



THE UNIVERSITY *of* EDINBURGH

Edinburgh Research Explorer

Discovery of 42 genome-wide significant loci associated with dyslexia

Citation for published version:

23andMe Research Team, Quantitative Trait Working Group of the GenLang Consortium, Pourcain, BS, Francks, C, Marioni, RE, Zhao, J, Paracchini, S, Talcott, JB, Monaco, AP, Stein, JF, Gruen, JR, Olson, RK, Willcutt, EG, DeFries, JC, Pennington, BF, Smith, SD, Wright, MJ, Martin, NG, Auton, A, Bates, TC, Fisher, SE & Luciano, M 2022, 'Discovery of 42 genome-wide significant loci associated with dyslexia', *Nature Genetics*. <https://doi.org/10.1038/s41588-022-01192-y>

Digital Object Identifier (DOI):

[10.1038/s41588-022-01192-y](https://doi.org/10.1038/s41588-022-01192-y)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Publisher's PDF, also known as Version of record

Published In:

Nature Genetics

General rights

Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.



Discovery of 42 genome-wide significant loci associated with dyslexia

Received: 28 August 2021

Accepted: 23 August 2022

Published online: 20 October 2022

 Check for updates

Catherine Doust¹, Pierre Fontanillas², Else Eising³, Scott D. Gordon⁴, Zhengjun Wang⁵, Gökberk Alagöz³, Barbara Molz³, 23andMe Research Team*, Quantitative Trait Working Group of the GenLang Consortium*, Beate St Pourcain^{3,6,7}, Clyde Francks^{3,6}, Riccardo E. Marioni⁸, Jingjing Zhao⁵, Silvia Paracchini⁹, Joel B. Talcott¹⁰, Anthony P. Monaco¹¹, John F. Stein¹², Jeffrey R. Gruen¹³, Richard K. Olson^{14,15}, Erik G. Willcutt^{14,15}, John C. DeFries^{14,15}, Bruce F. Pennington¹⁶, Shelley D. Smith¹⁷, Margaret J. Wright¹⁸, Nicholas G. Martin⁴, Adam Auton, Timothy C. Bates¹, Simon E. Fisher^{3,6} and Michelle Luciano¹✉

Reading and writing are crucial life skills but roughly one in ten children are affected by dyslexia, which can persist into adulthood. Family studies of dyslexia suggest heritability up to 70%, yet few convincing genetic markers have been found. Here we performed a genome-wide association study of 51,800 adults self-reporting a dyslexia diagnosis and 1,087,070 controls and identified 42 independent genome-wide significant loci: 15 in genes linked to cognitive ability/educational attainment, and 27 new and potentially more specific to dyslexia. We validated 23 loci (13 new) in independent cohorts of Chinese and European ancestry. Genetic etiology of dyslexia was similar between sexes, and genetic covariance with many traits was found, including ambidexterity, but not neuroanatomical measures of language-related circuitry. Dyslexia polygenic scores explained up to 6% of variance in reading traits, and might in future contribute to earlier identification and remediation of dyslexia.

The ability to read is crucial for success at school and access to employment, information and health and social services, and is related to attained socioeconomic status¹. Dyslexia is a neurodevelopmental disorder characterized by severe reading difficulties, present in 5–17.5% of the

population, depending on diagnostic criteria^{2,3}. It often involves impaired phonological processing (the decoding of sound units, or phonemes, within words) and frequently co-occurs with psychiatric and other developmental disorders⁴, especially attention-deficit hyperactivity disorder

¹Department of Psychology, University of Edinburgh, Edinburgh, UK. ²23andMe, Inc., Sunnyvale, CA, USA. ³Language and Genetics Department, Max Planck Institute for Psycholinguistics, Nijmegen, the Netherlands. ⁴Genetic Epidemiology Laboratory, QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia. ⁵School of Psychology, Shaanxi Normal University and Shaanxi Key Research Center of Child Mental and Behavioral Health, Xi'an, China. ⁶Donders Institute for Brain, Cognition and Behaviour, Radboud University, Nijmegen, the Netherlands. ⁷MRC Integrative Epidemiology Unit, University of Bristol, Bristol, UK. ⁸Centre for Genomic and Experimental Medicine, Institute of Genetics and Cancer, University of Edinburgh, Edinburgh, UK. ⁹School of Medicine, University of St Andrews, St Andrews, UK. ¹⁰Institute of Health and Neurodevelopment, Aston University, Birmingham, UK. ¹¹Office of the President, Tufts University, Medford, MA, USA. ¹²Department of Physiology, Anatomy and Genetics, Oxford University, Oxford, UK. ¹³Departments of Pediatrics and Genetics, Yale Medical School, New Haven, CT, USA. ¹⁴Department of Psychology and Neuroscience, University of Colorado, Boulder, CO, USA. ¹⁵Institute for Behavioral Genetics, University of Colorado, Boulder, CO, USA. ¹⁶Department of Psychology, University of Denver, Denver, CO, USA. ¹⁷Department of Neurological Sciences, College of Medicine, University of Nebraska Medical Center, Omaha, NE, USA. ¹⁸Queensland Brain Institute, University of Queensland, Brisbane, Queensland, Australia. *Lists of authors and their affiliations appear at the end of the paper. ✉e-mail: michelle.luciano@ed.ac.uk

(ADHD)^{5,6} and speech and language disorders^{7,8}. Dyslexia may represent the low extreme of a continuum of reading ability, a complex multifactorial trait with heritability estimates ranging from 40% to 80%^{9,10}. Identifying genetic risk factors not only aids increased understanding of the biological mechanisms, but may also expand diagnostic capabilities, facilitating earlier identification of individuals prone to dyslexia and co-occurring disorders for specific support.

Previous genome-wide investigations of dyslexia have been limited to linkage analyses of affected families¹¹ or modest ($n < 2,300$ cases) association studies of diagnosed children and adolescents¹². Candidate genes from linkage studies show inconsistent replication, and genome-wide association studies (GWAS) have not found significant associations, although *LOC388780* and *VEPFI* were supported in gene-based tests¹². Larger cohorts are vital for increasing sensitivity to detect new genetic associations of small effect. Here, we present the largest dyslexia GWAS to date, with 51,800 adults self-reporting a dyslexia diagnosis and 1,087,070 controls, all of whom are research participants with the personal genetics company 23andMe, Inc. We validate our association discoveries in independent cohorts, provide functional annotations of significant variants (mainly single-nucleotide polymorphisms (SNPs)) and potential causal genes, and estimates of SNP-based heritability. Lastly, we investigate genetic correlations with reading and related skills, health, socioeconomic, and psychiatric measures, and evaluate the evidence for previously implicated dyslexia candidate genes in our well-powered results.

Results

Genome-wide associations

The full dataset included 51,800 (21,513 males, 30,287 females) participants responding 'yes' to the question 'Have you been diagnosed with dyslexia?' (cases) and 1,087,070 (446,054 males, 641,016 females) participants responding 'no' (controls). Participants were aged 18 years or over (mean ages of cases and controls were 49.6 years (s.d. 16.2) and 51.7 years (s.d. 16.6), respectively). We identified 42 independent genome-wide significant associated loci ($P < 5 \times 10^{-8}$) and 64 loci with suggestive significance ($P < 1 \times 10^{-6}$) (Fig. 1 and Supplementary Table 1). Genomic inflation was moderate ($\lambda_{GC} = 1.18$) and consistent with polygenicity (see Q-Q plot, Extended Data Fig. 1). We also performed sex-specific GWAS and age-specific GWAS (younger or older than 55 years) because dyslexia prevalence was higher in our younger (5.34% in 20- to 30-year-olds) than older (3.23% in 80- to 90-year-olds) participants. These subsample analyses showed high consistency with the main GWAS (of the full sample). Genetic correlation estimated by linkage disequilibrium (LD) score regression (LDSC) was 0.91 (95% confidence intervals (CI): 0.86–0.96; $P = 8.26 \times 10^{-253}$) in males and females, and 0.97 (95% CI: 0.91–1.02; $P = 2.32 \times 10^{-268}$) between younger and older adults.

Of the 17 genome-wide significant variants in the female GWAS (Extended Data Fig. 2), all but four (rs61190714, rs4387605, rs12031924 and rs57892111) were significant in the main GWAS and, of these four, three were in LD with an SNP that approached significance ($P < 3.3 \times 10^{-7}$ or smaller) in the main analysis. Intergenic SNP rs57892111 (located between *TFAP2B* and *PKHD1* on chromosome 6p) was not among the significant or suggestive SNPs of the main analysis, and so may represent a female-specific variant. There is no evidence from existing GWAS that this SNP is associated with any other human trait. Of the six genome-wide significant variants in the male GWAS (Extended Data Fig. 3), all were significant in the main GWAS.

In the main GWAS, all significant variants were autosomal, except rs5904158 at Xq27.3 (for regional association plots, see Supplementary Fig. 1). A total of 17 index variants were in high LD with published (genome-wide significant) associated SNPs in the NHGRI GWAS Catalog¹³ (15 were associated with cognitive/educational traits; Supplementary Tables 1 and 2). Thus, a total of 27 associated loci showed no evidence of published genome-wide associations with traits expected

to overlap with dyslexia (for example, educational attainment, cognitive ability) and were considered new (Table 1).

Of 38 associated loci (the 4 remaining were tagged by indels unavailable in validation cohorts), 3 (rs13082684, rs34349354 and rs11393101) were significant at a Bonferroni-corrected level ($P < 0.05/38$) in the GenLang consortium GWAS meta-analysis of reading ($n = 33,959$) and spelling ($n = 18,514$) ability¹⁴. At $P < 0.05$, 18 were associated in GenLang, 3 in the NeuroDys case-control GWAS¹² ($n = 2,274$ cases), and 5 in the Chinese Reading Study (CRS) of reading accuracy and fluency ($n = 2,270$; Supplementary Note) (Table 1 and Supplementary Tables 3–6).

Gene-based tests identified 173 significantly associated genes (Supplementary Table 7) but no significantly enriched biological pathways (Supplementary Table 8). We estimated the LDSC liability-scale SNP-based heritability of dyslexia to be $h^2_{SNP} = 0.152$ (standard error = 0.006) using the 23andMe sample prevalence of 5%, and $h^2_{SNP} = 0.189$ (standard error = 0.008) using a 10% prevalence of dyslexia, which is more typical of the general population^{2,3}.

Fine-mapping and functional annotations

Within the credible variant set (Supplementary Table 1), missense variants were the most common (55%) of the coding variants; Extended Data Figure 4 summarizes all predicted variant effects. Predicted deleterious variants by SIFT (Sorting Intolerant From Tolerant) score were identified in *R3HCC1L*, *SH2B3*, *CCDC171*, *C1orf87*, *LOXL4*, *DLAT*, *ALG9* and *SORT1*. Within the credible variant set, no genes were especially intolerant to functional variation (smallest LoFtool (Loss-of-Function) percentile was 0.39). For the 42 associated loci, the most probable gene targets of each were estimated by the Overall V2G (Variant-to-Gene) score from OpenTargets (Supplementary Table 9). Two index variants (missense variant rs12737449 (*C1orf87*) and rs3735260 (*AUTS2*)) could be causal because they had combined annotation dependent depletion (CADD) scores suggestive of deleteriousness to gene function according to Kircher et al.¹⁵ (Supplementary Table 10). The *AUTS2* variant RegulomeDB rank of 2b indicated a regulatory role; its chromatin state supported location at an active transcription start site^{16,17}.

Of the 173 significant genes from genome-wide gene-based tests in MAGMA (see Supplementary Table 11 for their functions), 129 could be functionally annotated (Supplementary Table 12). Protein-coding and noncoding sequences are actively conserved in approximately three-quarters of these genes, 63% are more intolerant to variation than average and 33% are intolerant to loss-of-function mutations. Gene property analysis for general tissues and 13 brain tissues confirmed the importance of the brain and specific brain regions (Supplementary Tables 13 and 14). Levels of brain expression for 125 of the 173 significant genes from gene-based tests could be mapped in FUMA and are shown in Supplementary Table 15. A total of 20 genes showed high general brain expression levels and, of these, 3 (*PPP1R1B*, *NPM1* and *WASF3*) were located near significant SNP associations. Of the 12 brain regions assessed, gene expression was generally highest in the cerebellar hemisphere, cerebellum, and cerebral cortex, consistent with the results of gene property analysis.

