

# Common genetic variants contribute to risk of rare severe neurodevelopmental disorders

Mari E. K. Niemi<sup>1</sup>, Hilary C. Martin<sup>1</sup>, Daniel L. Rice<sup>1</sup>, Giuseppe Gallone<sup>1</sup>, Scott Gordon<sup>2</sup>, Martin Kelemen<sup>1</sup>, Kerrie McAloney<sup>2</sup>, Jeremy McRae<sup>1</sup>, Elizabeth J. Radford<sup>1,3</sup>, Sui Yu<sup>4</sup>, Jozef Gecz<sup>5,6</sup>, Nicholas G. Martin<sup>2</sup>, Caroline F. Wright<sup>7</sup>, David R. Fitzpatrick<sup>8</sup>, Helen V. Firth<sup>1,9</sup>, Matthew E. Hurles<sup>1</sup> & Jeffrey C. Barrett<sup>1\*</sup>

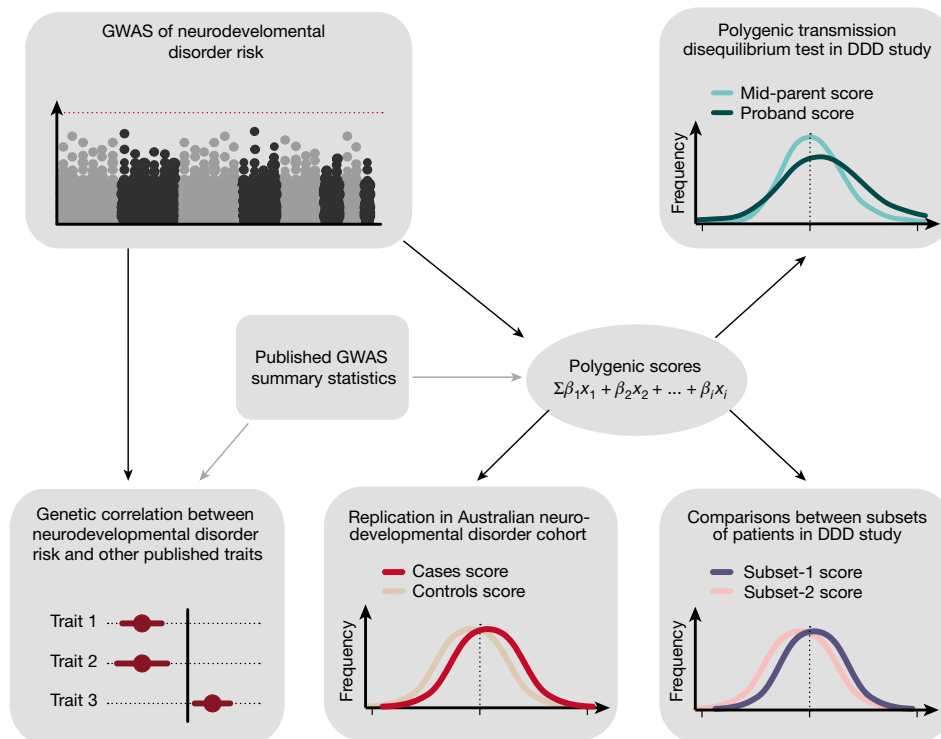
**There are thousands of rare human disorders that are caused by single deleterious, protein-coding genetic variants<sup>1</sup>. However, patients with the same genetic defect can have different clinical presentations<sup>2–4</sup>, and some individuals who carry known disease-causing variants can appear unaffected<sup>5</sup>. Here, to understand what explains these differences, we study a cohort of 6,987 children assessed by clinical geneticists to have severe neurodevelopmental disorders such as global developmental delay and autism, often in combination with abnormalities of other organ systems. Although the genetic causes of these neurodevelopmental disorders are expected to be almost entirely monogenic, we show that 7.7% of variance in risk is attributable to inherited common genetic variation. We replicated this genome-wide common variant burden by showing, in an independent sample of 728 trios (comprising a child plus both parents) from the same cohort, that this burden is over-transmitted from parents to children with neurodevelopmental disorders. Our common-variant signal is significantly positively correlated with genetic predisposition to lower educational attainment, decreased intelligence and risk of schizophrenia. We found that common-variant risk was not significantly different between individuals with and without a known protein-coding diagnostic variant, which suggests that common-variant risk affects patients both with and without a monogenic diagnosis. In addition, previously published common-variant scores for autism, height, birth weight and intracranial volume were all correlated with these traits within our cohort, which suggests that phenotypic expression in individuals with monogenic disorders is affected by the same variants as in the general population. Our results demonstrate that common genetic variation affects both overall risk and clinical presentation in neurodevelopmental disorders that are typically considered to be monogenic.**

We carried out a genome-wide association study (GWAS) in 6,987 patients with severe neurodevelopmental disorders and 9,270 ancestry-matched controls, using common variants with a minor allele frequency  $\geq 5\%$  (Fig. 1, Extended Data Fig. 1, Supplementary Tables 1, 2 and Methods). The patients were recruited by senior clinical geneticists in the UK and Ireland as part of the Deciphering Developmental Disorders (DDD) study<sup>6,7</sup>. They all had at least one abnormality that affects the morphology or physiology of the central nervous system, and to be recruited to the study their clinical features were sufficiently severe that their disorder was thought likely to be monogenic. In addition to neurodevelopmental defects—for example, global developmental delay, intellectual disability, cognitive impairment or learning disabilities in 86% of the cohort, and autism spectrum disorders in 16% of the cohort (Fig. 2a)—88% of the recruited patients also had abnormalities in at least one other organ system (Fig. 2b and Extended Data Table 1).

We did not find any single-variant associations at genome-wide significance (Extended Data Fig. 2a), which was unsurprising given the heterogeneity of our clinical phenotype and the presumption that these disorders are monogenic. We did, however, observe a modest inflation in the test statistics ( $\lambda = 1.097$ , Extended Data Fig. 2b), which could indicate either residual bias between cases and controls or a polygenic contribution of common variants to disease risk. We therefore estimated common-variant heritability using linkage-disequilibrium score (LD score) regression<sup>8</sup>, which can differentiate between these two possibilities, and found that 7.7% (standard error (s.e.) = 2.1%) of variance in risk (on the liability scale) for neurodevelopmental disorders in our sample was attributable to common genetic variants, when assuming a population prevalence of 1% (Methods). This common variant heritability estimate ( $h^2$ ) is similar to that which has been reported for common disorders such as autism ( $h^2 = 11.8\%$ , s.e. = 1.0%)<sup>9</sup> and major depressive disorder ( $h^2 = 8.9\%$ , s.e. = 0.4%)<sup>10</sup>. To replicate this signal, we analysed an independent set of 728 trios recruited as part of the same study, but who were not in the initial GWAS. We calculated polygenic scores for each individual by summing the genetic effects across all independent variants from our discovery GWAS (Fig. 1 and Methods). We then performed a polygenic transmission disequilibrium test<sup>11</sup>, which compares the mean parental polygenic scores to those of the affected children. We found that our neurodevelopmental disorder risk score was over-transmitted in these trios ( $P = 0.0035$ ,  $t = 2.48$ , degrees of freedom = 727, one-sided  $t$ -test), which confirms that common variants contribute to risk of disorders widely presumed to be monogenic.

Previous studies have shown that the risk of more common neuropsychiatric disorders—for example, schizophrenia and bipolar disorder<sup>12,13</sup>—and variation in other brain-related traits, including educational attainment<sup>13</sup>, is driven in part by shared common genetic effects. We therefore used the LD score method<sup>14</sup> to test for genetic correlation between our GWAS of neurodevelopmental disorders and available GWAS data for common neuropsychiatric disorders, cognitive and educational traits and anthropometric traits, as well as negative-control diseases that have well-powered GWAS but are not related to neurodevelopment. We found that genetic risk for neurodevelopmental disorders was significantly negatively correlated with genetic predisposition (as measured by Spearman's  $\rho$ ) to higher educational attainment<sup>15</sup> ( $r_g = -0.49$ , s.e. = 0.08,  $P = 5.3 \times 10^{-10}$ ) and intelligence<sup>16</sup> ( $r_g = -0.44$ , s.e. = 0.10,  $P = 2.2 \times 10^{-5}$ ), and positively correlated with genetic risk of schizophrenia ( $r_g = 0.28$ , s.e. = 0.07,  $P = 2.7 \times 10^{-5}$ ) (Fig. 3 and Extended Data Table 2). None of the anthropometric or negative-control traits were significantly genetically correlated with our data, after accounting for multiple testing. We also used partitioned LD score regression<sup>17</sup> to show that heritability of neurodevelopmental disorders was nominally significantly enriched

<sup>1</sup>Wellcome Sanger Institute, Wellcome Genome Campus, Hinxton, UK. <sup>2</sup>QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia. <sup>3</sup>Department of Paediatrics, University of Cambridge, Cambridge, UK. <sup>4</sup>Department of Genetics and Molecular Pathology, SA Pathology, Women's and Children's Hospital, Adelaide, South Australia, Australia. <sup>5</sup>Adelaide Medical School and Robinson Research Institute, Faculty of Health and Medical Sciences, University of Adelaide, Adelaide, South Australia, Australia. <sup>6</sup>South Australian Health and Medical Research Institute, Adelaide, South Australia, Australia. <sup>7</sup>University of Exeter Medical School, Institute of Biomedical and Clinical Science, RILD, Royal Devon & Exeter Hospital, Exeter, UK. <sup>8</sup>MRC Human Genetics Unit, MRC IGMM, University of Edinburgh, Western General Hospital, Edinburgh, UK. <sup>9</sup>Department of Clinical Genetics, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK. \*e-mail: jeff.barrett@genomicsplc.com



**Fig. 1 | Outline of analysis exploring the contribution of common variants to risk of severe neurodevelopmental disorders.** We first conducted a discovery GWAS in a large dataset of patients with neurodevelopmental disorders, and replicated the common-variant contribution by analysing polygenic transmission in independent trios from the same cohort. Next, we looked for overlap of common-variant

effects between neurodevelopmental disorder risk and other published GWAS, and replicated these findings in an independent Australian cohort. Finally, we explored how polygenic effects were distributed within our discovery cohort of patients, and whether common variants contributed to expressivity of specific phenotypes.

