysis stratifying analyses by the year conscription procedure took place (before or after 2000). The results of the group-differences familiality were similar for those undergoing the conscription procedure before or after the year 2000 (Figs. S3 and S4).

**Discussion**

In summary, probands with mild ID had siblings with IQ scores that were intermediate between probands and controls. Group-differences familiality was 43–47% and the group-differences heritability estimate was 46% with a shared environment estimate of 30%. Individual-differences heritability and shared environment estimates were similar: 55% and 28%, respectively. In contrast, probands with severe ID had siblings with normal-average IQ scores, and group-differences familiality was negligible. To our knowledge this is the first time that significant differences in group-differences familiality between mild and severe ID have been demonstrated. The results provide the strongest evidence supporting the hypothesis that most ID is caused by the same genetic and environmental influences responsible for the normal distribution of IQ, but that severe ID is not. Using large population-based samples with virtually complete ascertainment protects against bias and enhances generalizability, thus enabling a rigorous test of the hypothesis.

Modern behavioral genetic research and recent molecular genetic studies have shown that common traits are caused by many genes [e.g., educational attainment (4, 11)]. The results presented here also support the position that common disorders are the quantitative extreme of the normal distribution (12). Therefore, similar to IQ, mild ID is caused by many genes of small effect (4). However, the findings of this study highlight a different model for rare, severe disorders. Rare and severe disorders may be etiologically distinct from the rest of the distribution. Results of a recent study on height also support such a hypothesis. Applying both molecular and behavioral genetic methods, it was demonstrated that common genetic variants associated with height in the general population were similarly associated with height at the top and bottom tails of the height distribution. However, height in individuals with extreme short stature (bottom 0.25 percentile) was less determined by common variants (13).

One possible mechanism for noninherited severe ID could involve de novo point mutations. Such mutations can occur in the germ line during embryogenesis or somatically (14). Molecular genetic studies reported associations between rare de novo point mutations and severe ID (5, 15), but more research is needed to prove the causal role of such mutations and what portion of severe ID they account for. Imprinting may also be involved. Imprinting is a form of gene regulation in which gene expression depends on whether the allele was inherited from the male or female parent. When imprinted genes are paternally expressed, the maternal genes are reciprocally silenced and the contrary is true for maternally expressed genes (16). One of the mechanisms for gene silencing is DNA methylation (17). Genetic imprinting has been associated with severe ID (17, 18). Although our understanding of genetic imprinting is nascent, it merits consideration in severe ID.

These hypothesized mechanisms for severe ID are genomically, although not inherited. It is important to keep in mind, however, that environmental factors could also cause severe ID. Several environmental factors have been associated with severe ID. Multiple studies documented hypoxia around birth as potentially causal for severe ID, and the association was confirmed in a recent meta-analysis (19). Maternal infections during pregnancy (e.g., rubella) have been associated with severe ID in the offspring (20), as well as exposure to environmental toxins (e.g., lead) during pregnancy or after birth (21–23). Another group of potential environmental risks comprises conditions in pregnancy and birth (e.g., diabetes, preterm birth, and growth restriction) (24). These have multiple potential etiologies, and their causal role in severe ID requires further research. Conditions in pregnancy and birth have also been associated with IQ and
mild ID (25). When considering environmental factors, timing of exposure could be of critical importance. There are periods in brain development during which the nervous system is especially sensitive to certain environmental exposures (26, 27). Detrimental effects of environmental factors may therefore depend on timing and/or dose of exposure. For example, maternal nutrition before or early in pregnancy, but not later in pregnancy, was associated with language development (28). Maternal viral infections can interfere with neurodevelopment and the earlier in pregnancy they occur, the more severe their effect. Adverse consequences of maternal rubella were present when infection occurred early, but not in mid-pregnancy (29). In SI Materials and Methods and Table S1 we explored this hypothesis and examined the relationship between birth variables representing environmental events of early and late gestation and mild and severe ID. Although we observed a stronger relationship between the birth variables and severe ID than that between the birth variables and mild ID, the relationship was particularly strong for adverse events happening around birth (Table S1), providing preliminary evidence for the potential importance of timing of environmental effects in causing severe ID.

Further research is needed to test the hypotheses about potential mechanisms of severe ID. Here we identified several future directions for research, but interpretation of our data has some limitations. First, we were not able to use the twin data to examine severe ID because the number of twin pairs with severe ID and information on zygosity was very low. Replication in other cohorts is important, particularly in samples including sufficient numbers of twins with severe ID. Larger samples could also help test the specific hypotheses about the role of de novo mutations and environmental factors in severe ID. A germ line de novo mutation is identical for MZ twins, but not for DZ twins or siblings. Therefore, the de novo hypothesis does not negate high MZ twin concordance for severe ID.