Partitioned heritability

SNP-based heritability of dyslexia partitioned by functional annotation showed significant enrichment for conserved regions and H3K4me1 clusters (Supplementary Table 16 and Extended Data Fig. 5). There was enrichment in genes expressed in the frontal cortex, cortex and anterior cingulate cortex ($P < 4.17 \times 10^{-3}$) (Supplementary Table 17 and Extended Data Fig. 6), but not for brain cell type (Supplementary Table 18 and Extended Data Fig. 7). Enrichment was seen in enhancer and promoter regions, identified by the presence of H3K4me1 and H3K4me3 chromatin marks, respectively, in multiple central nervous system (CNS) tissues (Supplementary Tables 19 and 20 and Extended Data Figs. 8 and 9). Reading, an offshoot of spoken language, is a uniquely human

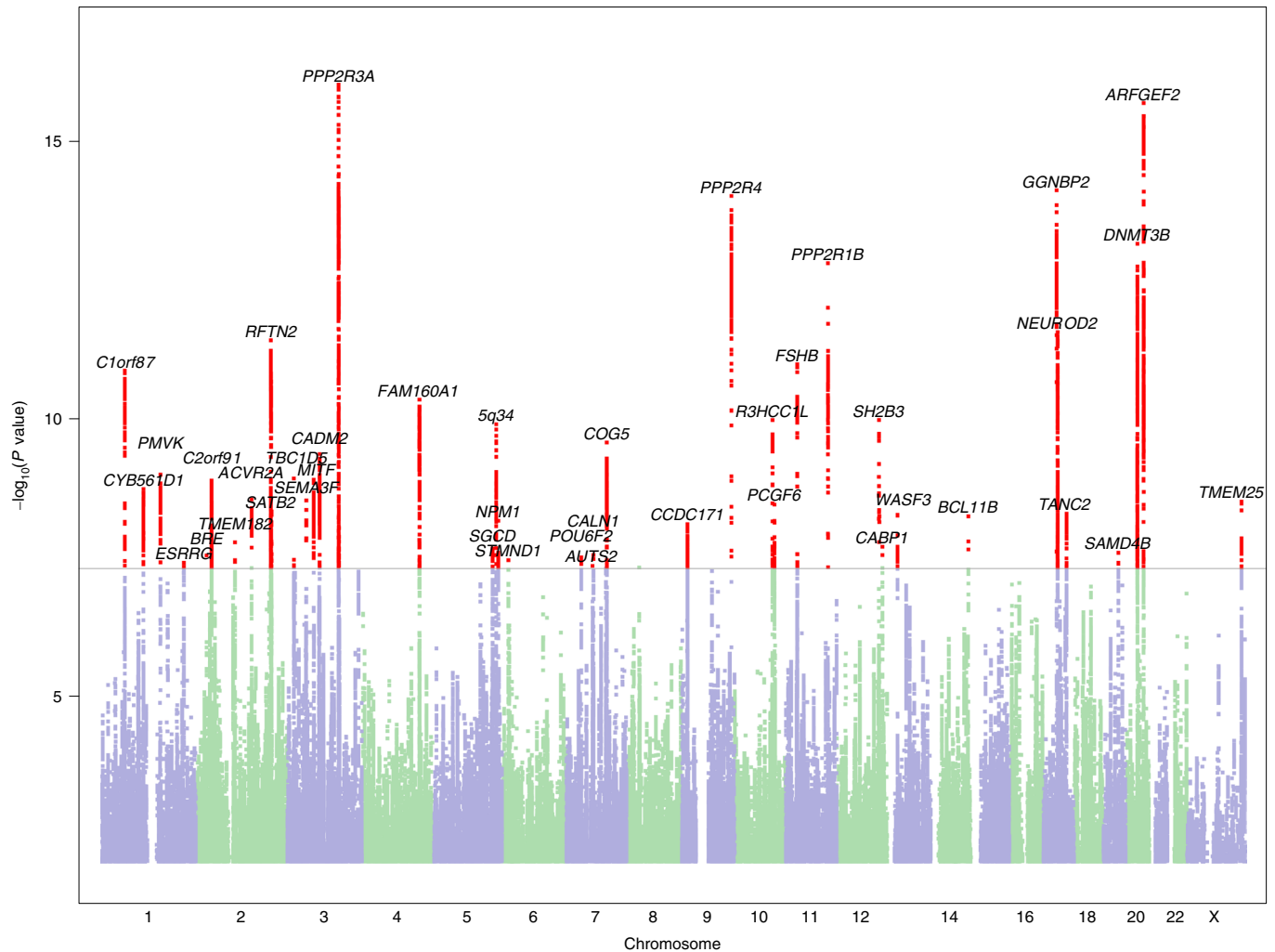


Fig. 1 | Manhattan plot of the genome-wide association analysis of dyslexia.

The y axis represents the $-\log_{10}P$ value for association of SNPs with self-reported dyslexia diagnosis from 51,800 individuals and 1,087,070 controls. The threshold for genome-wide significance ($P < 5 \times 10^{-8}$) is represented by a horizontal grey

line. Genome-wide significant variants in the 42 genome-wide significant loci are red. Variants located within a distance of <250 kb of each other are considered as one locus.

trait, but there was no enrichment for a range of annotations related to human evolution spanning the last 30 million to 50,000 years¹⁸ (Supplementary Table 21).

Genetic correlations and LDSC

Genetic correlations were estimated for 98 traits (Fig. 2 and Supplementary Table 22), including reading and spelling measures, from GenLang (Fig. 3), and brain subcortical structure volumes, total cortical surface area and thickness from the Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA) consortium. A total of 63 traits showed genetic correlations with dyslexia at the Bonferroni-corrected significance threshold ($P < 0.05/98$; Fig. 2). Genetic correlations (r_g) with quantitative reading and spelling measures ranged from -0.70 to -0.75 (lowest 95% CI of -0.60 , highest 95% CI of -0.86), and were -0.62 (95% CI: $-0.50, -0.74$) and -0.45 (95% CI: $-0.26, -0.64$) with phoneme awareness and nonword repetition measures, respectively. The childhood/adolescent performance (nonverbal) intelligence quotient (IQ) r_g was lower (-0.19 ; 95% CI: $-0.08, -0.30$) than that for adult verbal-numerical reasoning¹⁹ (-0.50 ; 95% CI: $-0.45, -0.55$) but similar to that for childhood IQ²⁰ (-0.32 ; 95% CI: $-0.21, -0.43$) and educational attainment²¹ (-0.22 ; 95% CI: $-0.15, -0.29$). Traits showing positive r_g included jobs involving heavy manual work²¹ (0.40 ; (95% CI: $0.34, 0.45$)), work-related/vocational qualifications²¹ (0.50 ; 95% CI:

$0.41, 0.59$), ADHD²² (0.53 ; 95% CI: $0.29, 0.77$), equal use of right and left hands²¹ (0.38 ; 95% CI: $0.19, 0.57$) and pain measures²¹ (average = 0.31 ; 95% CI: $0.21, 0.41$). Of the 11 ENIGMA measures tested, only intracranial volume was significantly correlated with dyslexia ($r_g = -0.14$; 95% CI: $-0.06, -0.22$). Targeted investigation of 80 structural neuroimaging measures from UK Biobank, including surface-based morphometry and diffusion-weighted imaging for brain circuitry linked to language, were nonsignificant at a Bonferroni-corrected significance level for number of independent traits. Phenotype independence was estimated by spectral decomposition of the phenotypic correlation matrix implied by the bivariate LDSC intercept from GWAS summary statistics of these traits, using the PhenoSpD toolkit²³ (Supplementary Table 23).

Polygenic score analyses

Dyslexia polygenic scores (PGS) based on the 23andMe dyslexia GWAS were computed in four independent cohorts and, overall, higher PGS were associated with lower reading and spelling accuracy (Supplementary Table 24). In two Australian population-based samples (1,647 adolescents, 1,163 adults), the dyslexia PGS explained up to 3.6% of variance in the reading and spelling measures, being most predictive of lower performance on tests of nonword reading, an index of phonological decoding. Dyslexia PGS did not correlate with scores on tests of nonword repetition (considered a marker of phonological short-term

Table 1 | New SNP associations with dyslexia, including gene-based results, eQTL status, expression in brain and validation in three independent cohorts (GenLang Consortium, CRS and NeuroDys)

Cytoband	SNP	Effect allele	Frequency	Odds Ratio	GWAS <i>P</i>	Gene(s)	Most probable gene	Validation cohort (<i>P</i> uncorrected for multiple testing)
chr1q21.3	rs4845687	A	0.56	1.044	1.1×10^{-9}	<i>KCNN3</i> , <i>PMVK</i>	<i>PMVK</i> ^{ab}	GenLang (0.02)
chr2q22.3	rs497418	A	0.38	1.043	3.0×10^{-9}	<i>ACVR2A</i>	<i>AC062032.1</i> ^c	GenLang (0.009)
chr2q33.1	rs72916919	G	0.51	1.049	4.1×10^{-12}	<i>RFTN2</i>	<i>MARS2</i> ^a	NeuroDys (0.02), GenLang (0.02)
chr3p12.1	rs10511073	A	0.37	1.046	4.6×10^{-10}	<i>CADM2</i>	<i>CADM2</i> ^a	GenLang (0.02)
chr3q22.3	rs13082684	A	0.24	1.069	1.0×10^{-16}	<i>PPP2R3A</i>	<i>PPP2R3A</i> (intron) ^a	GenLang (0.0004); not in CRS
chr6p22.3	rs2876430	T	0.34	1.041	3.7×10^{-8}	<i>ATXN1</i> , <i>STMND1</i>	<i>STMND1</i>	GenLang (0.04)
chr7p14.1	rs62453457	G	0.48	1.039	3.3×10^{-8}	<i>POU6F2</i>	<i>POU6F2</i>	CRS (0.04)
chr7q11.22	rs3735260	G	0.08	1.075	4.7×10^{-8}	<i>AUTS2</i>	<i>AUTS2</i>	GenLang (0.02)
chr7q11.22	rs77059784	G	0.97	1.123	3.0×10^{-8}	<i>CALN1</i>	<i>CALN1</i>	GenLang (0.02); not in CRS
chr9q34.11	rs9696811	C	0.69	1.069	1.1×10^{-16}	<i>PPP2R3A</i>	AL158151.4 ^{abc}	GenLang (0.03)
chr11q23.1	rs138127836	A	0.65	1.056	1.7×10^{-13}	<i>PPP2R1B</i>	<i>PPP2R1B</i> (intron) ^{ab}	GenLang (0.02)
chr17q23.3	rs72841395 ^c	C	0.77	1.049	5.4×10^{-9}	<i>TANC2</i>	<i>TANC2</i> ^a	GenLang (0.005)
chrXq27.3	rs5904158	GTA	0.65	1.037	3.3×10^{-8}	<i>TMEM257</i> , <i>CXorf51B</i> ^b	AL109653.3 ^c	GenLang (0.02); not in NeuroDys/CRS
chr2q12.1	rs367982014	CAAT	0.29	1.045	1.8×10^{-8}	<i>TMEM182</i>	<i>MFSD9</i> ^a	Not available
chr3p24.3	rs373178590	G	0.51	1.046	1.3×10^{-9}	<i>TBC1D5</i>	<i>TBC1D5</i> (intron) ^a	Not available
chr10q24.33	rs34732054	C	0.57	1.045	3.7×10^{-9}	<i>PCGF6</i>	<i>USMG5</i> ^a	Not available
chr13q12.13	rs375018025	CA	0.57	1.044	5.6×10^{-9}	<i>CDK8</i> , <i>WASF3</i>	<i>WASF3</i>	Not available
chr1p32.1	rs12737449	G	0.85	1.070	1.4×10^{-11}	<i>C1orf87</i>	<i>C1orf87</i> (missense) ^a	Not significant
chr2p23.2	rs1969131	T	0.17	1.053	3.0×10^{-8}	<i>BABAM2</i>	<i>BABAM2</i>	Not significant
chr3q26.33	rs7625418	C	0.21	1.056	4.3×10^{-9}	<i>PEX5L</i> , <i>TTC14</i>	<i>TTC14</i> ^a	Not significant
chr3p13	rs13097431	G	0.58	1.044	1.3×10^{-9}	<i>MITF</i>	<i>MITF</i> ^a	Not significant
chr5q33.3	rs867009	G	0.36	1.041	2.3×10^{-9}	<i>SGCD</i>	<i>SGCD</i> ^a	Not significant
chr9p22.3	rs3122702	T	0.5	1.041	8.3×10^{-9}	<i>CCDC171</i>	<i>CCDC171</i> ^{ab}	Not significant
chr10q24.2	rs10786387	C	0.68	1.049	1.1×10^{-10}	<i>CRAC1</i> , <i>R3HCC1L</i>	<i>R3HCC1L</i> ^a	Not significant
chr11p14.1	rs676217	G	0.37	1.050	1.1×10^{-11}	<i>KCNA4</i> , <i>FSHB</i>	<i>ARL14EP</i> ^{ab}	Not significant
chr19q13.2	rs60963584	A	0.89	1.065	2.7×10^{-8}	<i>GMFG</i> , <i>SAMD4B</i>	<i>SAMD4B</i> ^a	Not significant
chr20q11.21	rs4911257	C	0.39	1.055	7.5×10^{-14}	<i>DNMT3B</i>	<i>DNMT3B</i> (intron) ^{ab}	Not significant

Statistics for each variant are from the 23andMe GWAS (see Supplementary Table 1 for all 42 significant variants). Genes that are significant in gene-based tests are set in bold. Multi-allelic effect alleles represent insertions. The most probable gene is that most likely to be causal based on genetic and functional genomic data tied to the tag SNP (<https://platform.opentargets.org/>). ^aeQTL. ^beQTL linked to brain expression. ^cNot available in gene-based results.

memory). In developmental cohorts enriched for reading difficulties, the dyslexia PGS explained 3.7% (UKdys; $n = 930$) and 5.6% (CLDRC; $n = 717$) of variance in word recognition tests.