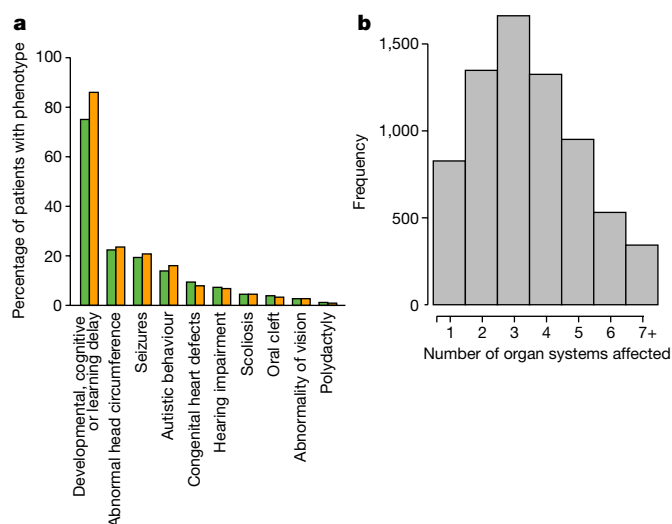
in cells of the central nervous system ( $P = 0.02$ ), and in mammalian constrained regions<sup>18</sup> ( $P = 0.009$ ) (Supplementary Table 2), consistent with similar analyses for other neuropsychiatric and cognitive traits. Together, these results suggest that thousands of common variants have individually small effects on brain development or function, which in turn influences neuropsychiatric disease risk, cognitive traits and risk for severe neurodevelopmental disorders.

We next investigated how general our genetic correlation findings were by attempting to replicate them in another cohort of patients with neurodevelopmental disorders (Fig. 1). We obtained GWAS data for 1,270 neurodevelopmental disorder cases from Australia, and 1,688 ancestry-matched Australian controls. This sample size is too small to do direct genetic discovery or to reliably apply LD score regression, so we tested common-variant polygenic scores using summary statistics from our discovery GWAS and published GWAS, including educational attainment<sup>15</sup> and intelligence<sup>16</sup>. This approach requires specification of  $P$ -value thresholds and is less robust to population structure and cryptic relatedness, but it produced similar results to the genetic correlation analyses in our discovery GWAS and we therefore believe it is well-suited to a replication analysis. We replicated our observation of lower polygenic scores for educational attainment and intelligence in neurodevelopmental disorder cases from Australia, as compared to controls ( $P = 1.0 \times 10^{-8}$  and  $P = 7.6 \times 10^{-4}$  for educational attainment and intelligence, respectively), and found that cases had a nominally significantly increased score for schizophrenia ( $P = 0.014$ ) (Methods and Extended Data Table 3). We did not see a significant difference between Australian cases and controls for the score constructed from our own discovery GWAS. If the two cohorts had identical phenotypes, we should have had 95% power (Methods) to detect a difference; this suggests that differences in how the British and Australian cohorts were recruited diluted our ability to quantify their shared genetics.

These findings could mean that common variants entirely explain a subset of patients with neurodevelopmental disorders and are not

relevant in the remainder, or that the disorders of all patients have both rare- and common-variant contributions (Fig. 1). We have exome-sequenced our cohort of patients as well as their parents, and have previously reported a variety of both de novo and inherited diagnostic variants<sup>19,20</sup>. We therefore compared polygenic scores for cognitive traits and neuropsychiatric disorders between patients for whom we had identified diagnostic or probably diagnostic variants in a known developmental-disorder gene<sup>21</sup> ( $n = 1,127$ ) and those who had no candidate diagnostic variant ( $n = 2,479$ ), and found no significant differences for any polygenic score that we tested, after controlling for multiple testing (Extended Data Table 4 and Methods). We showed by simulations that if the ‘diagnosed’ cases had the same distribution of the polygenic score for educational attainment as did controls, we would have had sufficient power to detect a difference between them and the undiagnosed cases (Methods). This is consistent with a previous study in autism<sup>11</sup> that similarly found no evidence for a difference in polygenic risk scores between autism cases with a de novo diagnostic mutation compared to those without such a mutation. This suggests that in many patients both common and rare variants contribute to their neurodevelopmental disorder. However, as the DDD project continues to identify new diagnoses, we anticipate that the increase in power may show that monogenic and polygenic contributions are not purely additive.

In addition to showing that common variation affects overall risk of severe neurodevelopmental disorders, we sought to determine whether it can also affect individual presentation of symptoms. We identified four phenotypes measured in our neurodevelopmental disorder cohort for which independent GWAS data are available: autism (16% of the cohort), birth weight, height and intracranial volume. Compared to the age and sex-adjusted population average, our patients with neurodevelopmental disorders were—on average—0.72 s.d. shorter and weighed 0.15 s.d. less, and had a head circumference that was 1.20 s.d. smaller. We constructed common-variant polygenic scores for the four

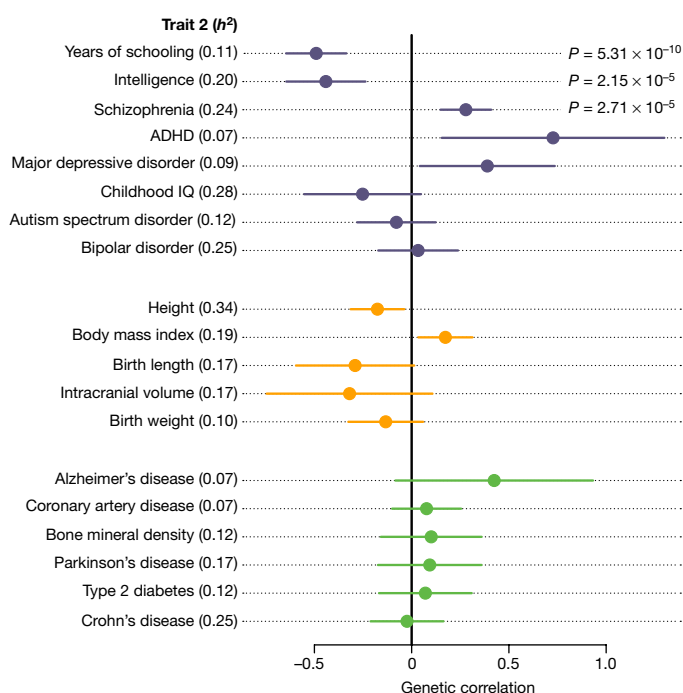


**Fig. 2 | Patients recruited to the DDD study have diverse phenotypes.**

**a**, Examples of specific phenotypes that affect different organ systems, observed in the full DDD cohort ( $n = 13,598$ ; green) and the subset of European patients with neurodevelopmental disorders ( $n = 6,987$ ; orange). **b**, Distribution of the number of distinct organ systems that were affected in the set of 6,987 patients with neurodevelopmental abnormalities (Methods).

phenotypes as described above, and tested for an association between the relevant score and phenotype in our cohort. In all four cases, there was significant association (Table 1 and Extended Data Table 5), which demonstrates that common variation contributes to the expression of these traits in our study. Consistent with previous reports<sup>9</sup>, we also found in our cohort that individuals with autism had higher polygenic scores for educational attainment compared to those without autism. We next tested for an association between the educational-attainment polygenic score and severity of the overall neurodevelopmental phenotype. We found that patients with severe intellectual disability or developmental delay ( $n = 911$ , Methods) had higher scores (that is, genetic predisposition to greater educational attainment; a proxy for higher cognitive function,  $P = 0.004$ , Table 1) than those with mild or moderate disability or delay ( $n = 1,902$ ). This finding—which might seem initially counter-intuitive—is consistent with epidemiological studies<sup>22</sup> that have found that the siblings of patients with severe intellectual disability showed a normal distribution of IQ, whereas the siblings of patients with milder intellectual disability had lower IQ than average, which suggests that mild intellectual disability represents the tail-end of the distribution of polygenic effects on intelligence and severe intellectual disability has a different aetiology.

The study of human disease genetics has often been segregated into rare, single-gene disorders and common, complex disorders. There is abundant evidence that rare variants in individual genes can cause phenotypes that are seen much more commonly in individuals without



**Fig. 3 | Genetic correlations between neurodevelopmental disorder risk (6,987 cases and 9,270 controls) against nineteen other traits.** Cognitive or psychiatric (purple), anthropometric (orange) and negative-control traits (green), with single-nucleotide polymorphism (SNP) heritability ( $h^2$ ) displayed for the trait. SNP heritability for dichotomous traits is displayed on the liability scale. Genetic correlation was calculated using bivariate LD score correlation<sup>14</sup>, with the bars representing 95% confidence intervals (using standard error) before correction for multiple testing. Uncorrected  $P$  values are from a two-sided  $z$ -score, and are shown only if they pass Bonferroni correction for 19 traits. Sample sizes for 19 other GWAS are shown in Extended Data Table 2.

a monogenic cause, including genes for maturity onset diabetes of the young<sup>23</sup> and familial Parkinson's disease<sup>24</sup>. There is also emerging evidence that the cumulative effect of common variants can modify the penetrance of rare variants in complex phenotypes such as educational attainment<sup>25</sup>, schizophrenia<sup>26</sup> and breast cancer<sup>27</sup>. Here we have shown that the same interplay between rare and common variation exists even in severe neurodevelopmental disorders that are typically presumed to be monogenic. Previous studies have shown that the penetrance and expression of these disorders are affected by the specific missense variant that is carried<sup>28</sup> and the presence of mutations in secondary modifier genes<sup>29</sup>. Here we have demonstrated that phenotypic expression is also modified by common variants that influence neurodevelopmental traits in the general population. We analysed individuals of European ancestry—as do the vast majority of published GWAS—and, as the genetic architecture of neurodevelopmental disorders may differ

**Table 1 | Polygenic score analyses in the DDD study**

Measured trait	Polygenic score	Results <sup>a</sup>			
		$\beta$	s.e.	$P$ value	$R^2$
Birth weight ( $n = 6,496$ )	Birth weight	0.187	0.017	$2.55 \times 10^{-28}$	0.020
Height ( $n = 5,465$ )	Height	0.408	0.033	$1.18 \times 10^{-35}$	0.033
Head circumference ( $n = 6,074$ )	Intracranial volume	0.132	0.031	$1.79 \times 10^{-5}$	0.004
Autistic behaviour: affected ( $n = 1,121$ ), unaffected ( $n = 5,866$ )	Autism spectrum disorder	0.120	0.033	$2.53 \times 10^{-4}$	0.006 <sup>c</sup>
Developmental delay or intellectual disability: severe ( $n = 911$ ), mild or moderate ( $n = 1,902$ ) <sup>b</sup>	Educational attainment	0.116	0.040	0.004	0.008 <sup>c</sup>

<sup>a</sup>Linear or logistic regression of measured traits in the DDD study against the respective polygenic score, including ten ancestry principal components as covariates.  $P$  values are two-sided, from  $t$ -distribution (linear) and  $z$ -score distribution (logistic).