Second, data on diagnosis of ID and data on IQ scores come from different sources. The former is based on diagnoses in childhood by health services, whereas the latter is derived from the IQ testing by the military. However, the diagnosis of ID has been shown to be reliable and is carried out by well-trained diagnostic teams.

Third, because the IQ data used were collected for military placement, some individuals may have an incentive to underperform, thus leading to measurement errors that depend on true IQ. Moreover, intentional underperforming may have a shared environmental component that could confound the relationship between the birth variables and severe ID. However, some individuals may have an incentive to underperform, whereas the latter is derived from the IQ testing by the military. Although the diagnosis of ID has been shown to be reliable and is carried out by well-trained diagnostic teams.

We conclude that the most severe form of ID is a distinct disorder, the etiology of which is qualitatively different from mild ID. Despite the well-known single-gene causes of severe ID, most severe ID is caused by idiosyncratic factors not related to inherited influences on intelligence. In contrast, mild ID represents the low genetic extreme of the normal distribution of intelligence, which supports the proposition that common disorders represent the extremes of quantitative traits (11, 12). Thus, most ID is likely to be caused by the same genetic factors responsible for the rest of the distribution of intelligence so genes found to be associated with intelligence will also be associated with ID other than severe ID.

Materials and Methods

This study was approved by the regional ethics committee at the Karolinska Institutet, Stockholm, and by the ethics committee of the Sheba Medical Center, Tel Hashomer, Israel. Because the study used existing databases and analytic datasets were deidentified, it received a waiver of informed consent from human subjects.

Samples

Swedish cohorts. Data came through linkage of population-based registers in Sweden that use unique personal identification numbers assigned to each Swedish citizen at birth or upon arrival in Sweden as immigrants, enabling accurate linkage:

- A total of 3,095,168 men who were eligible for conscription at age 18 to the Swedish military between January 1968 and December 2012 were identified through the Multi-Generation Register (MGR), which includes information on all individuals in Sweden born from January 1932 onward who were alive and residing in Sweden on January 1960 or later (36). Conscription is mandatory for men. Only men with a severe handicap or a chronic disease were exempt (35, 37).

The conscription procedure consists of a series of tests of physical and mental health status and personality and intellectual capacity. The IQ test consists of the following four subtests—verbal comprehension; spatial ability; problem solving, reasoning, and mathematical and general knowledge; and technical and physical problem solving (35, 37)—and was validated against standard measures of intelligence (30). The IQ score was standardized against the entire population to follow a Gaussian distribution between 1 and 9 with a mean of 5 (SD = 2). We obtained data on IQ at age 18 from the conscription database.

We identified 598 men within the cohort who were exempt from conscription with at least one diagnosis of severe intellectual disability (as defined by code 313–314 in the International Classification of Diseases, 8th Revision (ICD-8); code 318.1–318.2 in ICD-9; and code F72-F73 in ICD-10) in the National Patient Register in Sweden. The National Patient Register contains diagnostic information on all those with psychiatric hospitalizations since 1973 and outpatient diagnoses since 1993. The hospital discharge data are cause-specific descriptions of specific diagnoses (see ref. 38 for details). All infants and preschool children are regularly seen at well-child care clinics and undergo routine medical and developmental screening. In Sweden, all children aged 4 undergo routine general health screening, which includes mandatory developmental assessment (motor, language, cognitive, and social development) conducted by a nurse and pediatrician. Children with additional developmental disabilities (including intellectual disability) are referred for further assessment by a specialized team in a child psychiatry unit or habilitation service. During the study period, diagnoses were made by diagnostic teams with a psychiatrist, clinical psychologist, and speech therapist or occupational therapist, depending on clinical manifestations. For a diagnosis of intellectual disability the evaluation is made by a psychologist according to standardized tests with high reliability.

Among eligible men included in the MGR, male full siblings were identified using family relationship information recorded in the registry. To minimize potential differences in the family environment, pairs of male siblings born closest to each other were included. Each family contributed only one sibling pair to the analysis. In total, 381,622 male–male sibling pairs were identified in this manner. A total of 400 sibling pairs were discordant for intellectual disability (i.e., had one sibling with a diagnosis of severe intellectual disability and one without).

Twins were identified as two male siblings recorded as being born on the same day. Zygosity was identified by linkage to the Swedish Twin Registry (39, 40). A full description of zygosity assignments was previously published (40). In total, 3,039 MZ male twin pairs and 3,196 DZ male twin pairs were identified in this manner.