Analyses of dyslexia associations from the literature

Of 75 previously reported dyslexia associations, none showed genome-wide significance in our analyses (Supplementary Table 25). Of these targeted variants, 19 (in *ATP2C2*, *CMIP*, *CNTNAP2*, *DCDC2*, *DIP2A*, *DYX1C1*, *FOXP2*, *KIAA0319L* and *PCNT*) showed association surviving Bonferroni correction that accounted for LD ($P < 0.05/68.7$). In gene-based tests of 14 candidate genes from the literature^{24,25},

association at a Bonferroni level ($P < 0.05/14$) was seen for *KIAA0319L* ($P = 1.84 \times 10^{-4}$) and *ROBO1* ($P = 1.53 \times 10^{-3}$) (Supplementary Table 26). The *CNTNAP2* association approached corrected replication-level significance ($P = 0.004$). Targeted gene set analysis of three pathways previously implicated in dyslexia (Supplementary Table 27) showed replication-level support ($P = 2.00 \times 10^{-3}$) for the axon guidance pathway (comprising 216 genes).

Discussion

In the largest GWAS of dyslexia to date (>50,000 self-reported diagnoses), we identified 42 significant independent loci. Of these,

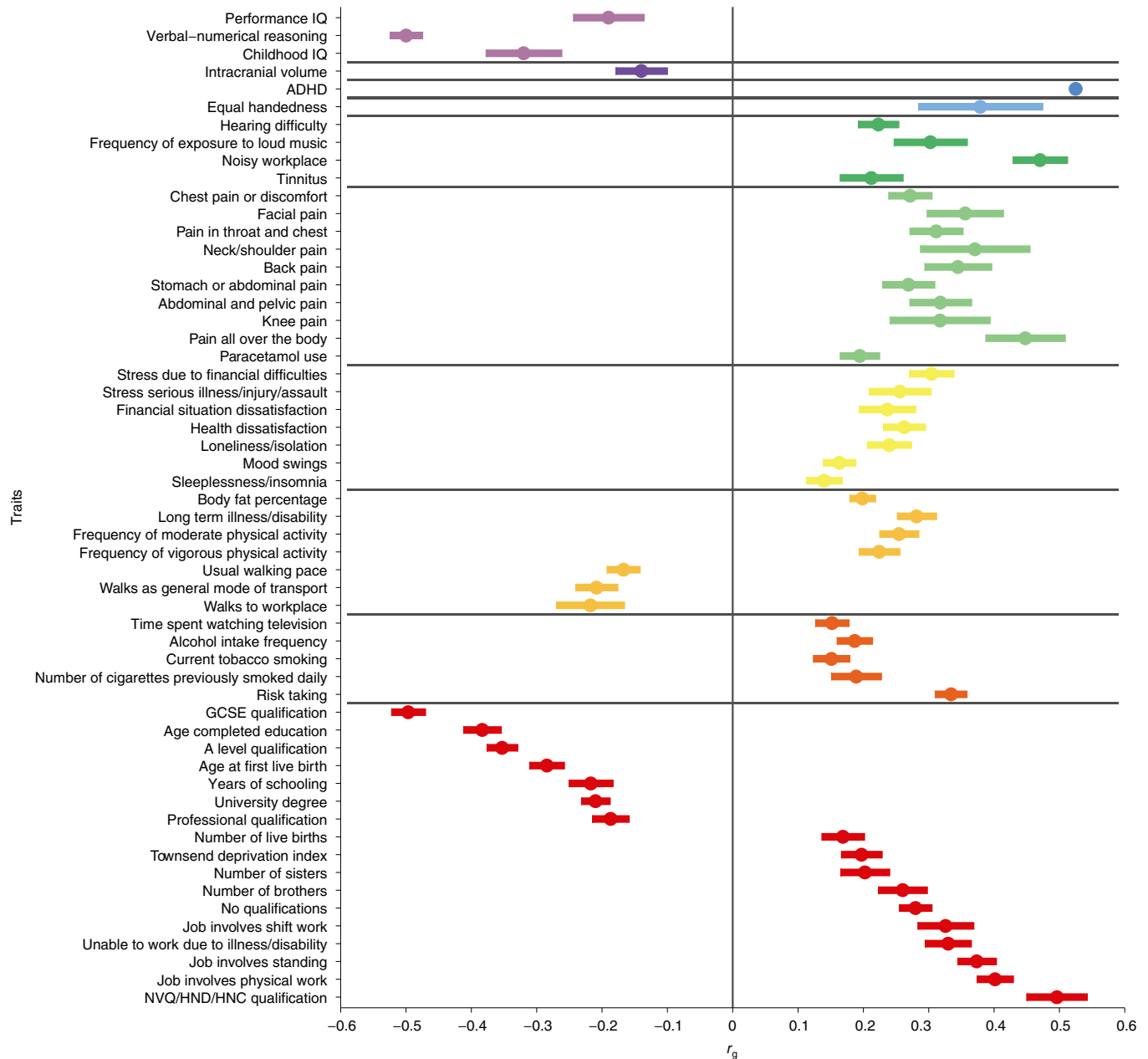


Fig. 2 | Genetic correlations of dyslexia with other phenotypes. Significant ($P < 5 \times 10^{-4}$) genetic correlations (r_g) between self-reported dyslexia diagnosis from 23andMe and other phenotypes from the LD Hub database and Enhancing Neuro Imaging Genetics Through Meta-Analysis (ENIGMA). We tested 98 traits but present only those that were significant after Bonferroni correction. Center points represent genetic correlations, and error bars represent standard errors

around the estimate; exact values can be found in Supplementary Table 22. The vertical line indicates a genetic correlation of zero, and the horizontal lines divide groups of related traits. GCSE, General Certificate of Secondary Education; HNC, Higher National Certificate; HND, Higher National Diploma; NVQ, National Vocational Qualification.

27 represent new associations that have not been uncovered in GWAS of related cognitive traits; 12 of the new associations were validated in the GenLang consortium GWAS meta-analysis of reading/spelling in English and other European languages¹⁴, and 1 in a Chinese language cohort. Of the significant SNPs, 36% overlapped with variants from general cognitive ability GWAS, consistent with twin studies that find that genetic variation in reading disability is explained by general and reading-specific cognitive ability¹⁰. Similar to other complex traits, and consistent with high polygenicity, each significant locus showed small effects (odds ratios (ORs) ranging from 1.04 to 1.12). Our estimated SNP-based heritability of 19% (assuming a 10% dyslexia population prevalence) was equal to that reported in a smaller GWAS¹², but lower than heritability estimates from twin studies (40–80%)^{26,27}. This

difference may be due partly to effects of rare and structural variants²⁸, which have been implicated in reading and related traits^{29,30}.

Whereas *AUTS2* has been implicated in autism³¹, intellectual disability³² and dyslexia³³, the variant we uncovered (rs3735260) represents the strongest *AUTS2* SNP association with a neurodevelopmental trait to date. Amongst our findings were other known neurodevelopmental genes, such as *TANC2* (implicated in language delay and intellectual disability^{34,35}) and, especially, *GGNBP2* (linked to neurodevelopmental delay³⁶ and autism³⁷) with variant rs34349354 supported in all our validation cohorts. However, rs34349354 is also associated with cognitive performance³⁸, and based on expression quantitative trait loci (eQTL) evidence is more likely linked to *ZNHIT3*, colocalizing with molecular QTLs (opentargets.org). Notably, none of the more established

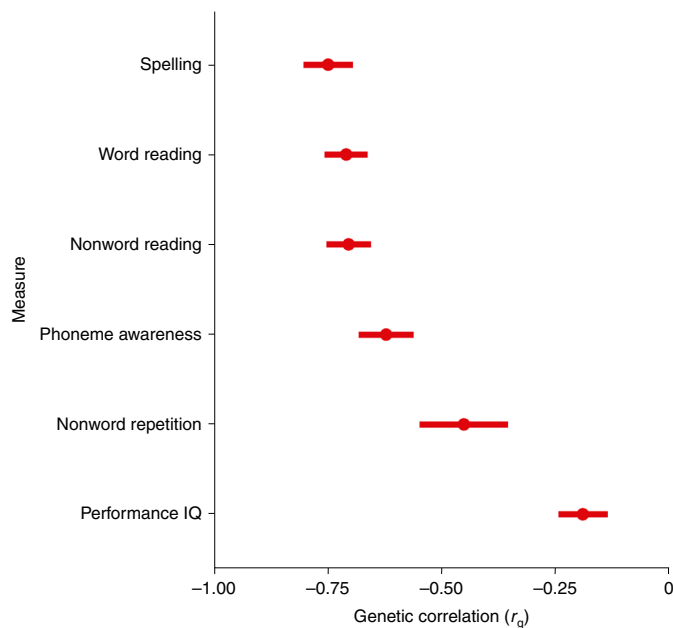


Fig. 3 | Genetic correlations between dyslexia and measures of reading, language and nonverbal IQ. Genetic correlations (r_g) between self-reported dyslexia diagnosis from 23andMe and measures of reading, language and performance (nonverbal) IQ in the GenLang consortium. Center points represent genetic correlations estimated in LDSC, and error bars represent standard errors around the estimate; exact values can be found in Supplementary Table 22.

candidate genes for dyslexia approached genome-wide significance in our results.

Like other human complex traits, partitioning of SNP-based heritability revealed enrichment in conserved regions³⁹. We further observed enrichment in the histone mark H3K4me1 (which has also been reported for ASD⁴⁰), and at H3K4me1 and H3K4me3 clusters in the CNS (marking enhancers and promoters, respectively). Since reading/writing systems are built on our capacities for spoken language, it is plausible that evolutionary changes on the human lineage helped shape the underlying genetic architecture⁴¹. However, we did not find enrichment of significant associations for curated annotations spanning different periods of hominin prehistory.

Our self-reported dyslexia diagnosis binary trait showed strong negative genetic correlations with quantitative reading and spelling measures, supporting the validity of this measure in the 23andMe cohort, and suggesting that reading skills and disorder are not qualitatively distinct. The positive genetic correlation between hearing difficulties and dyslexia is consistent with genetic correlations reported for childhood reading skill⁴², suggesting that hearing problems at an early age could affect acquisition of phonological processing skills.

Dyslexia showed moderately negative genetic correlations with adult verbal-numerical reasoning, but there was a lack of a strong genetic correlation of dyslexia with (nonverbal) performance IQ. This would be consistent with phenotypic observations that individuals with dyslexia are disadvantaged on verbal IQ tests⁴³. Educational attainment correlations were also not strong, which might reflect school adjustments and other support that counteract disadvantage in academic learning.

There was little evidence of common genetic variation in dyslexia being related to interindividual differences in subcortical volumes, or structural connectivity and morphometry for brain regions implicated in language processing in adults. Thus, the phenotypic correlations previously reported between dyslexia and aspects of neuroanatomy may in large part reflect environmental shaping of the brain, perhaps through the process of reading itself⁴⁴. Left-handedness

and ambidexterity show small genetic overlap with each other⁴⁵ yet are both phenotypically linked to neurodevelopmental disorders/cognitive abilities^{46,47}. We report a significant genetic correlation between dyslexia and self-reported equal hand use, but not left-handedness, supporting theories linking ambidexterity and dyslexia⁴⁸.

Dyslexia and ADHD^{5,6} often co-occur (24% reporting ADHD in our cases versus 9% in controls), and we show a moderate genetic correlation between the two, potentially reflecting shared endophenotypes like deficits in working memory and attention⁴⁹. Although we did not find significant genetic correlations between dyslexia and ASD, the GWAS for the latter encompassed diverse neurodevelopmental phenotypes, including subgroups with varying educational attainment and IQ⁴⁰. Genetic correlations with pain-related traits suggest that individuals with dyslexia may have a lower threshold for pain perception. Links between pain and other neurodevelopmental disorders have been reported^{50,51}.

Dyslexia polygenic scores were correlated with lower achievement on reading and spelling tests in population-based and reading-disorder enriched samples, especially for nonword reading, a measure of phonological decoding that is typically impaired in dyslexia. Polygenic scores could become a valuable tool to help identify children with a propensity for dyslexia, enabling learning support before development of reading skills. However, a limitation of our study is the potential for collider bias arising from sample selection (that is, people without dyslexia and from higher socioeconomic positions), which we were unable to quantify; thus, care should be taken in future research when using polygenic scores based on many variants⁵².

In summary, we report 42 new independent genome-wide significant loci associated with dyslexia, 27 of which have not been associated with cognitive-educational traits and should be prioritized for follow up as dyslexia candidates. Functional annotation of the variants highlights the importance of conserved and enhancer regions of the genome for this trait. Dyslexia shows positive genetic correlations with ADHD, vocational qualifications, physical occupations, ambidexterity and pain perception, and negative correlations with academic qualifications and cognitive ability; family-based methods are needed to dissociate pleiotropic and causal effects.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at <https://doi.org/10.1038/s41588-022-01192-y>.