<sup>b</sup>Severe cases were labelled as 1 in the logistic regression.

<sup>c</sup>Nagelkerke  $R^2$ .

between populations<sup>20</sup>, further studies will be required to generalize our findings. Our findings suggest that fully understanding the genetic architecture of neurodevelopmental disorders will require considering the full spectrum of alleles, from those unique to an individual to those shared across continents.

## Online content

Any methods, additional references, Nature Research reporting summaries, source data, statements of data availability and associated accession codes are available at <https://doi.org/10.1038/s41586-018-0566-4>.

Received: 4 May 2018; Accepted: 4 September 2018;

Published online 26 September 2018.

- Boycott, K. M. et al. International cooperation to enable the diagnosis of all rare genetic diseases. *Am. J. Hum. Genet.* **100**, 695–705 (2017).
- Owen, C. I. et al. Extending the phenotype associated with the *CSNK2A1*-related Okur-Chung syndrome—a clinical study of 11 individuals. *Am. J. Med. Genet. A* **176**, 1108–1114 (2018).
- Singh, T. et al. Rare loss-of-function variants in *SETD1A* are associated with schizophrenia and developmental disorders. *Nat. Neurosci.* **19**, 571–577 (2016).
- Balasubramanian, M. et al. Delineating the phenotypic spectrum of Bainbridge-Ropers syndrome: 12 new patients with *de novo*, heterozygous, loss-of-function mutations in *ASXL3* and review of published literature. *J. Med. Genet.* **54**, 537–543 (2017).
- Minikel, E. V. et al. Quantifying prion disease penetrance using large population control cohorts. *Sci. Transl. Med.* **8**, 322ra9 (2016).
- Wright, C. F. et al. Genetic diagnosis of developmental disorders in the DDD study: a scalable analysis of genome-wide research data. *Lancet* **385**, 1305–1314 (2015).
- The Deciphering Developmental Disorders Study. Large-scale discovery of novel genetic causes of developmental disorders. *Nature* **519**, 223–228 (2015).
- Bulik-Sullivan, B. K. et al. LD score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nat. Genet.* **47**, 291–295 (2015).
- Grove, J. et al. Common risk variants identified in autism spectrum disorder. Preprint at <https://www.doi.org/10.1101/224774> (2017).
- Wray, N. R. et al. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *Nat. Genet.* **50**, 668–681 (2018).
- Weiner, D. J. et al. Polygenic transmission disequilibrium confirms that common and rare variation act additively to create risk for autism spectrum disorders. *Nat. Genet.* **49**, 978–985 (2017).
- The International Schizophrenia Consortium. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature* **460**, 748–752 (2009).
- The Brainstorm Consortium. Analysis of shared heritability in common disorders of the brain. *Science* **360**, eaap8757 (2018).
- Bulik-Sullivan, B. et al. An atlas of genetic correlations across human diseases and traits. *Nat. Genet.* **47**, 1236–1241 (2015).
- Lee, J. J. et al. Gene discovery and polygenic prediction from a genome-wide association study of educational attainment in 1.1 million individuals. *Nat. Genet.* **50**, 1112–1121 (2018).
- Sniekers, S. et al. Genome-wide association meta-analysis of 78,308 individuals identifies new loci and genes influencing human intelligence. *Nat. Genet.* **49**, 1107–1112 (2017).
- Finucane, H. K. et al. Partitioning heritability by functional annotation using genome-wide association summary statistics. *Nat. Genet.* **47**, 1228–1235 (2015).
- Lindblad-Toh, K. et al. A high-resolution map of human evolutionary constraint using 29 mammals. *Nature* **478**, 476–482 (2011).
- The Deciphering Developmental Disorders Study. Prevalence and architecture of *de novo* mutations in developmental disorders. *Nature* **542**, 433–438 (2017).
- Martin, H. C. et al. Quantifying the contribution of recessive coding variation to developmental disorders. Preprint available at <https://www.doi.org/10.1101/201533> (2017).
- Firth, H. V. et al. DECIPHER: database of chromosomal imbalance and phenotype in humans using Ensembl resources. *Am. J. Hum. Genet.* **84**, 524–533 (2009).
- Reichenberg, A. et al. Discontinuity in the genetic and environmental causes of the intellectual disability spectrum. *Proc. Natl Acad. Sci. USA* **113**, 1098–1103 (2016).
- Flannick, J., Johansson, S. & Njølstad, P. R. Common and rare forms of diabetes mellitus: towards a continuum of diabetes subtypes. *Nat. Rev. Endocrinol.* **12**, 394–406 (2016).
- Hernandez, D. G., Reed, X. & Singleton, A. B. Genetics in Parkinson disease: Mendelian versus non-Mendelian inheritance. *J. Neurochem.* **139**, 59–74 (2016).
- Ganna, A. et al. Ultra-rare disruptive and damaging mutations influence educational attainment in the general population. *Nat. Neurosci.* **19**, 1563–1565 (2016).
- Tansey, K. E. et al. Common alleles contribute to schizophrenia in CNV carriers. *Mol. Psychiatry* **21**, 1085–1089 (2016).
- Kuchenbaecker, K. B. et al. Evaluation of polygenic risk scores for breast and ovarian cancer risk prediction in *BRCA1* and *BRCA2* mutation carriers. *J. Natl Cancer Inst.* **109**, djw302 (2017).
- Martinelli, S. et al. Functional dysregulation of *CDC42* causes diverse developmental phenotypes. *Am. J. Hum. Genet.* **102**, 309–329 (2018).
- Khanna, H. et al. A common allele in *RPGRIP1L* is a modifier of retinal degeneration in ciliopathies. *Nat. Genet.* **41**, 739–745 (2009).

**Acknowledgements** We thank the families involved in the DDD study for their participation and patience, the DDD study clinicians, research nurses and clinical scientists in the recruiting centres for their hard work on behalf of families, M. Niemi for help making Fig. 1 and V. Warrier for useful discussions. The DDD study presents independent research commissioned by the Health Innovation Challenge Fund (grant number HICF-1009-003), a parallel funding partnership between Wellcome and the Department of Health, and the Wellcome Sanger Institute (grant number WT098051). The views expressed in this publication are those of the author(s) and not necessarily those of Wellcome or the Department of Health. The research team acknowledges the support of the National Institute for Health Research, through the Comprehensive Clinical Research Network. This study makes use of data generated by the DECIPHER community. Funding for the project was provided by the Wellcome Trust. We used data from 'Understanding Society: The UK Household Longitudinal Study', which is led by the Institute for Social and Economic Research at the University of Essex and funded by the Economic and Social Research Council (grant number ES/M008592/1). The data were collected by NatCen and the genome-wide scan data were analysed by the Wellcome Trust Sanger Institute. Data governance was provided by the METADAC data access committee, funded by ESRC, Wellcome and MRC (grant number MR/N01104X/1). Australian controls from the Brisbane Longitudinal Twin Study were collected and genotyped with grants from the National Health and Medical Research Council. We thank A. Pardiñas for producing the PGC-CLOZUK summary statistics without the Australian controls.

**Reviewer information** Nature thanks D. Arking, C. Lewis and S. Ripke for their contribution to the peer review of this work.

**Author contributions** J.C.B., C.F.W., D.R.F., H.V.F. and M.E.H. designed the study. M.E.K.N., H.C.M., D.L.R., G.G., M.K., J.M. and E.J.R. contributed to data analysis. S.Y., J.G. and N.G.M. performed data collection for the Australian cohort. K.M. and S.G. prepared data from the Australian cohort. M.E.K.N., H.C.M. and J.C.B. wrote the paper. H.C.M. and J.C.B. supervised the analyses and J.C.B. supervised the project.

**Competing interests** M.E.H. is a co-founder of, consultant to and holds shares in Congenica, a genetics diagnostic company. J.C.B. is an employee of Genomics plc.

## Additional information

**Extended data** is available for this paper at <https://doi.org/10.1038/s41586-018-0566-4>.

**Supplementary information** is available for this paper at <https://doi.org/10.1038/s41586-018-0566-4>.

**Reprints and permissions information** is available at <http://www.nature.com/reprints>.

**Correspondence and requests for materials** should be addressed to J.C.B.

**Publisher's note:** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.



## METHODS

No statistical methods were used to predetermine sample size. The experiments were not randomized and investigators were not blinded to allocation during experiments and outcome assessment.