Israel cohort. Data came from the Israeli military Draft Board Registry (DBR), which includes information on the unselected Israeli Jewish population of adolescents aged 17 y. The Draft Board mandatory assessment determines intellectual, medical, and psychiatric eligibility for compulsory military service. The population assessed by the draft board therefore includes
individuals who would be eligible for military service, as well as those who will be exempt owing to medical, psychiatric, or social reasons. A total of 2,600 probands and 2,551 matched sex-matched, non-institutionalized, non-disabled male siblings were recruited to the DBR. IQ tests consist of the following four subtests: an Otis-type verbal intelligence test; a verbal reasoning test; a nonverbal reasoning test similar to the Raven’s Progressive Matrices; and a mathematical knowledge test (31, 34, 41). The tests are progressive, beginning with relatively simple questions and becoming more difficult. The tests are group-administered and time-limited. All of the scores are based on the number of correct answers. The IQ score is standardized against population norms and follows a Gaussian distribution between 1 and 9 with a mean of 5.4 (SD = 1.95). The sum of the scores for the four tests forms a validated measure of general intelligence (IQ) (31, 34). The correlation between the draft board scale and the Wechsler IQ scale was 0.79 (32).

During the time covered by this study the draft board assigned diagnoses based on the International Classification of Diseases, 8th Revision (ICD-8), 9th Revision (ICD-9), and 10th Revision (ICD-10). Psychiatric diagnoses are assigned by a board-certified psychiatrist experienced in treating adolescents. The standard procedure for psychiatric diagnosis includes a face-to-face assessment described in detail elsewhere (42). For individuals with developmental disabilities (including intellectual disability) the standard procedure is modified. At age 17 y, their medical status is reported in detail to the draft board by government agencies and other organizations responsible for their care and protection. Such reports include a diagnosis according to the original childhood diagnosis and subsequent clinical history up to age 17 y are also commonly reported. The draft board generally assigns a diagnosis based on review of these materials rather than a face-to-face assessment (43).

Among eligible men included in the DBR, full siblings were identified using family relationship information recorded in the registry (44). This information is based on the unique personal identification number assigned to each Israeli citizen at birth or upon immigration. To minimize potential differences in the family environment, pairs of male siblings born closest to each other were included. Each family contributed only one sibling pair to the analysis. In total, 246,214 male–male sibling pairs were identified in this manner. A total of 297 sibling pairs were discordant for intellectual disability (i.e., had one sibling with a diagnosis of severe intellectual disability and one without).

A total of 120,973 female–female sibling pairs and 250,301 opposite-sex sibling pairs were identified using family relationship information. The proportion of female–female pairs is lower because orthodox Jewish women (about 25% of women) are exempt from military induction and data on females assessed by the Draft Board is maintained for only 25 y.

Statistical Analysis

Descriptive statistics. Descriptive statistics, including distribution of IQ scores and means, were computed. Differences between unselected co-siblings and control siblings were compared using Analysis of Covariance models adjusting for year of birth. A sibling’s individual-differences facetality was computed using a intraclass correlation coefficient. P values were set at 0.05 (two-tailed).

Individual and group familiality. Quantitative genetics offers an approach to the issue of the relation between the etiology of the mean of selected groups (such as IQ) and the etiology of individual differences throughout the population. This approach, developed by DeFries and colleagues for samples based on the unique personal identification number assigned to each Israeli citizen at birth or upon immigration. To minimize potential differences in the family environment, pairs of male siblings born closest to each other were included. Each family contributed only one sibling pair to the analysis. In total, 246,214 male–male sibling pairs were identified in this manner. A total of 297 sibling pairs were discordant for intellectual disability (i.e., had one sibling with a diagnosis of severe intellectual disability and one without).

A total of 120,973 female–female sibling pairs and 250,301 opposite-sex sibling pairs were identified using family relationship information. The proportion of female–female pairs is lower because orthodox Jewish women (about 25% of women) are exempt from military induction and data on females assessed by the Draft Board is maintained for only 25 y.

Statistical Analysis

Descriptive statistics. Descriptive statistics, including distribution of IQ scores and means, were computed. Differences between unselected co-siblings and control siblings were compared using Analysis of Covariance models adjusting for year of birth. A sibling’s individual-differences facetality was computed using a intraclass correlation coefficient. P values were set at 0.05 (two-tailed).

Individual and group familiality. Quantitative genetics offers an approach to the issue of the relation between the etiology of the mean of selected groups (such as IQ) and the etiology of individual differences throughout the population. This approach, developed by DeFries and colleagues for samples based on the unique personal identification number assigned to each Israeli citizen at birth or upon immigration. To minimize potential differences in the family environment, pairs of male siblings born closest to each other were included. Each family contributed only one sibling pair to the analysis. In total, 246,214 male–male sibling pairs were identified in this manner. A total of 297 sibling pairs were discordant for intellectual disability (i.e., had one sibling with a diagnosis of severe intellectual disability and one without).

A total of 120,973 female–female sibling pairs and 250,301 opposite-sex sibling pairs were identified using family relationship information. The proportion of female–female pairs is lower because orthodox Jewish women (about 25% of women) are exempt from military induction and data on females assessed by the Draft Board is maintained for only 25 y.