References

- Ritchie, S. J. & Bates, T. C. Enduring links from childhood mathematics and reading achievement to adult socioeconomic status. *Psychol. Sci.* **24**, 1301–1308 (2013).
- Shaywitz, S. E., Shaywitz, B. A., Fletcher, J. M. & Escobar, M. D. Prevalence of reading disability in boys and girls: results of the Connecticut Longitudinal Study. *JAMA* **264**, 998–1002 (1990).
- Katusic, S. K., Colligan, R. C., Barbaresi, W. J., Schaid, D. J. & Jacobsen, S. J. Incidence of reading disability in a population-based birth cohort, 1976–1982, Rochester, Minn. *Mayo Clin. Proc.* **76**, 1081–1092 (2001).
- Carroll, J. M., Maughan, B., Goodman, R. & Meltzer, H. Literacy difficulties and psychiatric disorders: evidence for comorbidity. *J. Child Psychol. Psychiatry* **46**, 524–532 (2005).
- Margari, L. et al. Neuropsychopathological comorbidities in learning disorders. *BMC Neurol.* **13**, 198 (2013).
- Willcutt, E. G., Pennington, B. F. & DeFries, J. C. Twin study of the etiology of comorbidity between reading disability and attention-deficit/hyperactivity disorder. *Am. J. Med. Genet.* **96**, 293–301 (2000).

7. McArthur, G. M., Hogben, J. H., Edwards, V. T., Heath, S. M. & Mengler, E. D. On the 'specifics' of specific reading disability and specific language impairment. *J. Child Psychol. Psychiatry* **41**, 869–874 (2000).
8. Catts, H. W., Fey, M. E., Tomblin, J. B. & Zhang, X. A longitudinal investigation of reading outcomes in children with language impairments. *J. Speech Lang. Hear. Res.* **45**, 1142–1157 (2002).
9. Bates, T. C. et al. Genetic and environmental bases of reading and spelling: a unified genetic dual route model. *Read. Writ.* **20**, 147–171 (2007).
10. Haworth, C. M. A. et al. Generalist genes and learning disabilities: a multivariate genetic analysis of low performance in reading, mathematics, language and general cognitive ability in a sample of 8000 12-year-old twins. *J. Child Psychol. Psychiatry* **50**, 1318–1325 (2009).
11. Fisher, S. E. & DeFries, J. C. Developmental dyslexia: genetic dissection of a complex cognitive trait. *Nat. Rev. Neurosci.* **3**, 767–780 (2002).
12. Gialluisi, A. et al. Genome-wide association study reveals new insights into the heritability and genetic correlates of developmental dyslexia. *Mol. Psychiatry* **26**, 3004–3017 (2021).
13. Buniello, A. et al. The NHGRI-EBI GWAS catalog of published genome-wide association studies, targeted arrays and summary statistics 2019. *Nucleic Acids Res.* **47**, D1005–D1012 (2018).
14. Eising, E. et al. Genome-wide analyses of individual differences in quantitatively assessed reading- and language-related skills in up to 34,000 people. *Proc. Natl Acad. Sci. USA* **119**, e2202764119 (2022).
15. Kircher, M. et al. A general framework for estimating the relative pathogenicity of human genetic variants. *Nat. Genet.* **46**, 310–315 (2014).
16. Ernst, J. & Kellis, M. ChromHMM: automating chromatin-state discovery and characterization. *Nat. Methods* **9**, 215–216 (2012).
17. Kundaje, A. et al. Integrative analysis of 111 reference human epigenomes. *Nature* **518**, 317–330 (2015).
18. Tilot, A. K. et al. The evolutionary history of common genetic variants influencing human cortical surface area. *Cerebral Cortex* **31**, 1873–1887 (2020).
19. 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).
20. Benyamin, B. et al. Childhood intelligence is heritable, highly polygenic and associated with FBNPIL. *Mol. Psychiatry* **19**, 253–258 (2014).
21. Bycroft, C. et al. The UK Biobank resource with deep phenotyping and genomic data. *Nature* **562**, 203–209 (2018).
22. Middeldorp, C. M. et al. A genome-wide association meta-analysis of attention-deficit/hyperactivity disorder symptoms in population-based pediatric cohorts. *J. Am. Acad. Child Adolesc. Psychiatry* **55**, 896–905.e6 (2016).
23. Zheng, J. et al. PhenoSpD: an integrated toolkit for phenotypic correlation estimation and multiple testing correction using GWAS summary statistics. *Gigascience* **7**, giy090 (2018).
24. Luciano, M., Gow, A. J., Pattie, A., Bates, T. C. & Deary, I. J. The influence of dyslexia candidate genes on reading skill in old age. *Behav. Genet.* **48**, 351–360 (2018).
25. Doust, C. et al. The association of dyslexia and developmental speech and language disorder candidate genes with reading and language abilities in adults. *Twin Res. Hum. Genet.* **23**, 23–32 (2020).
26. Davis, C. J., Knopik, V. S., Olson, R. K., Wadsworth, S. J. & DeFries, J. C. Genetics and environmental influences on rapid naming and reading ability. *Ann. Dyslexia* **51**, 231–247 (2001).
27. Gayán, J. & Olson, R. K. Genetic and environmental influences on orthographic and phonological skills in children with reading disabilities. *Dev. Neuropsychol.* **20**, 483–507 (2001).
28. Hannula-Jouppi, K. et al. The axon guidance receptor gene *ROBO1* is a candidate gene for developmental dyslexia. *PLoS Genet.* **1**, e50 (2005).
29. Ganna, A. et al. Ultra-rare disruptive and damaging mutations influence educational attainment in the general population. *Nat. Neurosci.* **19**, 1563–1565 (2016).
30. Gialluisi, A. et al. Investigating the effects of copy number variants on reading and language performance. *J. Neurodev. Disord.* **8**, 17–17 (2016).
31. Oksenberg, N., Stevison, L., Wall, J. D. & Ahituv, N. Function and regulation of *AUTS2*, a gene implicated in autism and human evolution. *PLoS Genet.* **9**, e1003221 (2013).
32. Beunders, G. et al. Two male adults with pathogenic *AUTS2* variants, including a two-base pair deletion, further delineate the *AUTS2* syndrome. *Eur. J. Human Genet.* **23**, 803–807 (2015).
33. Girirajan, S. et al. Relative burden of large CNVs on a range of neurodevelopmental phenotypes. *PLoS Genet.* **7**, e1002334 (2011).
34. Wessel, K. et al. 17q23.2q23.3 de novo duplication in association with speech and language disorder, learning difficulties, incoordination, motor skill impairment, and behavioral disturbances: a case report. *BMC Med. Genet.* **18**, 119 (2017).
35. Guo, H. et al. Disruptive mutations in *TANC2* define a neurodevelopmental syndrome associated with psychiatric disorders. *Nat. Commun.* **10**, 4679 (2019).
36. Pasmant, E. et al. Characterization of a 7.6-Mb germline deletion encompassing the *NF1* locus and about a hundred genes in an *NF1* contiguous gene syndrome patient. *Eur. J. Hum. Genet.* **16**, 1459–1466 (2008).
37. Takata, A. et al. Integrative analyses of de novo mutations provide deeper biological insights into autism spectrum disorder. *Cell Reports* **22**, 734–747 (2018).
38. 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).
39. Finucane, H. K. et al. Partitioning heritability by functional annotation using genome-wide association summary statistics. *Nat. Genet.* **47**, 1228–1235 (2015).
40. Grove, J. et al. Identification of common genetic risk variants for autism spectrum disorder. *Nat. Genet.* **51**, 431–444 (2019).
41. Mozzi, A. et al. The evolutionary history of genes involved in spoken and written language: beyond *FOXP2*. *Sci. Rep.* **6**, 22157 (2016).
42. Schmitz, J., Abbondanza, F. & Paracchini, S. Genome-wide association study and polygenic risk score analysis for hearing measures in children. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* **186**, 318–328 (2021).
43. Vellutino, F. Alternative conceptualizations of dyslexia: evidence in support of a verbal-deficit hypothesis. *Harvard Educ. Rev.* **47**, 334–354 (2012).
44. Dehaene, S., Cohen, L., Morais, J. & Kolinsky, R. Illiterate to literate: behavioural and cerebral changes induced by reading acquisition. *Nat. Rev. Neurosci.* **16**, 234–244 (2015).
45. Cuellar-Partida, G. et al. Genome-wide association study identifies 48 common genetic variants associated with handedness. *Nat. Hum. Behav.* **5**, 59–70 (2021).
46. Papadatou-Pastou, M. et al. Human handedness: a meta-analysis. *Psychol. Bull.* **146**, 481–524 (2020).
47. Peters, M., Reimers, S. & Manning, J. T. Hand preference for writing and associations with selected demographic and behavioral variables in 255,100 subjects: the BBC internet study. *Brain Cogn.* **62**, 177–189 (2006).

48. Brandler, W. M. & Paracchini, S. The genetic relationship between handedness and neurodevelopmental disorders. *Trends Mol. Med.* **20**, 83–90 (2014).
49. Willcutt, E. G., Pennington, B. F., Olson, R. K., Chhabildas, N. & Hulslander, J. Neuropsychological analyses of comorbidity between reading disability and attention deficit hyperactivity disorder: in search of the common deficit. *Dev. Neuropsychol.* **27**, 35–78 (2005).
50. Gu, X. et al. Heightened brain response to pain anticipation in high-functioning adults with autism spectrum disorder. *Eur. J. Neurosci.* **47**, 592–601 (2018).
51. Whitney, D. G. & Shapiro, D. N. National prevalence of pain among children and adolescents with autism spectrum disorders. *JAMA Pediatr.* **173**, 1203–1205 (2019).
52. Munafò, M. R., Tilling, K., Taylor, A. E., Evans, D. M. & Davey Smith, G. Collider scope: when selection bias can substantially influence observed associations. *Int. J. Epidemiol.* **47**, 226–235 (2018).

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

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit <http://creativecommons.org/licenses/by/4.0/>.

© The Author(s) 2022

23andMe Research Team

Stella Aslibekyan², Adam Auton², Elizabeth Babalola², Robert K. Bell², Jessica Bielenberg², Katarzyna Bryc², Emily Bullis², Daniella Coker², Gabriel Cuellar Partida², Devika Dhamija², Sayantan Das², Sarah L. Elson², Teresa Filshtein², Kipper Fletez-Brant², Pierre Fontanillas², Will Freyman², Pooja M. Gandhi², Karl Heilbron², Barry Hicks², David A. Hinds², Ethan M. Jewett², Yunxuan Jiang², Katelyn Kukar², Keng-Han Lin², Maya Lowe², Jey McCreight², Matthew H. McIntyre², Steven J. Micheletti², Meghan E. Moreno², Joanna L. Mountain², Priyanka Nandakumar², Elizabeth S. Noblin², Jared O'Connell², Aaron A. Petrakovitz², G. David Poznik², Morgan Schumacher², Anjali J. Shastri², Janie F. Shelton², Jingchunzi Shi², Suyash Shringarpure², Vinh Tran², Joyce Y. Tung², Xin Wang², Wei Wang², Catherine H. Weldon², Peter Wilton², Alejandro Hernandez², Corinna Wong² and Christophe Toukam Tchakouté²

Quantitative Trait Working Group of the GenLang Consortium

Filippo Abbondanza⁹, Andrea G. Allegrini¹⁹, Till F. M. Andlauer^{20,21}, Cathy L. Barr^{22,23,24}, Timothy C. Bates¹, Manon Bernard²⁵, Kirsten Blokland²³, Milene Bonte²⁶, Dorret I. Boomsma^{27,28,29}, Thomas Bourgeron^{30,31}, Daniel Brandeis^{32,33,34,35}, Manuel Carreiras^{36,37,38}, Fabiola Ceroni^{39,40}, Valéria Csépe^{41,42}, Philip S. Dale⁴³, John C. DeFries^{14,15}, Peter F. de Jong⁴⁴, Jean Francois Démonet⁴⁵, Eveline L. de Zeeuw²⁸, Else Eising³, Yu Feng⁴⁶, Simon E. Fisher^{3,6}, Marie-Christine J. Franken⁴⁷, Clyde Francks^{3,6}, Margot Gerritse³, Alessandro Gialluisi^{20,48}, Scott D. Gordon⁴, Jeffrey R. Gruen¹³, Sharon L. Guger⁴⁹, Marianna E. Hayiou-Thomas⁵⁰, Juan Hernández-Cabrera⁵¹, Jouke-Jan Hottenga²⁸, Charles Hulme⁵², Philip R. Jansen^{53,54,55}, Juha Kere^{56,57}, Elizabeth N. Kerr^{49,58,59}, Tanner Koomar⁶⁰, Karin Landerl^{61,62}, Gabriel T. Leonard⁶³, Zhijie Liao⁶⁴, Maureen W. Lovett^{23,59}, Michelle Luciano¹, Heikki Lyytinen⁶⁵, Nicholas G. Martin⁴, Angela Martinelli⁹, Urs Maurer⁶⁶, Jacob J. Michaelson⁶⁰, Nazanin Mirza-Schreiber⁶⁷, Kristina Moll⁶⁸, Anthony P. Monaco¹¹, Angela T. Morgan^{69,70,71}, Bertram Müller-Myhsok^{20,72}, Dianne F. Newbury⁴⁰, Markus M. Nöthen⁷³, Richard K. Olson^{14,15}, Silvia Paracchini⁹, Tomas Paus^{74,75,76}, Zdenka Pausova^{25,77}, Craig E. Pennell^{78,79,80}, Bruce F. Pennington¹⁶, Robert J. Plomin¹⁹, Kaitlyn M. Price^{23,24,46}, Franck Ramus⁸¹, Sheena Reilly^{69,82}, Louis Richer⁸³, Kaili Rimfeld¹⁹, Gerd Schulte-Körne⁶⁸, Chin Yang Shapland^{7,84}, Nuala H. Simpson⁸⁵, Shelley D. Smith¹⁷, Margaret J. Snowling^{85,86}, Beate St Pourcain^{3,6,7}, John F. Stein⁸⁷, Lisa J. Strug^{88,89}, Joel B. Talcott¹⁰, Henning Tiemeier^{53,90}, J. Bruce Tomblin⁹¹, Dongnhu T. Truong¹³, Elsje van Bergen^{27,28,92}, Marc P. van der Schoeff^{93,94}, Marjolein Van Donkelaar³, Ellen Verhoef³, Carol A. Wang^{78,79}, Kate E. Watkins⁸⁵, Andrew J. O. Whitehouse⁹⁵, Karen G. Wigg⁴⁶, Erik G. Willcutt^{14,15}, Margaret Wilkinson²³, Margaret J. Wright¹⁸ and Gu Zhu⁴

¹⁹Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK.