**Phenotypes of the DDD cohort.** Recruitment and phenotyping of DDD patients is described in detail elsewhere<sup>6,7</sup>. The DDD study has UK Research Ethics Committee approval (10/H0305/83, granted by the Cambridge South Research Ethics Committee and GEN/284/12, granted by the Republic of Ireland Research Ethics Committee). Families gave informed consent for participation. In brief, the DDD study recruited patients with a previously undiagnosed developmental disorder, in the UK and Ireland. Patient phenotypes were systematically recorded by clinical geneticists using Human Phenotype Ontology (HPO) terms in a central database, DECIPHER<sup>21</sup>.

The DDD cohort is very heterogeneous in terms of patient phenotypes, and so we narrowed our analyses to singleton patients and trios where the proband had at least one of the following HPO terms (or daughter terms of these HPO terms): abnormal metabolic brain imaging by MRS (HP:0012705), abnormal brain positron emission tomography (HP:0012657), abnormal synaptic transmission (HP:0012535), abnormal nervous system electrophysiology (HP:0001311), behavioural abnormality (HP:0000708), seizures (HP:0001250), encephalopathy (HP:001298), abnormality of higher mental function (HP:0011446), neurodevelopmental abnormality (HP:0012759), abnormality of the nervous system morphology (HP:0012639). This ‘neurodevelopmental’ subset included individuals who have—since their recruitment to the DDD study—been found to carry diagnostic exome mutations in protein-coding genes<sup>6,19,20,30</sup>, and individuals who are awaiting diagnosis. We therefore define our main phenotype (‘neurodevelopmental disorder risk’) as the risk of having a previously undiagnosed developmental disorder and being included in the DDD study, and having at least one neurodevelopmental HPO. In addition to HPOs, some DDD patients also had a clinical record of growth measurements such as height, birth weight and head circumference.

We counted the proportion of DDD patients with particular medically relevant HPOs, displayed in Fig. 2a. Individuals with the HPO were counted using a word search of the particular HPO and its daughter nodes. When counting the number of distinct organ systems affected in each DDD patient (Fig. 2b), we faced the issue that some HPOs fell under multiple organ systems: for example, microcephaly—which is a common term in the cohort—falls under three categories, ‘nervous system’, ‘head or neck’ and ‘skeletal system’. To assign each HPO into only one organ system, we first ranked organ systems based on the number of raw counts of individuals with at least one term under that system (Extended Data Table 1) in the full DDD cohort. We then looked for individuals with at least one HPO under the organ system ranked most-commonly affected, and assigned these individuals an organ system count of 1. We then removed these HPOs from the lists of patients, before continuing to identify individuals with at least one HPO in the organ system ranked second-most prevalently affected. We continued to count organs and remove HPOs until we had assigned all individuals a count of organs systems affected out of 19 non-overlapping systems.

**Developmental disorder phenotypes in the Australian cohort.** We obtained a replication cohort of 1,270 cases of developmental disorder from South Australia, originally genotyped (using the Illumina Infinium CytoSNP-850k BeadChip) as part of routine clinical care to ascertain pathogenic copy-number variants. The majority (>95%) were under 18 years old. Between 50% and 60% were recruited through clinical genetics units, and the rest through neurologists, neonatologists, paediatricians and cardiologists. Based on reviewing information on the request forms, the majority of patients had developmental delay or intellectual disability, and malformations involving at least one organ (for example, brain, heart and kidney). Between 15% and 20% were recruited as neonates with multiple malformations involving brain, heart and/or other organs, and were too young to be diagnosed with developmental delay or intellectual disability.

**Datasets and quality control.** We genotyped 11,304 patients and 930 full trios recruited to the DDD study on Illumina HumanCoreExome and HumanOmniExpress chips, respectively. Genotyping was carried out by the Wellcome Trust Sanger Institute genotyping facility. As controls for the discovery GWAS, we used genotype data for 10,484 individuals from the UK-based ‘Understanding Society’ UK Household Longitudinal Study (UKHLS)<sup>31,32</sup>. Recruitment to this study was carried out through UK-wide household longitudinal survey. For replication, we obtained GWAS data from a cohort of cases of neurodevelopmental disorder from South Australia, and population-matched controls from the Brisbane Longitudinal Twin Study (Queensland Institute of Medical Research<sup>33,34</sup>). All data were on GRCh37, and detailed information of genotyping chips is shown in Supplementary Table 1.

We performed variant and sample quality control for each dataset separately. We removed samples of patients whose reported sex was inconsistent with the genotype data, who had high sample missingness ( $\geq 3\%$  of minor allele frequency (MAF)  $\geq 10\%$  variants), samples with high or low heterozygosity ( $\pm 3$  s.d. from

the mean, using MAF  $\geq 10\%$  variants) to control for admixture and inbreeding, and sample duplicates (alleles identical by descent  $\geq 98\%$ , using MAF  $>10\%$  variants). We removed one individual from pairs of related individuals (alleles identical by descent  $>12\%$ , using PLINK) from the case-control cohorts. Individuals in the discovery cohort were not related to the independent DDD trios. We also removed trios with a high number of Mendelian errors ( $>2,000$  errors). For variant quality control, we removed variants if they had high genotype missingness ( $\geq 3\%$ ), Hardy–Weinberg equilibrium test  $P < 1 \times 10^{-5}$ , no strand information, if they were duplicates, if the alleles were discordant between case and control datasets, or if alleles and their frequency in Europeans were discordant with HRC v.1.1 imputation reference panel. We only included variants on chromosomes 1–22. For the HumanCoreExome data and the Australian data, we removed rare variants with MAF  $\leq 0.5\%$  before imputation. Post-imputation, we removed imputed variants with imputation quality score INFO  $\leq 0.9$  or high missingness ( $\geq 5\%$ ).

We defined sample ancestry based on a projection principal component analysis (PCA) using PLINK with 1000 Genomes Phase 3 populations, using SNPs that overlapped between the datasets (DDD + UKHLS and Australian cases + controls separately) and the reference populations. For this, we used SNPs with a MAF  $\geq 10\%$ , excluded A/T and G/C SNPs, removed regions of extended linkage disequilibrium (including the HLA region), and thinned the SNPs by pruning those with pairwise  $r^2 > 0.2$  in batches of 50 SNPs with sliding windows of 5 (‘-indep-pairwise 50 5 0.2’ in PLINK). This left 52,836 SNPs for the projection PCA with the DDD and UKHLS data, and 40,626 SNPs with the Australian data. For analyses described in this paper, we carried forward individuals of European ancestry, defined by selecting samples clustering around the 1000 Genomes Great British (GBR) samples in the PCA (Extended Data Figs. 1, 3). The distribution of ancestries was different between cases and controls, probably due to marked differences in ascertainment (for example, individuals from ancestries with high levels of consanguinity are more likely to be recruited to studies of rare genetic disorders). Because we tightly filtered based on PCA, these differences do not affect our results.

**Phasing and imputation.** After sample and variant quality control, we imputed European samples from all datasets to boost the coverage of the genome for association testing and to increase overlap of datasets genotyped on different chips. We used reference-based haplotype phasing and imputation. The discovery GWAS cohorts genotyped on the HumanCoreExome backbone were phased and imputed together using variants that intersected between the different versions of the chip. Trios were phased and imputed in a second batch because they were genotyped on a different chip. We phased and imputed the Australian GWAS data in a third batch, using variants that intersected between the CytoSNP-850K chip and the Illumina 610K chip. None of the analyses in our paper were directly across batches, so there is no bias introduced by this approach. We used the Sanger Institute Imputation Service<sup>35</sup> to carry out phasing (using Eagle2 (v.2.0.5)<sup>36</sup>) and imputation (using PBWT<sup>37</sup>) on the DDD discovery dataset, DDD trios dataset and Australian dataset, selecting the Haplotype Reference Consortium as the reference panel (release 1.1, chromosomes 1–22 and X)<sup>35</sup>.

**Discovery GWAS of neurodevelopmental disorder risk.** We carried out a GWAS for neurodevelopmental disorder risk in the discovery neurodevelopmental set of 6,987 cases and 9,270 controls of European ancestry only, using BOLT linear mixed models<sup>38</sup> with sex as a covariate. We included in our analysis genotyped variants or high-confidence imputed variants (INFO  $\geq 0.9$ ) with a MAF of  $\geq 5\%$ .

**SNP heritability.** From the discovery GWAS summary statistics, we removed the MHC region (chromosome 6 region 26–34 Mb), and estimated trait heritability using LD score<sup>8</sup> in LD Hub<sup>39</sup>. Given the ascertainment of the DDD neurodevelopmental cases in this study, estimating the true population prevalence was not feasible. We therefore estimated SNP heritability for our discovery GWAS on the liability scale for a range of prevalence between 0.2% and 2%, and found that SNP heritability varies from 5.5% (s.e. = 1.5%) to 9.1% (s.e. = 2.5%). We report heritability assuming a prevalence of 1% in the population. Heritability on the observed scale in our discovery GWAS was 13.8% (s.e. = 3.7%).

**Polygenic transmission disequilibrium test.** We used the previously described polygenic transmission disequilibrium test (pTDT) method<sup>41</sup> to investigate transmission disequilibrium of effect alleles for traits within DDD trios, using imputed genotype data. In brief, the test compares the means of two polygenic score distributions: one comprising the scores of the probands, and the other the average parent–pair scores. The test is equivalent to a one-sample *t*-test, assessing whether the mean of score distribution in probands deviates from the mean of parent–pair score average. We report a one-sided *P* value for over-transmission.

**Genetic correlation.** We carried out genetic correlation of the neurodevelopmental disorder risk in the discovery GWAS against multiple published traits, using bivariate LD score<sup>14</sup>. For traits included in LD Hub, we used the online server, and for traits not included in LD Hub, we used the LD score software. For genetic correlation with neurodevelopmental disorder risk, we pre-selected a range of different types of traits and diseases: traits relating to cognitive performance, education, psychiatric traits and diseases, anthropometric traits and non-brain related traits

and diseases. Ninety-five per cent confidence intervals in Fig. 3 are shown before correction for multiple testing. We set the significance threshold to  $P < 0.0026$  (0.05 divided by the 19 tests).