²⁰Translational Research in Psychiatry, Max Planck Institute of Psychiatry, Munich, Germany. ²¹Department of Neurology, Klinikum rechts der Isar, School of Medicine, Technical University of Munich, Munich, Germany. ²²Division of Experimental and Translational Neuroscience, Krembil Research Institute, University Health Network, Toronto, Ontario, Canada. ²³Program in Neuroscience and Mental Health, Hospital for Sick Children, Toronto, Ontario, Canada.

²⁴Department of Physiology, University of Toronto, Toronto, Ontario, Canada. ²⁵Departments of Physiology and Nutritional Sciences, Hospital for Sick Children, Toronto, Ontario, Canada. ²⁶Department of Cognitive Neuroscience and Maastricht Brain Imaging Center, Faculty of Psychology and Neuroscience, Maastricht University, Maastricht, the Netherlands. ²⁷Netherlands Twin Register, Amsterdam, the Netherlands. ²⁸Department of Biological Psychology, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands. ²⁹Amsterdam Reproduction and Development (AR&D) Research Institute, Amsterdam, the Netherlands. ³⁰Human Genetics and Cognitive Functions Unit, Institut Pasteur, Paris, France. ³¹CNRS UMR 3571, Université de Paris, Paris, France. ³²Department of Child and Adolescent Psychiatry and Psychotherapy, Psychiatric Hospital, University of Zurich, Zurich, Switzerland. ³³Zurich Center for Integrative Human Physiology (ZIHP), University of Zurich and ETH Zurich, Zurich, Switzerland. ³⁴Neuroscience Center Zurich, University of Zurich and ETH Zurich, Zurich, Switzerland. ³⁵Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany. ³⁶Basque Center on Cognition, Brain and Language (BCBL), Donostia-San Sebastian, Spain. ³⁷Ikerbasque, Basque Foundation for Science, Bilbao, Spain. ³⁸Lengua Vasca y Comunicación, University of the Basque Country (UPV/EHU),

Bilbao, Spain. ³⁹Department of Pharmacy and Biotechnology, University of Bologna, Bologna, Italy. ⁴⁰Faculty of Health and Life Sciences, Oxford Brookes University, Oxford, UK. ⁴¹Brain Imaging Centre, Research Centre for Natural Sciences, Budapest, Hungary. ⁴²Multilingualism Doctoral School, Faculty of Modern Philology and Social Sciences, University of Pannonia, Veszprém, Hungary. ⁴³Department of Speech and Hearing Sciences, University of New Mexico, Albuquerque, NM, USA. ⁴⁴Department of Child Development and Education, University of Amsterdam, Amsterdam, the Netherlands. ⁴⁵Leenaards Memory Centre, Department of Clinical Neurosciences Lausanne University Hospital (CHUV), University of Lausanne, Lausanne, Switzerland. ⁴⁶Genetics and Development Division, Krembil Research Institute, University Health Network, Toronto, Ontario, Canada. ⁴⁷Department of Otorhinolaryngology, Erasmus University Medical Centre, Rotterdam, the Netherlands. ⁴⁸Department of Epidemiology and Prevention, IRCCS Istituto Neurologico Mediterraneo Neuromed, Pozzilli, Italy. ⁴⁹Department of Psychology, Hospital for Sick Children, Toronto, Ontario, Canada. ⁵⁰Department of Psychology, University of York, York, UK. ⁵¹Departamento de Psicología Clínica Psicobiología y Metodología, Universidad de La Laguna, Santa Cruz de Tenerife, Spain. ⁵²Department of Education, University of Oxford, Oxford, UK. ⁵³Department of Child and Adolescent Psychiatry/Psychology, Erasmus University Medical Center, Rotterdam, the Netherlands. ⁵⁴Department of Complex Trait Genetics, Center for Neurogenomics and Cognitive Research, Amsterdam Neuroscience, VU University, Amsterdam, the Netherlands. ⁵⁵Department of Human Genetics, VU Medical Center, Amsterdam UMC, Amsterdam, the Netherlands. ⁵⁶Department of Biosciences and Nutrition, Karolinska Institutet, Stockholm, Sweden. ⁵⁷Stem Cells and Metabolism Research Program, University of Helsinki, and Folkhälsan Research Center, Helsinki, Finland. ⁵⁸Department of Neurology, Hospital for Sick Children, Toronto, Ontario, Canada. ⁵⁹Department of Paediatrics, The University of Toronto, Toronto, Ontario, Canada. ⁶⁰Department of Psychiatry, University of Iowa, Iowa City, IA, USA. ⁶¹Institute of Psychology, University of Graz, Graz, Austria. ⁶²BioTechMed-Graz, Graz, Austria. ⁶³Cognitive Neuroscience Neurology and Neurosurgery, Montreal, Quebec, Canada. ⁶⁴Department of Psychology, University of Toronto, Toronto, Ontario, Canada. ⁶⁵Department of Psychology, University of Jyväskylä, Jyväskylä, Finland. ⁶⁶Department of Psychology, The Chinese University of Hong Kong, Hong Kong, China. ⁶⁷Institute of Neurogenomics, Helmholtz Zentrum München, Munich, Germany. ⁶⁸Department of Child and Adolescent Psychiatry, Psychosomatics, and Psychotherapy, LMU University Hospital Munich, Munich, Germany. ⁶⁹Speech and Language, Murdoch Children's Research Institute, Melbourne, Victoria, Australia. ⁷⁰Department of Audiology and Speech Pathology, University of Melbourne, Melbourne, Victoria, Australia. ⁷¹Speech Pathology Department, Royal Children's Hospital, Melbourne, Victoria, Australia. ⁷²Department of Health Science, University of Liverpool, Liverpool, UK. ⁷³Institute of Human Genetics, University Hospital of Bonn, Bonn, Germany. ⁷⁴Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada. ⁷⁵Departments of Psychiatry and Neuroscience and Centre Hospitalier Universitaire Sainte Justine, University of Montreal, Montreal, Quebec, Canada. ⁷⁶Department of Psychology, University of Toronto, Toronto, Ontario, Canada. ⁷⁷Hospital for Sick Children, Toronto, Ontario, Canada. ⁷⁸School of Medicine and Public Health, College of Health, Medicine and Wellbeing, University of Newcastle, Newcastle, New South Wales, Australia. ⁷⁹Mothers and Babies Research Centre, Hunter Medical Research Institute, Newcastle, New South Wales, Australia. ⁸⁰Maternity and Gynaecology, John Hunter Hospital, Newcastle, New South Wales, Australia. ⁸¹Laboratoire de Sciences Cognitives et Psycholinguistique, Ecole Normale Supérieure, PSL University, EHESS, CNRS, Paris, France. ⁸²Menzies Health Institute Queensland, Griffith University, Gold Coast, Queensland, Australia. ⁸³Department of Health Sciences, Université du Québec à Chicoutimi, Chicoutimi, Quebec, Canada. ⁸⁴Population Health Sciences, University of Bristol, Bristol, UK. ⁸⁵Department of Experimental Psychology, University of Oxford, Oxford, UK. ⁸⁶St John's College, University of Oxford, Oxford, UK. ⁸⁷Department of Physiology, Anatomy and Genetics, Oxford University, Oxford, UK. ⁸⁸Departments of Statistical Sciences and Computer Science and Division of Biostatistics, University of Toronto, Toronto, Ontario, Canada. ⁸⁹Program in Genetics and Genome Biology and The Centre for Applied Genomics, Hospital For Sick Children, Toronto, Ontario, Canada. ⁹⁰Harvard T.H. Chan School of Public Health, Boston, MA, USA. ⁹¹Communication Sciences and Disorders, University of Iowa, Iowa City, IA, USA. ⁹²Research Institute LEARN!, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands. ⁹³Department of Otolaryngology, Head and Neck Surgery, Erasmus MC, Rotterdam, the Netherlands. ⁹⁴Generation R Study Group, Erasmus MC, Rotterdam, the Netherlands. ⁹⁵Telethon Kids Institute, The University of Western Australia, Perth, Western Australia, Australia.

Methods

GWAS participants

Participants were drawn from the customer base of 23andMe, Inc., a consumer genetics company. Participants provided informed consent and participated in the research online, under a protocol approved by the external AAHRPP-accredited IRB, Ethical and Independent Review Services (www.eandireview.com). They included 51,800 (21,513 male, 30,287 female) participants who responded 'yes' to the question 'Have you been diagnosed with dyslexia?' (cases) and 1,087,070 (446,054 male, 641,016 female) participants who responded 'no' (controls). Age ranged from 18 to 110 years, with the prevalence of dyslexia higher for younger participants (5.34% in those aged 20–30 years) than older participants (3.23% in those aged 80–90 years). The negative linear relationship between dyslexia prevalence and participant age was expected given that screening for specific learning difficulties has only become commonplace in more recent decades. Moreover, this aligns with findings from the subsample (4.3%) of participants who reported age of diagnosis: younger participants were diagnosed at an earlier age (for example, 9.7 years (± 4.7) for 20- to 30-year-olds) than older participants (for example, 22.4 years (± 17.8) for 80- to 90-year-olds). The prevalence of dyslexia in our sample was similar for women (4.51%) and men (4.6%), although the slightly higher prevalence in males in this very large sample was statistically significant ($P < 8.7 \times 10^{-6}$). Such a prevalence lies at the lower end of the range typically reported in the US population³ and might represent the more severe cases of dyslexia given that a formal diagnosis was required; additionally, people with dyslexia might opt out of survey research that requires reading, further restricting the sample range.

Genotyping and imputation

DNA was extracted from saliva samples and genotyped on one of five genotyping platforms by the National Genetics Institute (NGI). In the present analysis, only participants with European ancestry were included. Details about the genotyping arrays, quality control of samples and ancestry derivation can be found in Fontanillas et al.⁵³ and the Supplementary Note. Phased genotypes were imputed to a combined reference panel of the 1000 Genomes Phase 3 haplotypes (May 2015) and the UK10K imputation reference panel using Minimac3 (see Das et al.⁵⁴).

Association analysis

Association analysis was performed on genotyped and imputed SNP dosage data using logistic regression and assuming an additive model of allelic effects. For X-chromosome analysis, male genotypes were treated as homozygous diploid. Covariates included age, age squared, gender, the first five ancestry principal components and genotype platform. SNP significance was evaluated by a likelihood ratio test, and genome-wide significance was determined as $P < 5 \times 10^{-8}$ (suggestive significance level as $P < 1 \times 10^{-6}$). Only reliably imputed SNPs ($r^2 > 0.80$) and those with minor allele frequency (MAF) > 0.01 are presented ($n = 7,995,923$). We define associated regions by first identifying all variants with $P < 5 \times 10^{-8}$, then grouping these variants into regions separated by gaps of at least 250 kb. Index variants are the variants with smallest P value within each associated region. We use the same approach for regions with suggestive associations, but by first identifying all variants with $P < 10^{-5}$. Subsidiary genome-wide association analysis of separate male ($n = 21,513$ cases, 446,054 controls) and female ($n = 30,287$ cases, 641,016 controls) groups, and younger (below 55 years; $n = 30,763$ cases, 582,276 controls) and older (55 and above; $n = 21,037$ cases, 504,794 controls) groups was performed. The latter was to check whether reliability of diagnosis (assumed to be higher in the younger sample whose recall of diagnosis should be better and who would have been exposed to greater levels of dyslexia screening) affected the GWAS signal.