**Partitioned heritability.** We used partitioned LD score<sup>17</sup> to look for enrichment of heritability in cell-type groups and functional genomic categories. To do this, we used the baseline model LD scores and regression weights available online. For cell-type groups and functional categories, we set the significance threshold to  $P < 0.005$  (0.05, divided by 10 tests) and  $P < 9.6 \times 10^{-4}$  (0.05, divided by 52 tests), respectively.

**Polygenic scores.** We constructed polygenic scores using summary statistics from our GWAS of neurodevelopmental disorder risk and seven published GWAS (educational attainment<sup>15</sup>, intelligence<sup>16</sup>, schizophrenia<sup>40</sup>, autism<sup>9</sup>, intracranial volume<sup>41</sup>, height<sup>42</sup> and birth weight<sup>43</sup>). For all traits, we included only variants that had a MAF  $\geq 5\%$  and were directly genotyped or imputed with high confidence (INFO  $\geq 0.9$ ) in the respective study cohort (discovery case and control, trios or Australian). To construct the polygenic scores for individuals, we then multiplied the variant effects ( $\beta$  values) with the allele counts of each individual. For imputed variants, we used genotype probabilities rather than hard-called allele counts. To find independent variants for our scores, we pruned variants intersecting the original study summary statistics and our GWAS data using PLINK, by taking the top variant and removing variants within 500 kb and that have  $r^2 \geq 0.1$  with the top variant. We then repeated the process until no variant had a  $P$  value below a predefined threshold, which we based on prior knowledge of variance in the phenotype explained. For the neurodevelopmental disorder risk score, we tested seven  $P$ -value thresholds ( $P < 1, 0.5, 0.1, 0.05, 0.01, 0.005$  and  $0.001$ ) and chose the one which resulted in a score that explained the most variance (Nagelkerke's  $R^2$ ) in case and control status in an independent subset of DDD patients. Specifically, we repeated our GWAS of neurodevelopmental disorder risk having removed a random subset of 20% of cases and controls, then calculated a score in this 'leave-out' subset, and performed a logistic regression to assess association of case-control status with the score. The threshold  $P < 1$  performed best in ten independent permutations, and we used this threshold to construct scores in pTDT and Australian case-control analyses. We additionally tested all seven thresholds when constructing scores in the Australian dataset; however, varying the threshold did not change our results. When deciding the  $P$ -value thresholds for published GWAS, we used the threshold that had been found to explain the most variation in other published studies for the trait (years in education<sup>44</sup>  $P < 1$ , intelligence<sup>16</sup> and schizophrenia<sup>40</sup>  $P < 0.05$ , and autism<sup>11</sup>  $P < 0.1$ ). For traits for which we had phenotype data in the DDD, we used thresholds that explained the most variation in DDD cases (intracranial volume  $P < 1$ , birth weight  $P < 0.01$  and height  $P < 0.005$ ). Thresholds and the number of variants used for each score are shown in Extended Data Tables 3–5. All scores were normalized to a mean of 0 and variance of 1. To test for association between trait and score, we used R (version 1.90b3) to perform logistic regression for binary traits and linear regression for quantitative traits, including the first ten principal components from the ancestry PCA to control for possible population stratification.

To assess power for detecting differences in scores between diagnosed and undiagnosed patients, we tested the hypothesis that diagnosed patients were effectively a random sample of controls with respect to their polygenic scores. Specifically, we randomly sampled 1,127 controls (that is, the same number as we had diagnosed patients) and compared the polygenic scores between them and the undiagnosed patients using logistic regression. We repeated this 10,000 times and determined the proportion of times we detected a significant difference  $P < 0.007$  ( $P < 0.05$ , divided by 7 (correcting for seven polygenic scores)) as proxy for power. This was 99.1% of simulations for educational attainment, 93.6% of simulations for schizophrenia and 61.2% of simulations for intelligence.

We used AVENGEME<sup>45</sup> to calculate power to find significant association (at  $P < 0.05$ ) between our polygenic score for neurodevelopmental disorders and case or control status in the Australian dataset. We assumed that the SNP heritability is the same (7.7%) in both the Australian and British cohorts, and that the genetic correlation between them was 1.

The PGC-CLOZUK study of schizophrenia included some controls from the Australian cohort used in our study, and therefore we ran polygenic score analyses in the Australians using summary statistics from PGC-CLOZUK (obtained from A. Pardiñas, personal communication) after these samples had been removed.

**Producing subsets from the DDD cohort.** We defined a set of patients with an exonic diagnosis and a set with no likely diagnostic variants. This was based on a previously described clinical filtering procedure<sup>6</sup>—which focuses on identifying rare, damaging variants in a set of genes known to cause developmental disorders (<https://www.ebi.ac.uk/gene2phenotype/>)—that fit an appropriate inheritance mode. Variants that pass clinical filtering are uploaded to DECIPHER, where the patients' clinicians classify them as 'definitely pathogenic', 'likely pathogenic', 'uncertain', 'likely benign' or 'benign'. This process of clinical classification is necessarily dynamic as new disorders are identified and patients manifest new

phenotypes. Our 'diagnosed' set consists of 1,127 patients who fulfilled one of the following criteria: (a) among the diagnosed set in a recent reanalysis of the first 1,133 trios<sup>46</sup>; (b) had at least one variant (or pair of compound heterozygous variants) rated as 'definitely pathogenic' or 'likely pathogenic' by a clinician; or (c) had at least one variant (or pair of compound heterozygous variants) in a class with a high positive-predictive value that passed clinical filtering but had not yet been rated by clinicians. We considered de novo or compound heterozygous loss-of-function (LOF) variants to have high positive-predictive value, as of the ones that had been rated by clinicians, 100% of compound heterozygous LOFs and 94.4% of de novo LOFs had been classed as 'definitely pathogenic' or 'likely pathogenic'. Our 'undiagnosed' set consists of 2,479 patients who had no variants that passed our clinical filtering, or in whom the variants that had passed clinical filtering had all been rated as 'likely benign' or 'benign' by clinicians, or who were among the undiagnosed set in the first 1,133 trios that have previously been extensively clinically reviewed<sup>6</sup>. Note that our diagnosed versus undiagnosed analysis excludes 3,375 patients who had one or more variants that passed clinical filtering in a class with a relatively low positive-predictive value, but that have not yet been rated by clinicians.

We defined patients to present with autistic behaviours if their phenotype included autistic behaviour (HP:0000729) or any of its daughter nodes. We defined patients as having 'mild/moderate intellectual disability or delay' if their HPO phenotypes included borderline, mild or moderate intellectual disability (HP:0006889, HP:0001256, HP:0002342) and/or mild or moderate global developmental delay (HP:0011342, HP:0011343). Patients were included in the 'severe ID or delay' set if they had severe or profound intellectual disability (HP:0010864, HP:0002187) and/or severe or profound global developmental delay (HP:0011344, HP:0012736). We excluded patients with intellectual disability or global developmental delay of undefined severity.

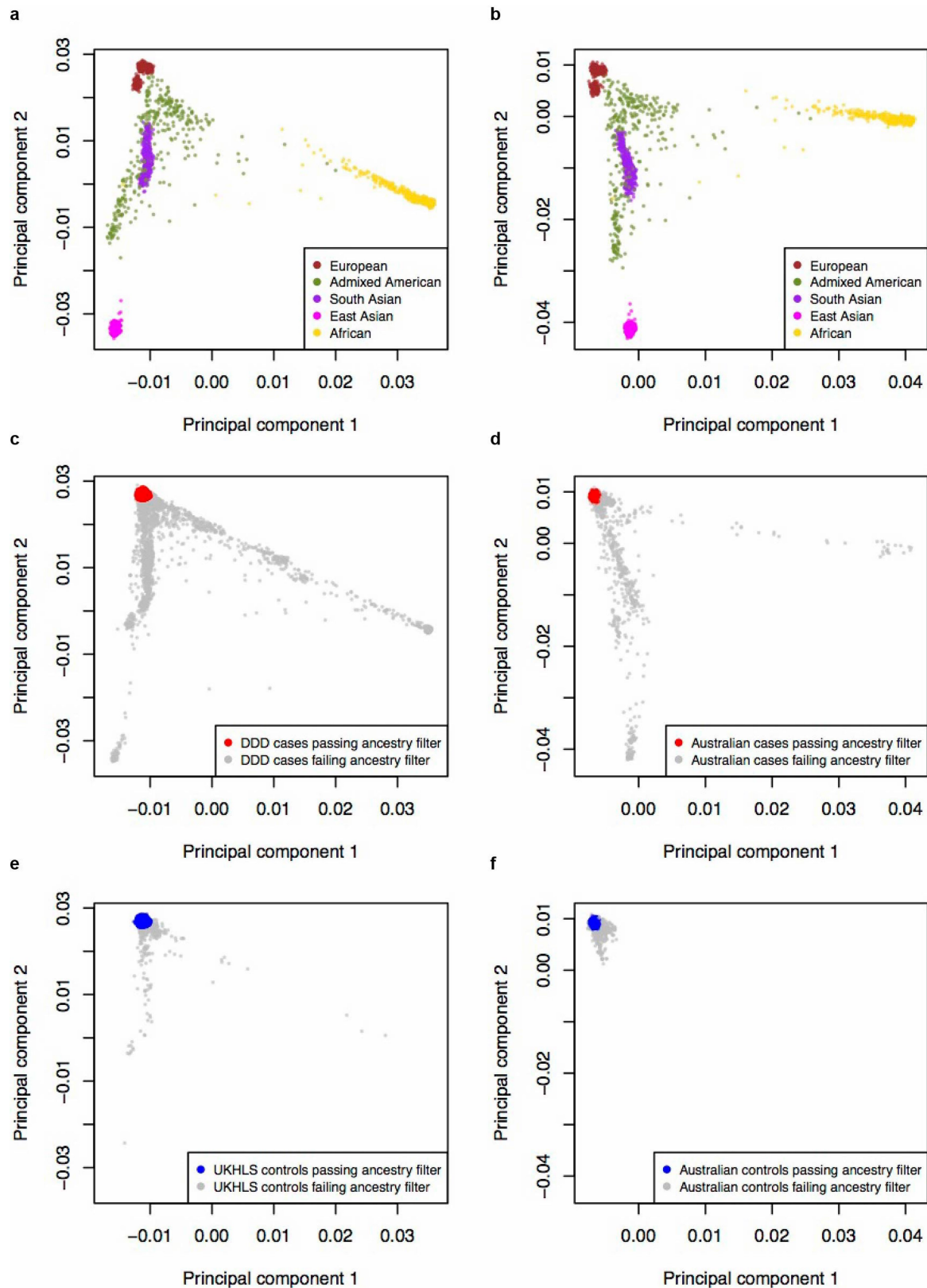
**Reporting summary.** Further information on research design is available in the Nature Research Reporting Summary linked to this paper.

## Data availability

The raw genotype data, post-quality-control genotype data and discovery GWAS summary statistics generated and/or analysed during the current study are available through European Genome-phenome Archive, under EGAS00001000775. This study makes use of data generated by the DECIPHER community: a full list of centres that contributed to the generation of the data is available from <http://decipher.sanger.ac.uk>, and via email from [decipher@sanger.ac.uk](mailto:decipher@sanger.ac.uk). Information on how to access the data from the UKHLS can be found on the 'Understanding Society' website, at <https://www.understandingsociety.ac.uk/>.

30. Short, P. J. et al. De novo mutations in regulatory elements in neurodevelopmental disorders. *Nature* **555**, 611–616 (2018).
31. University of Essex Institute for Social and Economic Research, NatCen Social Research & Kantar Public. *Understanding Society: Waves 1–7, 2009–2016 and Harmonised BHPS: Waves 1–18, 1991–2009* 10th edn (UK Data Service, 2018).
32. University of Essex Institute for Social and Economic Research. *Understanding Society: Waves 2 and 3 Nurse Health Assessment, 2010–2012* 3rd edn (UK Data Service, 2014).
33. Wright, M. J. & Martin, N. G. Brisbane adolescent twin study: outline of study methods and research projects. *Aust. J. Psychol.* **56**, 65–78 (2004).
34. Mina-Vargas, A. et al. Heritability and GWAS analyses of acne in Australian adolescent twins. *Twin Res. Hum. Genet.* **20**, 541–549 (2017).
35. The Haplotype Reference Consortium. A reference panel of 64,976 haplotypes for genotype imputation. *Nat. Genet.* **48**, 1279–1283 (2016).
36. Loh, P.-R. et al. Reference-based phasing using the Haplotype Reference Consortium panel. *Nat. Genet.* **48**, 1443–1448 (2016).
37. Durbin, R. Efficient haplotype matching and storage using the positional Burrows–Wheeler transform (PBWT). *Bioinformatics* **30**, 1266–1272 (2014).
38. Loh, P.-R. et al. Efficient Bayesian mixed-model analysis increases association power in large cohorts. *Nat. Genet.* **47**, 284–290 (2015).
39. Zheng, J. et al. LD Hub: a centralized database and web interface to perform LD score regression that maximizes the potential of summary level GWAS data for SNP heritability and genetic correlation analysis. *Bioinformatics* **33**, 272–279 (2017).
40. Pardiñas, A. F. et al. Common schizophrenia alleles are enriched in mutation-intolerant genes and in regions under strong background selection. *Nat. Genet.* **50**, 381–389 (2018).
41. Adams, H. H. H. et al. Novel genetic loci underlying human intracranial volume identified through genome-wide association. *Nat. Neurosci.* **19**, 1569–1582 (2016).
42. Wood, A. R. et al. Defining the role of common variation in the genomic and biological architecture of adult human height. *Nat. Genet.* **46**, 1173–1186 (2014).
43. Horikoshi, M. et al. Genome-wide associations for birth weight and correlations with adult disease. *Nature* **538**, 248–252 (2016).
44. Okbay, A. et al. Genome-wide association study identifies 74 loci associated with educational attainment. *Nature* **533**, 539–542 (2016).

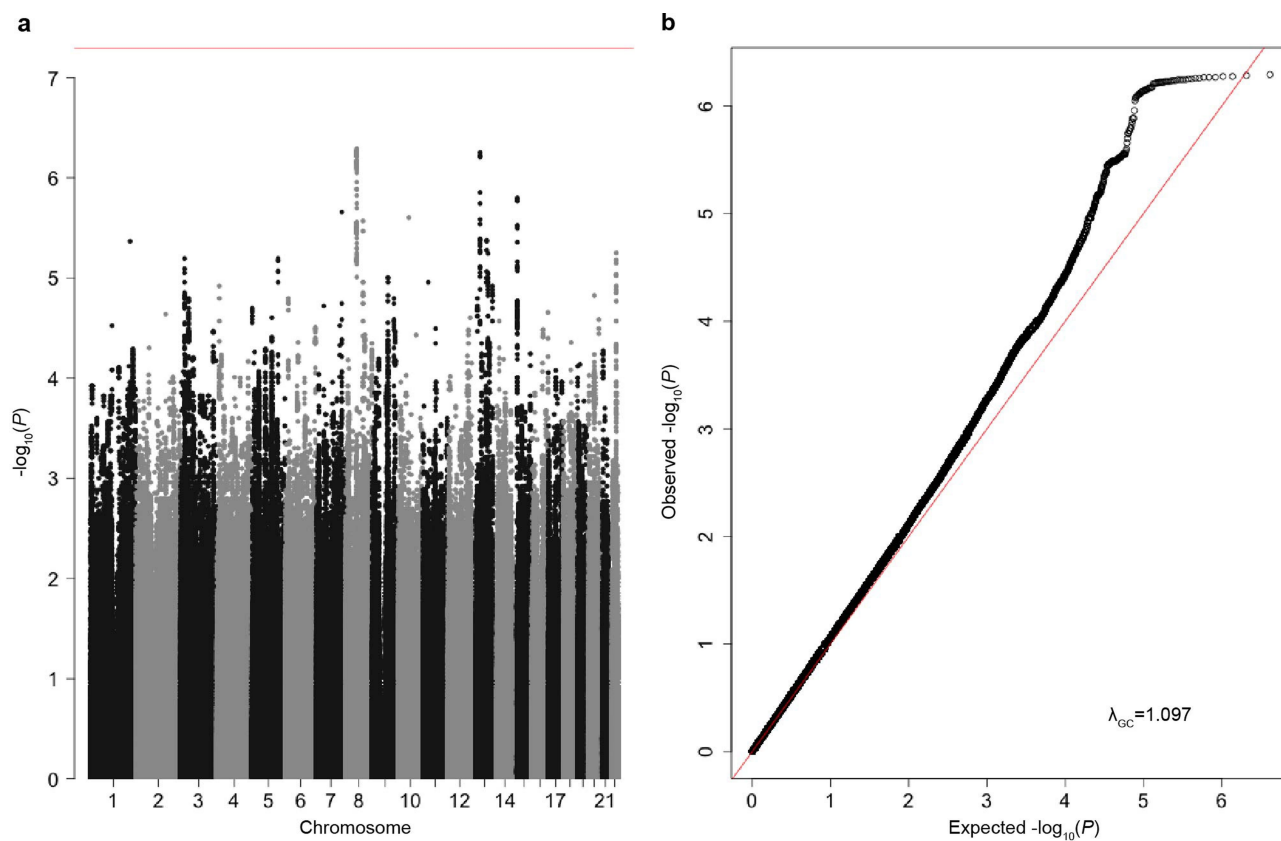
45. Palla, L. & Dudbridge, F. A fast method that uses polygenic scores to estimate the variance explained by genome-wide marker panels and the proportion of variants affecting a trait. *Am. J. Hum. Genet.* **97**, 250–259 (2015).
46. Wright, C. F. et al. Making new genetic diagnoses with old data: iterative reanalysis and reporting from genome-wide data in 1,133 families with developmental disorders. *Genet. Med.* <https://doi.org/10.1038/gim.2017.246> (2018).



**Extended Data Fig. 1 | Ancestry principal components analysis of UK and Australian samples.** **a, b,** Reference samples ( $n = 2,504$ ) from 1000 Genomes Phase 3, coloured by the five super-populations, used for a projection PCA of UK cohorts (DDD and UKHLS) (**a**) or Australian cohorts (**b**). **c, d,** All DDD cases (discovery  $n = 11,304$  and from trios  $n = 930$ ) (**c**) and all Australian cases ( $n = 2,283$ ) (**d**) from their respective projection PCA with 1000 Genomes. Case samples from individuals with European ancestry are plotted in red and non-Europeans in grey.