We also looked to independently validate our genome-wide significant variants within (1) a published GWAS meta-analysis of 2,274

dyslexia cases from nine European countries representing six different languages (NeuroDys) by Gialluisi et al.⁵⁵; (2) a population sample (Chinese Reading Study; CRS) of children measured on quantitative traits of reading accuracy and reading fluency ($n = 2,270$; described in the Supplementary Note), and; (3) within the GenLang quantitative trait GWAS meta-analysis of word reading (up to $n = 33,959$) and spelling (up to $n = 18,514$) skills measured in cohorts of children and adolescents from Europe, the United States and Australia, and representing seven European languages, of which English was the most common¹⁴.

Gene-based analyses

The GWAS results were used to calculate gene-based P values for association with dyslexia by performing the gene analysis in MAGMA v.1.08 (ref.⁵⁶) through the FUMA interface⁵⁷ using standard settings. In total, 19,039 genes were tested, and P values were judged based on a Bonferroni-corrected significance threshold of $P < 2.63 \times 10^{-6}$. We also performed gene set analyses for association of biological pathways (all available gene ontology (GO) terms and curated gene sets from the Molecular Signatures Database (MsigDB)^{58,59}) with dyslexia in MAGMA through the FUMA interface. The total number of pathways tested was 15,486, and P values were judged based on a Bonferroni-corrected significance threshold of $P < 3.23 \times 10^{-6}$.

Biological annotations

Genome-wide significant variants and nearby gene(s) were annotated using external reference data and evaluated for functional or regulatory impact. A 99% credible set of potentially causal variants for SNPs in significant regions was based on approximate Bayes factor (ABFs)⁶⁰ assuming a prior variance of 0.1, and using the method of Maller et al.⁶¹ to define these sets. Variant effect prediction of these was done in ENSEMBL (release 104)⁶². For genome-wide significant variants, we considered: gene context (whether a variant is intergenic or located within a specific functional region within a gene locus); deleteriousness (Combined Annotation Dependent Depletion (CADD) score); functionality (RegulomeDB (RDB) category); chromatin state (minimum and common 15-core chromatin state); and SNP-trait associations reported in the NHGRI GWAS Catalog¹³.

For each variant, the most probable gene target was identified using the Open Target Genetics portal⁶³, which draws on evidence from QTL and chromatin interaction experiments, functional predictions and distance from a gene's transcription start site. For genome-wide significant genes, we considered: loss-of-function intolerance (probability of loss-of-function Intolerance (pLI) score); variation intolerance (residual variation intolerance score, RVIS); variation intolerance in noncoding regions (noncoding RVIS, ncRVIS); evolutionary constraint of noncoding regions (noncoding genomic evolutionary rate profiling (ncGERP) score); evolutionary constraint of protein-coding regions (protein-coding genomic evolutionary rate profiling (pcGERP) score); deleteriousness across noncoding regions (noncoding CADD (ncCADD) score); combined functionality of variants in noncoding regions (noncoding genome-wide annotation of variants (ncGWAVA) score); and expression in 12 brain tissues (amygdala, anterior cingulate cortex, caudate basal ganglia, cerebellar hemisphere, cerebellum, cortex, frontal cortex, hippocampus, hypothalamus, nucleus accumbens basal ganglia, putamen basal ganglia and substantia nigra). All annotations were obtained through FUMA⁵⁷ except RVIS, ncGERP, pcGERP, ncCADD and ncGWAVA, which were taken from Petrovski et al.⁶⁴. Details of each annotation including original sources are in the Supplementary Note.

Partitioned heritability

We partitioned SNP heritability of dyslexia using stratified LDSC, as described by Finucane et al.³⁹, to determine whether SNPs that share the greatest proportion of the heritability are also clustered in specific functional categories in the genome. Overall, we performed 266 different

tests, which would give a very conservative Bonferroni-corrected significance level of 1.88×10^{-4} , but because there will be overlap among annotation groups, we also report corrections to significance within different classes of annotation, each of which we now describe. Partitioning was performed for the 24 main functional annotations defined by Finucane et al.³⁹. LD scores, regression weights and allele frequencies are from European ancestry samples and were retrieved from <https://alkesgroup.broadinstitute.org/LDSCORE>. Heritability estimates were considered statistically significant if the *P* value surpassed an α level of 2.08×10^{-3} , derived by Bonferroni correction based on 24 tests.

We also estimated the enrichment for heritability of dyslexia for tissue-specific annotations, while controlling for the annotations in the baseline model, including gene expression in three brain cell types, gene expression in 12 brain regions, and chromatin marks H3K4me1 and H3K4me3 in multiple tissues (108 and 114, respectively) since these marks are enriched at enhancers⁶⁵ and promoters⁶⁶, respectively. Enrichment is the proportion of SNP heritability divided by the proportion of SNPs. For the brain cell types, we estimated enrichment for heritability of dyslexia for genes expressed in neurons, astrocytes, and oligodendrocytes using data from Cahoy et al.⁶⁷. Enrichments were considered statistically significant if the *P* value surpassed an α level of 0.017, derived by Bonferroni correction based on three tests. The gene expression data used to estimate the enrichment of heritability in genes expressed in certain brain regions was from the GTEx database⁶⁸, and the Bonferroni-derived α level for enrichment was 4.17×10^{-3} (based on 12 tests). Chromatin annotations include data from the Roadmap Epigenomics consortium¹⁷ and EN-TEX^{69,70}. For H3K4me1, the Bonferroni-derived α level for enrichment was 4.63×10^{-4} (based on 108 tests) and, for H3K4me3, the Bonferroni-derived α level for enrichment was 4.39×10^{-4} (based on 114 tests).

Evolutionary annotations. Although reading and writing is a human cultural invention, it builds on fundamental pathways involved in language processing. Therefore, we investigated whether annotations related to human evolution were significantly enriched for heritability of dyslexia by applying an evolutionary analysis pipeline adapted from Tilot et al.¹⁸. These analyses capture a range of periods in an evolutionary timeframe on the lineage that led to humans, from approximately 30 million years ago to 50,000 years ago.

Enrichment of heritability was estimated in adult brain human gained enhancers (HGEs)⁷¹, fetal brain HGEs⁷², ancient selective sweep regions⁷³, Neanderthal-introgressed SNPs⁷⁴ and Neanderthal-depleted regions⁷⁵ (see Supplementary Note for a description of each annotation); and controlled for using the baselineLD v.2 model from Gazal et al.⁷⁶. Heritability enrichment in human adult and fetal HGEs were additionally controlled for adult and fetal brain active regulatory elements from the Roadmap Epigenomics resource¹⁷. Active regulatory elements were defined using chromHMM¹⁶. Enrichment *P* values were judged by an α level of 10^{-2} , derived by Bonferroni correction based on five tests.

Genetic correlations

Genetic correlations within the 23andMe GWAS of dyslexia. Genetic correlation between self-reported dyslexia diagnosis in males and females, and between younger (<55 years old) and older (≥ 55 years old) adults was calculated using LDSC^{77,78}.

Genetic correlations of dyslexia with other traits. We present the pairwise genetic correlation of dyslexia with 98 traits. Summary statistics for most of these traits are publicly available through LD Hub^{77–79} – a centralized database and web interface that automates the LDSC regression analysis pipeline. A selection of brain magnetic resonance imaging measures obtained from the ENIGMA-3 consortium^{80–83}, and measures of reading and spelling accuracy, and performance IQ from the GenLang Consortium¹⁴ were analyzed locally using LDSC. Word

reading accuracy in GenLang was measured by the number of correct words read aloud from a list in a time restricted or unrestricted fashion. Examples of tools that include this measure are Test of Word Reading Efficiency (TOWRE), the British Ability Scales (BAS) and the Wide Range Achievement Test (WRAT). Spelling accuracy in GenLang was measured by the number of words correctly spelled orally or in writing. The words were dictated as single words or in a sentence. Examples of tools that include this measure are the BAS, WRAT and Wechsler Objective Reading Dimensions (WORD). Performance IQ in GenLang was based on subtests of IQ tests that did not depend on verbal cues, as included for example in the BAS and Wechsler Intelligence Scale for Children (WISC). Trait descriptions and summary statistic sources are in Supplementary Table 22. Bonferroni correction for multiple testing derived an adjusted critical *P* value of 5.1×10^{-4} from 98 independent tests.

Genetic correlations were further estimated in a targeted analysis of structural brain magnetic resonance imaging measures from UK Biobank, which were more comprehensive than those currently available from ENIGMA, along with further advantages such as hemisphere-specific data and greater homogeneity in cohort and scanning procedures. GWAS summary statistics from brain imaging-derived phenotypes for 33,000 participants were downloaded from the Oxford Brain Imaging Genetics Server⁸⁴. Structural brain imaging traits encompassed both diffusion tensor imaging and surface-based morphometric phenotypes⁸⁵ where selected tracts or regions of interest had a known link to language. For diffusion tensor imaging, fractional anisotropy values derived from both tract-based-spatial statistics and probabilistic tractography were used for available tracts spanning the extended language network⁸⁶. For surface-based morphometric (cortical volume, surface area and thickness) GWAS, summary statistics for regions of interest derived from the Desikan-Killiany atlas (white surface) were used, again selected for their relevance in language processing, based on previous literature^{87–90}. To correct for multiple testing, phenotypic correlations between the UK Biobank imaging indices were derived and analyzed by PhenoSpD²³ to obtain the number of independent variables (36.08) to use for Bonferroni correction (adjusted critical *P* value of 1.39×10^{-3}).

Polygenic score analyses

Dyslexia polygenic scores were based on increasingly larger numbers of SNPs corresponding to their association *P* values from the 23andMe GWAS ($P < 5 \times 10^{-8}$, $P < 1 \times 10^{-5}$, $P < 0.001$, $P < 0.01$, $P < 0.05$, $P < 0.1$, $P < 0.5$, 1). They were calculated in four independent cohorts. Two were general population cohorts from Australia: $n = 1,640$ (772 families) adolescents/young adults (Brisbane adolescents)⁹¹; $n = 1,165$ (966 families) older adults (Brisbane adults)²⁵. The other two were family-based samples selected for dyslexia: one from the United Kingdom (UKdys), $n = 930$ (595 families); the other from the United States (Colorado Learning Disabilities Research Center, CLDRC), $n = 717$ (336 families)⁹². In the Australian samples, polygenic scores were calculated on 1000 Genomes Phase 3 (v.20101123) imputed genetic data using PLINK⁹³. Only reliably imputed SNPs ($R^2 > 0.80$) and those with a minor allele frequency > 0.01 were included, and the default clumping procedure was used where index SNPs formed a clump with other SNPs in LD ($R^2 > 0.1$) and within a 250 kb distance. In the UKdys and CLDRC samples, polygenic scores were calculated on Haplotype Reference Consortium imputed genetic data using PRSice⁹⁴, with the same imputation quality and MAF exclusions for the base (23andMe GWAS) sample, and clumping parameters.

Polygenic scores were then used as predictors in linear models of quantitative trait outcomes (Australia: word, nonword (phonetic), irregular word (lexical) reading and spelling tests from an extended version of the Components of Reading Examination⁹⁵, and two nonword repetition tests which are sensitive to developmental language disorders—Dollaghan and Campbell⁹⁶, Gathercole and Baddeley⁹⁷; UKdys and CLDRC: word recognition). All quantitative traits were pre-adjusted for sex, age and ancestry principal components (10 principal

components in UKdys and CLDR; 20 principal components in Australian samples). Further adjustments were made for imputation run (separate runs for different genotyping arrays) in the Australian samples, and for nonverbal IQ in all samples (except for the Australian adults), and for hearing difficulties in the Australian older adults. Because the cohorts included related family members (twins or siblings), linear mixed models (lme) were specified in RStudio⁹⁸, with family membership modeled as a random effect and the dyslexia polygenic score as a fixed effect. Where monozygotic twins were present, their trait scores were averaged and they were used as a single case.

Evaluation of candidates from previous literature

We used the results of the 23andMe dyslexia GWAS to assess variants, genes and biological pathways previously associated with or implicated in dyslexia and/or variation in reading and spelling ability in past association studies, linkage analyses and other studies.

Previously reported variants. We assessed 75 previously reported variants within our summary statistics, adopting a replication/validation significance threshold of $P < 7.28 \times 10^{-4}$, derived by Bonferroni correction based on 68.7 independent tests derived through matrix spectral decomposition, taking into account LD (see Doust et al.²⁵ for details on how these variants were selected). The sources for each variant are provided in Supplementary Table 26.

Dyslexia candidate genes. We evaluated gene-based results from MAGMA v.1.08 (ref.⁵⁶) for overrepresentation of genome-wide significant variants from the 23andMe dyslexia GWAS within the loci of 14 candidate genes from earlier literature: *CMIP*, *CNTNAP2*, *CYP19A1*, *DCDC2*, *DIP2A*, *DYX1C1*, *GCF2*, *KIAA0319*, *KIAA0319L*, *MRPL19*, *PCNT*, *PRMT2*, *SIOOB* and *ROBO1*. The rationale for this selection is detailed by Luciano et al.²⁴ and Doust et al.⁵. The critical P value, based on Bonferroni correction for 14 tests, was 3.57×10^{-3} .