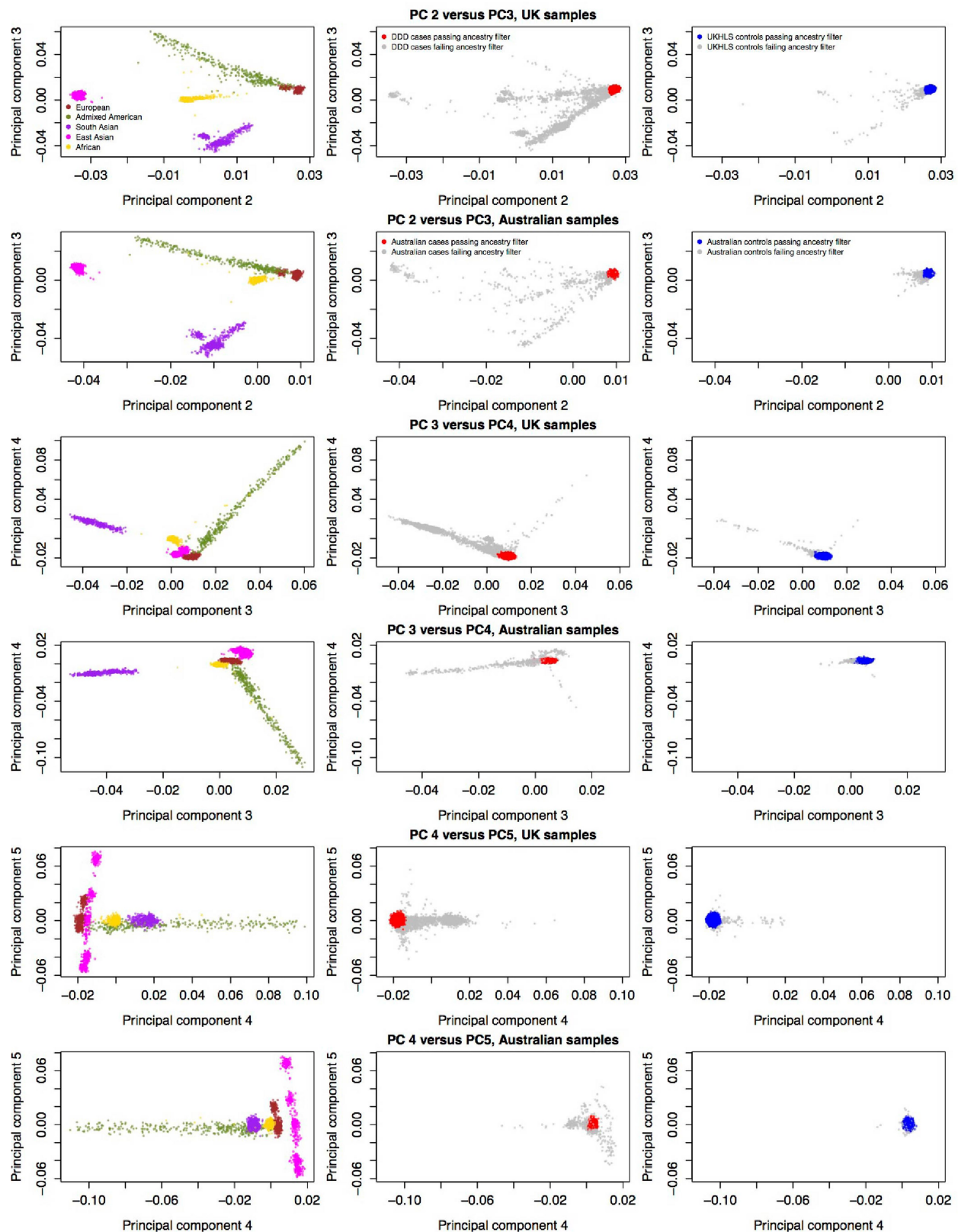
**e, f,** All UKHLS controls ( $n = 10,396$ ) (**e**) and all Australian controls ( $n = 4,274$ ) (**f**) from their respective projection PCA with 1000 Genomes. Control samples from individuals with European ancestry are plotted in blue and non-Europeans in grey. All cases and controls coloured in grey (in **c–f**) were excluded from analysis owing to non-European ancestry. UK cohorts are plotted after removal of samples that failed quality control, and Australian cohorts before removal of samples that failed quality control.





**Extended Data Fig. 2 | Discovery GWAS of neurodevelopmental disorder risk.** **a**, Manhattan plot of discovery GWAS of neurodevelopmental disorder risk, with 6,987 DDD cases and 9,270 ancestry-matched UKHLS controls (both for individuals with European ancestry), using 4,134,438 variants,  $MAF \geq 5\%$ , chromosomes 1–22.

$P$  values were from a two-tailed  $\chi^2$  distribution. Red line represents the threshold for genome-wide significance ( $P = 5 \times 10^{-8}$ ). **b**, Quantile–quantile plot of discovery GWAS of neurodevelopmental disorder risk. Red line represents the expected values under the null hypothesis.



**Extended Data Fig. 3 | Ancestry principal components analysis of samples from the UK and Australian (principal components 2–5).** Reference samples ( $n = 2,504$ ) from 1000 Genomes Phase 3—coloured by the five super-populations—are plotted on the left hand side, from projection PCAs with UK cohorts. Middle panels show the principal components plotted for DDD cases (discovery  $n = 10,556$  and from trios  $n = 911$ ) (UK samples) and Australian cases ( $n = 2,283$ ). Red, case samples from individuals with European ancestry. Grey, samples

from individuals of non-European ancestry; these individuals were excluded from analyses. Right-hand panels show principal components for UKHLS controls ( $n = 10,396$ ) (UK samples) and Australian controls ( $n = 4,274$ ). Blue, control samples from individuals with European ancestry. Grey, samples from individuals of non-European ancestry; these individuals were excluded from analyses. UK cohorts are plotted after removal of samples that failed quality control, and Australian cohorts before removal of samples that failed quality control.

**Extended Data Table 1 | Proportions of patients with a neurodevelopmental disorder who have at least one HPO term that belongs to a particular organ-system category**

Organ system	% All DDD patients (N=13,558)	% unrelated DDD patients, GBR ancestry (N=6,987)
Nervous system	87.0	100.0
Head or neck	68.9	71.2
Skeletal system	61.7	61.8
Limbs	35.1	35.3
Eye	34.9	35.3
Integument	31.2	31.9
Ear	20.1	19.7
Digestive system	20.0	19.1
Musculature	19.9	18.7
Cardiovascular system	15.1	13.5
Genitourinary system	12.4	11.4
Respiratory system	8.1	7.3
Connective tissue	7.4	6.3
Immune system	6.8	6.5
Endocrine system	4.1	4.1
Metabolism homeostasis	4.1	4.0
Breast	3.7	3.7
Blood and blood forming tissues	2.1	2.1
Voice	1.1	1.1

The HPO tree descends from 'phenotypic abnormality' through different organ systems down to specific terms that describe particular phenotypes. Each HPO term used by clinicians to describe patients was traced up the tree to the organ-system level. However, some HPOs may belong to more than one organ-system category: for example, microcephaly will be counted under 'nervous system', 'head or neck' and 'skeletal system' in the HPO tree whereas global developmental delay will appear only under 'nervous system'.

**Extended Data Table 2 | Genetic correlations between neurodevelopmental disorder risk and a range of traits, calculated using the LD score method**

Trait 2	Genetic correlation between developmental disorder risk and trait 2	Standard error	95% confidence interval (standard error) lower bound	95% confidence interval (standard error) upper bound	P-value	SNP heritability for trait 2 <sup>a</sup>	SE for trait 2 SNP heritability	Population prevalence used for liability scale conversion	N for trait 2 GWAS (Ncases:Ncontrols if dichotomous)
Years of schooling	-0.491	0.079	-0.336	-0.645	5.31x10 <sup>-10</sup>	0.112	0.004		766,345
Intelligence (Spearman's g)	-0.441	0.104	-0.237	-0.645	2.15x10 <sup>-5</sup>	0.203	0.013		78,308
Schizophrenia	0.279	0.066	0.148	0.409	2.71x10 <sup>-5</sup>	0.242	0.008	0.010	11,260:24,542
Attention deficit hyperactivity disorder	0.727	0.292	0.155	1.299	0.013	0.071	0.031		17,666
Major depressive disorder	0.389	0.177	0.042	0.736	0.028	0.087	0.017	0.150	9,240:9,519
Childhood IQ	-0.252	0.153	0.048	-0.553	0.100	0.279	0.051		12,441
Autism spectrum disorder	-0.078	0.103	0.123	-0.280	0.445	0.118	0.010	0.012	18,381:27,969
Bipolar disorder	0.033	0.105	-0.172	0.238	0.751	0.250	0.023	0.010	7,481:9,250
Height	-0.176	0.070	-0.038	-0.314	0.012	0.336	0.021		253,288
Body mass index	0.174	0.071	0.035	0.312	0.015	0.189	0.010		336,107
Child birth length	-0.291	0.155	0.013	-0.595	0.061	0.165	0.027		28,459
Intracranial volume	-0.319	0.218	0.107	-0.746	0.142	0.167	0.053		11,373
Birth weight	-0.133	0.098	0.059	-0.326	0.174	0.095	0.008		143,677
Alzheimer's disease	0.424	0.259	-0.083	0.932	0.101	0.068	0.013	0.050	17,008:37,154
Coronary artery disease	0.077	0.091	-0.101	0.254	0.396	0.070	0.005	0.050	60,801:123,504
Lumbar Spine bone mineral density	0.101	0.132	-0.158	0.360	0.447	0.116	0.018		44,731
Parkinson's disease	0.093	0.136	-0.173	0.359	0.494	0.167	0.050	0.002	1,713:3,978
Type 2 Diabetes	0.071	0.122	-0.168	0.309	0.562	0.120	0.147	0.015	12,171:56,862
Crohn's disease	-0.024	0.096	0.164	-0.211	0.804	0.252	0.027	0.003	5,956:14,927

Trait 2 is the trait to which neurodevelopmental disorder risk is compared. Uncorrected *P* values are from a two-sided *z*-score.

<sup>a</sup>SNP heritability for dichotomous traits is on the liability scale.



**Extended Data Table 3 | Polygenic score analyses comparing 1,266 Australian cases of neurodevelopmental disorders and 1,688 controls**

Polygenic score	Polygenic score parameters			Results <sup>a</sup>		
	r <sup>2</sup> for SNP pruning	P-value threshold for SNP pruning	Number of SNPs in score	Beta	Standard error	P-value
Educational attainment (SSGAC, 2018)	0.1	1	92,091	-0.218	0.038	9.97x10 <sup>-9</sup>
Height (Wood et al., 2014)	0.1	0.005	9,809	-0.155	0.040	8.84x10 <sup>-5</sup>
Intelligence (Sniekers et al., 2017)	0.1	0.05	21,551	-0.126	0.038	7.61x10 <sup>-4</sup>
Schizophrenia (QIMR removed) (Pardinas et al., 2018)	0.1	0.05	23,878	0.092	0.038	0.014
Intracranial volume (Adams et al., 2016)	0.1	1	90,928	-0.078	0.038	0.041
Autism (Grove et al., 2017)	0.1	0.1	26,846	0.070	0.038	0.063
Birth weight (Horikoshi et al., 2016)	0.1	0.01	6,828	-0.062	0.038	0.098
Developmental disorder risk (discovery GWAS)	0.1	1	67,001	-0.047	0.038	0.212

P values are uncorrected, two-sided and from z-score distribution. Data were obtained from previous studies<sup>9,15,16,40–43</sup>.