Candidate dyslexia gene sets. We performed a gene set analysis in MAGMA to test for overrepresentation of genome-wide significant variants within (1) a set of transcriptional targets of *FOXP2*, a highly conserved transcription factor linked to speech and language impairment⁹⁹; and (2) two biological pathways previously suggested to play a role in dyslexia susceptibility^{100,101}—axon guidance (GO:0007411: ‘chemotaxis process that directs the migration of an axon growth cone to a specific target site’; 216 genes) and neuron migration (GO:0001764: ‘movement of an immature neuron from germinal zones to specific positions where they will reside as they mature’; 145 genes). An adjusted critical P value of 0.017 was derived using Bonferroni correction based on three independent tests.

Ethical standards

Participants provided informed consent and participated in the research online, under a protocol approved by the external AAHRPP-accredited IRB, Ethical and Independent Review Services. Participants were included in the analysis on the basis of consent status as checked at the time data analyses were initiated.

Reporting summary

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

Data availability

The full summary statistics for each dyslexia GWAS presented in this paper will be made available through 23andMe website (<https://research.23andme.com/dataset-access/>) to qualified researchers under an agreement with 23andMe that protects the privacy of the 23andMe participants. The top 10,000 associated SNPs from the main GWAS can be downloaded from <https://doi.org/10.7488/ds/3465>.

References

- Fontanillas, P. et al. Disease risk scores for skin cancers. *Nat. Commun.* **12**, 160 (2021).
- Das, S. et al. Next-generation genotype imputation service and methods. *Nat. Genet.* **48**, 1284–1287 (2016).
- Gialluisi, A. et al. Genome-wide association scan identifies new variants associated with a cognitive predictor of dyslexia. *Transl. Psychiatry* **9**, 77 (2019).
- de Leeuw, C. A., Mooij, J. M., Heskes, T. & Posthuma, D. MAGMA: generalized gene-set analysis of GWAS data. *PLoS Comput. Biol.* **11**, e1004219 (2015).
- Watanabe, K., Taskesen, E., van Bochoven, A. & Posthuma, D. Functional mapping and annotation of genetic associations with FUMA. *Nat. Commun.* **8**, 1826 (2017).
- Subramanian, A. et al. Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles. *Proc. Natl Acad. Sci. USA* **102**, 15545–15550 (2005).
- Liberzon, A. et al. Molecular signatures database (MSigDB) 3.0. *Bioinformatics* **27**, 1739–1740 (2011).
- Wakefield, J. A Bayesian measure of the probability of false discovery in genetic epidemiology studies. *Am. J. Human Genet.* **81**, 208–227 (2007).
- Maller, J. B. et al. Bayesian refinement of association signals for 14 loci in 3 common diseases. *Nat. Genet.* **44**, 1294–1301 (2012).
- Howe, K. L. et al. Ensembl 2021. *Nucleic Acids Res.* **49**, D884–D891 (2020).
- Carvalho-Silva, D. et al. Open Targets Platform: new developments and updates two years on. *Nucleic Acids Res.* **47**, D1056–D1065 (2018).
- Petrovski, S. et al. The intolerance of regulatory sequence to genetic variation predicts gene dosage sensitivity. *PLoS Genet.* **11**, e1005492 (2015).
- Rada-Iglesias, A. Is H3K4me1 at enhancers correlative or causative? *Nat. Genet.* **50**, 4–5 (2018).
- Heintzman, N. D. et al. Distinct and predictive chromatin signatures of transcriptional promoters and enhancers in the human genome. *Nat. Genet.* **39**, 311–318 (2007).
- Cahoy, J. D. et al. A transcriptome database for astrocytes, neurons, and oligodendrocytes: a new resource for understanding brain development and function. *J. Neurosci.* **28**, 264 (2008).
- The GTEx Consortium. The Genotype-Tissue Expression (GTEx) pilot analysis: multitissue gene regulation in humans. *Science* **348**, 648 (2015).
- Finucane, H. K. et al. Heritability enrichment of specifically expressed genes identifies disease-relevant tissues and cell types. *Nat. Genet.* **50**, 621–629 (2018).
- Dunham, I. et al. An integrated encyclopedia of DNA elements in the human genome. *Nature* **489**, 57–74 (2012).
- Vermunt, M. W. et al. Epigenomic annotation of gene regulatory alterations during evolution of the primate brain. *Nat. Neurosci.* **19**, 494–503 (2016).
- Reilly, S. K. et al. Evolutionary genomics. Evolutionary changes in promoter and enhancer activity during human corticogenesis. *Science* **347**, 1155–1159 (2015).
- Peyrégne, S., Boyle, M. J., Dannemann, M. & Prüfer, K. Detecting ancient positive selection in humans using extended lineage sorting. *Genome Res.* **27**, 1563–1572 (2017).
- Simonti, C. N. et al. The phenotypic legacy of admixture between modern humans and Neandertals. *Science* **351**, 737–741 (2016).
- Vernot, B. et al. Excavating Neandertal and Denisovan DNA from the genomes of Melanesian individuals. *Science* **352**, 235–239 (2016).

76. Gazal, S. et al. Linkage disequilibrium-dependent architecture of human complex traits shows action of negative selection. *Nat. Genet.* **49**, 1421–1427 (2017).
77. Bulik-Sullivan, B. K. et al. LD score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nat. Genet.* **47**, 291–295 (2015).
78. Bulik-Sullivan, B. K. et al. An atlas of genetic correlations across human diseases and traits. *Nat. Genet.* **47**, 1236–1241 (2015).
79. 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 (2016).
80. Grasby, K. L. et al. The genetic architecture of the human cerebral cortex. *Science* **367**, eaay6690 (2020).
81. Satizabal, C. L. et al. Genetic architecture of subcortical brain structures in 38,851 individuals. *Nat. Genet.* **51**, 1624–1636 (2019).
82. Hibar, D. P. et al. Novel genetic loci associated with hippocampal volume. *Nat. Commun.* **8**, 13624 (2017).
83. Adams, H. H. et al. Novel genetic loci underlying human intracranial volume identified through genome-wide association. *Nat. Neurosci.* **19**, 1569–1582 (2016).
84. Smith, S. M. et al. An expanded set of genome-wide association studies of brain imaging phenotypes in UK Biobank. *Nat. Neurosci.* **24**, 737–745 (2021).
85. Alfaro-Almagro, F. et al. Image processing and Quality Control for the first 10,000 brain imaging datasets from UK Biobank. *Neuroimage* **166**, 400–424 (2018).
86. Forkel, S. J. & Catani, M. *The Oxford Handbook of Neurolinguistics: Diffusion Imaging Methods in Language Sciences* (Oxford Univ. Press, Oxford, 2019).
87. Price, C. J. The anatomy of language: a review of 100 fMRI studies published in 2009. *Ann. N. Y. Acad. Sci.* **1191**, 62–88 (2010).
88. Richardson, F. M. & Price, C. J. Structural MRI studies of language function in the undamaged brain. *Brain Struct. Funct.* **213**, 511–523 (2009).
89. Perdue, M. V., Mednick, J., Pugh, K. R. & Landi, N. Gray matter structure is associated with reading skill in typically developing young readers. *Cereb. Cortex* **30**, 5449–5459 (2020).
90. Roehrich-Gascon, D., Small, S. L. & Tremblay, P. Structural correlates of spoken language abilities: a surface-based region-of-interest morphometry study. *Brain Lang.* **149**, 46–54 (2015).
91. Luciano, M. et al. A genome-wide association study for reading and language abilities in two population cohorts. *Genes Brain Behav.* **12**, 645–652 (2013).
92. Gialluisi, A. et al. Genome-wide screening for DNA variants associated with reading and language traits. *Genes Brain Behav.* **13**, 686–701 (2014).
93. Purcell, S. et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am. J. Human Genet.* **81**, 559–575 (2007).
94. Euesden, J., Lewis, C. M. & O'Reilly, P. F. PRSice: polygenic risk score software. *Bioinformatics* **31**, 1466–1468 (2015).
95. Bates, T. C. et al. Behaviour genetic analyses of reading and spelling: a component processes approach. *Aust. J. Psychol.* **56**, 115–126 (2004).
96. Dollaghan, C. & Campbell, T. F. Nonword repetition and child language impairment. *J. Speech Lang. Hear. Res.* **41**, 1136–1146 (1998).
97. Gathercole, S. E., Willis, C. S., Baddeley, A. D. & Emslie, H. The Children's Test of Nonword Repetition: a test of phonological working memory. *Memory* **2**, 103–127 (1994).
98. RStudio Team. RStudio: Integrated Development for R. (Boston, MA, 2020).
99. Ayub, Q. et al. FOXP2 Targets show evidence of positive selection in European populations. *Am. J. Human Genet.* **92**, 696–706 (2013).
100. Poelmans, G., Buitelaar, J. K., Pauls, D. L. & Franke, B. A theoretical molecular network for dyslexia: integrating available genetic findings. *Mol. Psychiatry* **16**, 365–382 (2011).
101. Guidi, L. G. et al. The neuronal migration hypothesis of dyslexia: a critical evaluation 30 years on. *Eur. J. Neurosci.* **48**, 3212–3233 (2018).

Acknowledgements

We thank the research participants and employees of 23andMe Inc, the GenLang Consortium, the Brisbane Adults Reading Study, and the CRS. E.E., G.A., B.M., B.S.P., C.F. and S.E.F. are supported by the Max Planck Society (Germany). The CRS was supported by grants from the National Natural Science Foundation of China (Grant No. 61807023), Funds for Humanities and Social Sciences Research of the Ministry of Education (Grant No. 19YJC190023 and 17XJC190010) and General Project of Shaanxi Natural Science Basic Research Program (2018JQ8015) (Grant No. 2018JQ8015 and 2021JQ-309). S.P. is funded by the Royal Society. Acknowledgements for the GenLang Consortium appear in the Supplementary Note.

Author contributions

M.L., S.E.F., T.C.B. and N.G.M. conceived the study, with M.L. overseeing general analysis and A.A. overseeing 23andMe analysis. C.D., P.F., E.E., G.A., S.D.G., Z.W., B.M. and M.L. performed statistical and/or downstream annotation analysis. R.E.M. advised C.D. on some analysis. C.D. drafted the manuscript, with sections contributed by P.F., E.E., G.A., Z.W. and M.L. B.S.P., C.F. and S.E.F. supervised the GenLang GWAS. J.Z. managed the Chinese Reading Study. S.P., J.B.T., A.P.M. and J.F.S. managed the UKDys study. J.R.G., R.K.O., E.G.W., J.C.D., B.F.P. and S.D.S. managed the CLDRC study. M.J.W., T.C.B. and N.G.M. managed the Australian adolescent twin studies. M.L., T.C.B., S.E.F. and N.G.M. managed the Australian adult reading study. All authors critically reviewed the manuscript.

Competing interests

P.F., A.A. and the 23andMe Research Team are employed by and hold stock or stock options in 23andMe, Inc. The remaining authors declare no competing interests.