<sup>a</sup>Logistic regression of case or control status on polygenic score, using ten ancestry principal components as covariates.

**Extended Data Table 4 | Polygenic score analyses comparing patients from the DDD with an exome diagnosis ( $n = 1,127$ ) against undiagnosed patients ( $n = 2,479$ )**

Polygenic score trait	Parameters			Results <sup>a</sup>		
	r <sup>2</sup> for SNP pruning	P-value threshold for SNP pruning	Number of SNPs in score	Beta	Standard error	P-value
Educational attainment	0.1	1	79,292	0.080	0.037	0.028
Intelligence	0.1	0.05	19,387	0.063	0.036	0.080
Schizophrenia	0.1	0.05	21,321	0.017	0.036	0.644
Autism	0.1	0.1	23,648	-0.077	0.036	0.032
Intracranial volume	0.1	1	76,788	4.98x10 <sup>-3</sup>	0.036	0.891
Birth weight	0.1	0.01	6,212	1.54x10 <sup>-3</sup>	0.036	0.966
Height	0.1	0.005	9,019	1.34x10 <sup>-3</sup>	0.036	0.971

P values are uncorrected, two-sided and from z-score distribution.

<sup>a</sup>Logistic regression of diagnosed and undiagnosed status on polygenic score, using ten ancestry principal components as covariates.

Extended Data Table 5 | Polygenic score analyses in patients from the DDD for measured traits

Measured trait	Score parameters				Results <sup>a</sup>			
	Polygenic score	r <sup>2</sup> for SNP pruning	P-value threshold for SNP pruning	Number of SNPs in score	Beta	Standard error	P-value	R <sup>2</sup>
Birth weight (N=6,496)	Birth weight	0.1	0.01	6,212	0.187	0.017	2.55x10 <sup>-28</sup>	0.020
Height (N=5,465)	Height	0.1	0.005	9,019	0.408	0.033	1.18x10 <sup>-35</sup>	0.033
Head circumference (N=6,074)	Intracranial volume	0.1	1	76,788	0.132	0.031	1.79x10 <sup>-5</sup>	0.004
Autistic behavior: affected (N=1,121), unaffected (N=5,866)	Autism	0.1	0.1	23,648	0.120	0.033	2.53x10 <sup>-4</sup>	0.006 <sup>c</sup>
Developmental delay or intellectual disability: severe (N=911), mild/moderate (N=1,902) <sup>b</sup>	Educational attainment	0.1	1	79,292	0.116	0.040	0.004	0.008 <sup>c</sup>

P values are uncorrected, two-sided and from *t*-distribution (linear) and z-score distribution (logistic). <sup>a</sup>Linear or logistic regression on polygenic score. using ten ancestry principal components as covariates.

<sup>b</sup>Severe cases were labelled as 1 in the logistic regression.

<sup>c</sup>Nagelkerke R<sup>2</sup>.

## Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Research policies, see [Authors & Referees](#) and the [Editorial Policy Checklist](#).

### Statistical parameters

When statistical analyses are reported, confirm that the following items are present in the relevant location (e.g. figure legend, table legend, main text, or Methods section).

n/a Confirmed

- ☐ ☒ The exact sample size ( $n$ ) for each experimental group/condition, given as a discrete number and unit of measurement
- ☐ ☒ An indication of whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
- ☐ ☒ The statistical test(s) used AND whether they are one- or two-sided  
*Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
- ☐ ☒ A description of all covariates tested
- ☐ ☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
- ☐ ☒ A full description of the statistics including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
- ☐ ☒ For null hypothesis testing, the test statistic (e.g.  $F$ ,  $t$ ,  $r$ ) with confidence intervals, effect sizes, degrees of freedom and  $P$  value noted  
*Give  $P$  values as exact values whenever suitable.*
- ☒ ☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
- ☒ ☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
- ☐ ☒ Estimates of effect sizes (e.g. Cohen's  $d$ , Pearson's  $r$ ), indicating how they were calculated
- ☐ ☒ Clearly defined error bars  
*State explicitly what error bars represent (e.g. SD, SE, CI)*

Our web collection on [statistics for biologists](#) may be useful.

### Software and code

Policy information about [availability of computer code](#)

Data collection

Illumina GenCall software was used by the Wellcome Sanger Institute genotyping pipeline team to call the genotypes for all DDD Study samples.

Data analysis

We used PLINK v. 1.9b3 for sample and variant quality control, and variant pruning for polygenic risk scores. We used Eagle2 (v2.0.5) for genotype phasing, and PBWT (no version information available) for imputation, both through the Sanger Imputation Server. We used BOLT-LMM v2.2 for genome-wide association study. We used LD Hub for LD score regression and estimating heritability and genetic correlations, and LD Score software v1.0.0 for estimating genetic correlation for traits not included in LD Hub and for partitioned heritability analysis. We used R v. 2.14.1 for logistic and linear regression analyses and AVENGEME for assessing polygenic score power.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors/reviewers upon request. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research [guidelines for submitting code & software](#) for further information.



## Data

Policy information about [availability of data](#)

All manuscripts must include a [data availability statement](#). This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

The datasets generated during and/or analysed during the current study are available through EGA under number EGAS00001000775.

## Field-specific reporting

Please select the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see [nature.com/authors/policies/ReportingSummary-flat.pdf](https://www.nature.com/authors/policies/ReportingSummary-flat.pdf)

## Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

### Sample size

Our primary goal in this study was to investigate whether there was significant SNP heritability to be found in our discovery GWAS for neurodevelopmental disorder risk. We used the method LD score regression, and the authors of the method describe how a sample size of more than 5,000 is required to have enough power to detect SNP heritability in a GWAS. Our discovery case and control datasets came to a total sample of 16,257, which was sufficient to test for SNP heritability using LD score regression. From all cohorts used in this study, we selected individuals who were not related (alleles identical by descent >12%) to each other, and who were of European ancestry based on a projection principal component analysis with 1000 Genomes data. Sample size for each analysis was the maximum number of individuals with available genotype data who filled these requirements. All patients had some phenotype data, but this was not always complete for every measured phenotype. Therefore, for logistic and linear regression analyses on particular phenotypes measured in the DDD Study against polygenic scores, the sample size was determined as all individuals in our study who had the particular phenotype data available. We estimate that we should have had 95% power (using AVENGEME) to detect a difference if the two cohorts had identical phenotypes. This suggests that there may be differential phenotypic ascertainment between the British and Australian cohorts, which has diluted our ability to quantify their shared genetics using the neurodevelopmental disorder polygenic score.

### Data exclusions

We excluded the individual from each pair of related individuals (alleles identical by descent >12%) who had higher genotype missingness. We excluded individuals who had non-European ancestry based on their genotype. For analyses requiring phenotype data, we excluded individuals who did not have phenotype data. Both these requirements were pre-established and samples were removed in the quality control phase.

### Replication

We show in an independent cohort of Deciphering Developmental Disorders trios that parents over-transmit variants to their affected child that increased disease risk in our discovery genome-wide association study, confirming that the common variant heritability we found in the discovery case-control GWAS was due to polygenic effects on the neurodevelopmental phenotype and not confounding. We replicate all three statistically significant findings from discovery GWAS genetic correlation analysis, by constructing polygenic scores for these traits in the Australian case-control cohort, where the scores showed the same direction of effect and were at least nominally significant. We also tried this method to test whether the neurodevelopmental disorder risk would replicate in the Australian case-control cohort, however we did not find significant replications, and we discuss this in the main text.

### Randomization

DDD participants were allocated into groups based on their known phenotypes, which were annotated by the clinical geneticist who assessed them.

### Blinding

Investigators were not blinded because linking the phenotype data and genetic data was necessary to do sample filtering and analyses.

## Reporting for specific materials, systems and methods

## Materials &amp; experimental systems

n/a	Involved in the study
<input checked="" type="checkbox"/>	<input type="checkbox"/> Unique biological materials
<input checked="" type="checkbox"/>	<input type="checkbox"/> Antibodies
<input checked="" type="checkbox"/>	<input type="checkbox"/> Eukaryotic cell lines
<input checked="" type="checkbox"/>	<input type="checkbox"/> Palaeontology
<input checked="" type="checkbox"/>	<input type="checkbox"/> Animals and other organisms
<input type="checkbox"/>	<input checked="" type="checkbox"/> Human research participants

## Methods

n/a	Involved in the study
<input checked="" type="checkbox"/>	<input type="checkbox"/> ChIP-seq
<input checked="" type="checkbox"/>	<input type="checkbox"/> Flow cytometry
<input checked="" type="checkbox"/>	<input type="checkbox"/> MRI-based neuroimaging

## Human research participants

Policy information about [studies involving human research participants](#)

## Population characteristics

All patients in the Deciphering Developmental Disorders Study had a previously undiagnosed developmental disorder. Individual participants have heterogeneous phenotypes. Most patients are recruited at a young age with the mean decimal age at assessment being 7.7 years, although 6% of patients are recruited as adults. 41% of the patients are female. All individuals selected for analysis in this study had European ancestry in a projection principal component analysis with 1000 Genomes data.

## Recruitment

DDD study recruited patients with a previously undiagnosed developmental disorder, in the UK and Ireland. All patients were recruited by senior clinical geneticists who had assessed their developmental disorder was of sufficient severity that it was likely monogenic. Patient phenotypes were systematically recorded by clinical geneticists using Human Phenotype Ontology (HPO) terms in a central database, DECIPHER. Families gave informed consent for participation.