Additional information

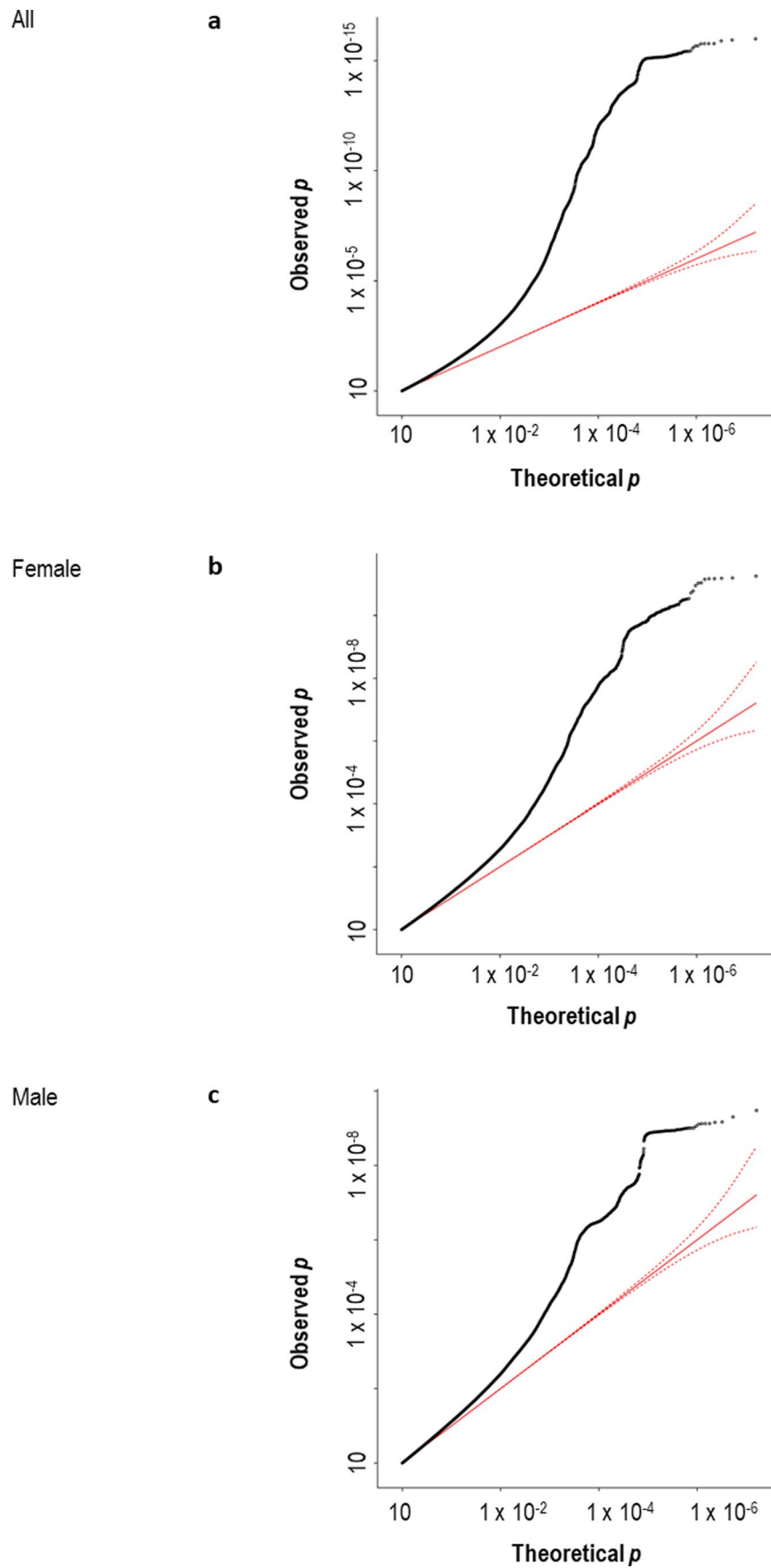
Extended data is available for this paper at <https://doi.org/10.1038/s41588-022-01192-y>.

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41588-022-01192-y>.

Correspondence and requests for materials should be addressed to Michelle Luciano.

Peer review information *Nature Genetics* thanks the anonymous reviewers for their contribution to the peer review of this work. Peer reviewer reports are available.

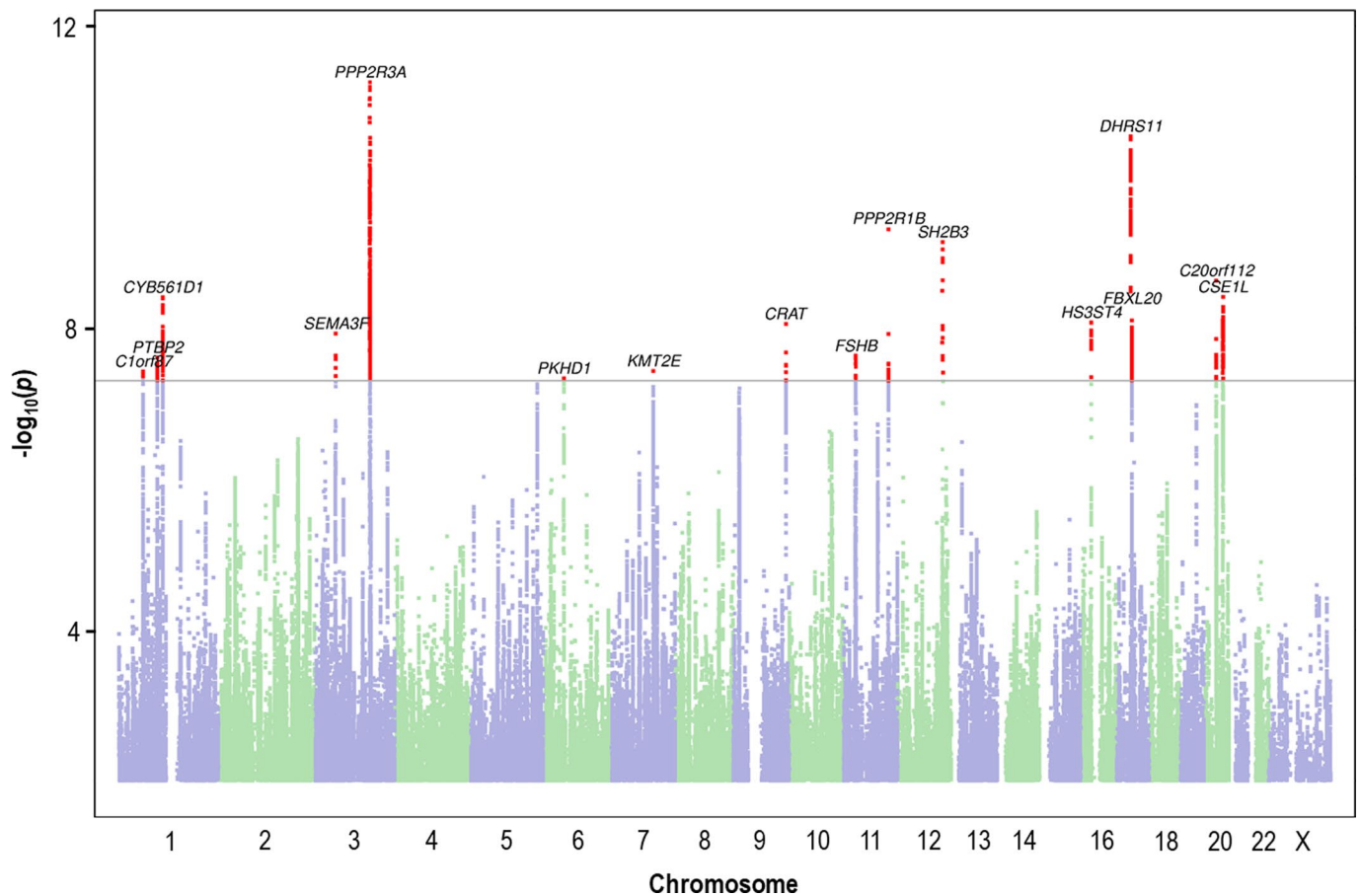
Reprints and permissions information is available at www.nature.com/reprints.



Extended Data Fig. 1 | See next page for caption.

Extended Data Fig. 1 | QQ plot of dyslexia GWAS results. a-c, Quantile-quantile (Q-Q) plots of observed versus expected P values for associations of single nucleotide polymorphisms with self-reported dyslexia diagnosis in a genome-wide association analysis for all participants ($n = 51,800$ cases, 1,087,070 controls) (**a**), female participants ($n = 30,287$ cases, 641,016 controls) (**b**), and

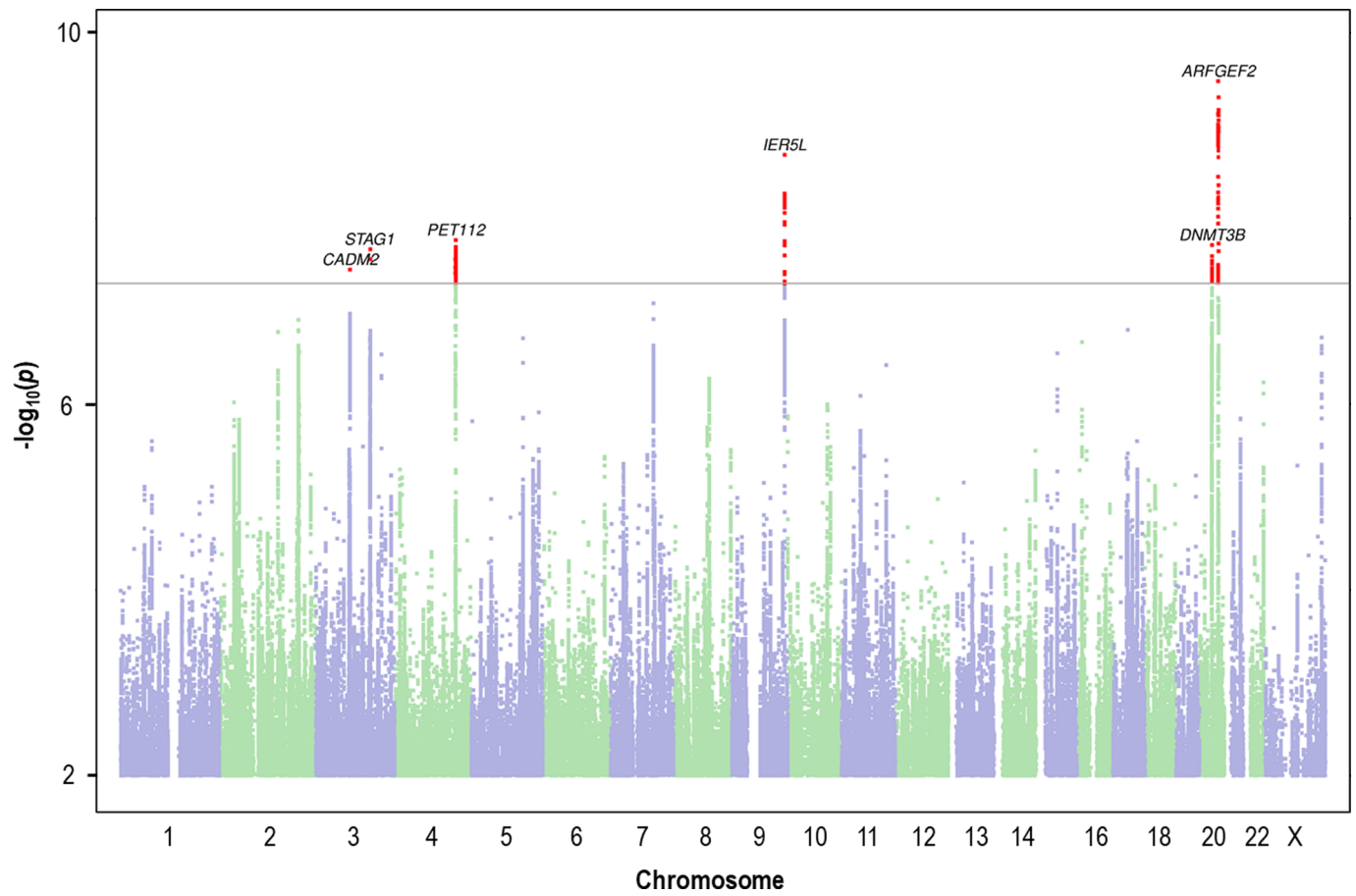
male participants ($n = 21,513$ cases, 446,054 controls) (**c**). The solid red line represents the distribution of P values under the null hypothesis, and the dashed red line represent 95% confidence intervals. The black circles represent the observed distribution of P values.



Extended Data Fig. 2 | Manhattan plot of dyslexia GWAS results for females.

The y-axis represents the $-\log_{10} P$ value for association of single nucleotide polymorphisms with self-reported dyslexia diagnosis from 30,287 female individuals and 641,016 female controls. The threshold for genome-wide

significance ($P < 5 \times 10^{-8}$) is represented by a horizontal grey line. Genome-wide significant variants in the 17 genome-wide significant loci are red. Variants located within a distance of 250 kb of each other are considered as one locus.



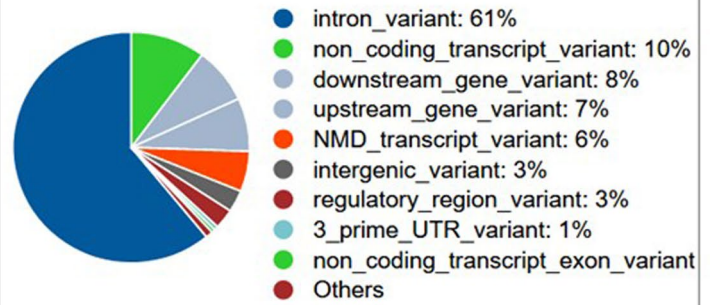
Extended Data Fig. 3 | Manhattan plot of dyslexia GWAS results for males.

The y-axis represents the $-\log_{10} P$ value for association of single nucleotide polymorphisms with self-reported dyslexia diagnosis from 21,513 male individuals and 446,054 male controls. The threshold for genome-wide

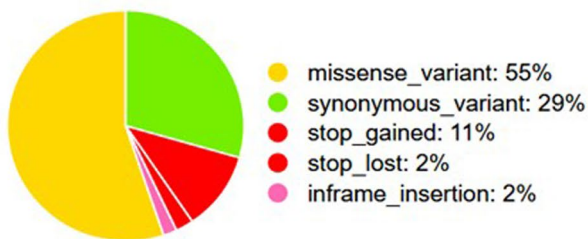
significance ($P < 5 \times 10^{-8}$) is represented by a horizontal grey line. Genome-wide significant variants in the 6 genome-wide significant loci are red. Variants located within a distance of 250 kb of each other are considered as one locus.

Category	Count
Variants processed	6210
Variants filtered out	0
Novel / existing variants	0 (0.0) / 6210 (100.0)
Overlapped genes	238
Overlapped transcripts	1176
Overlapped regulatory features	569

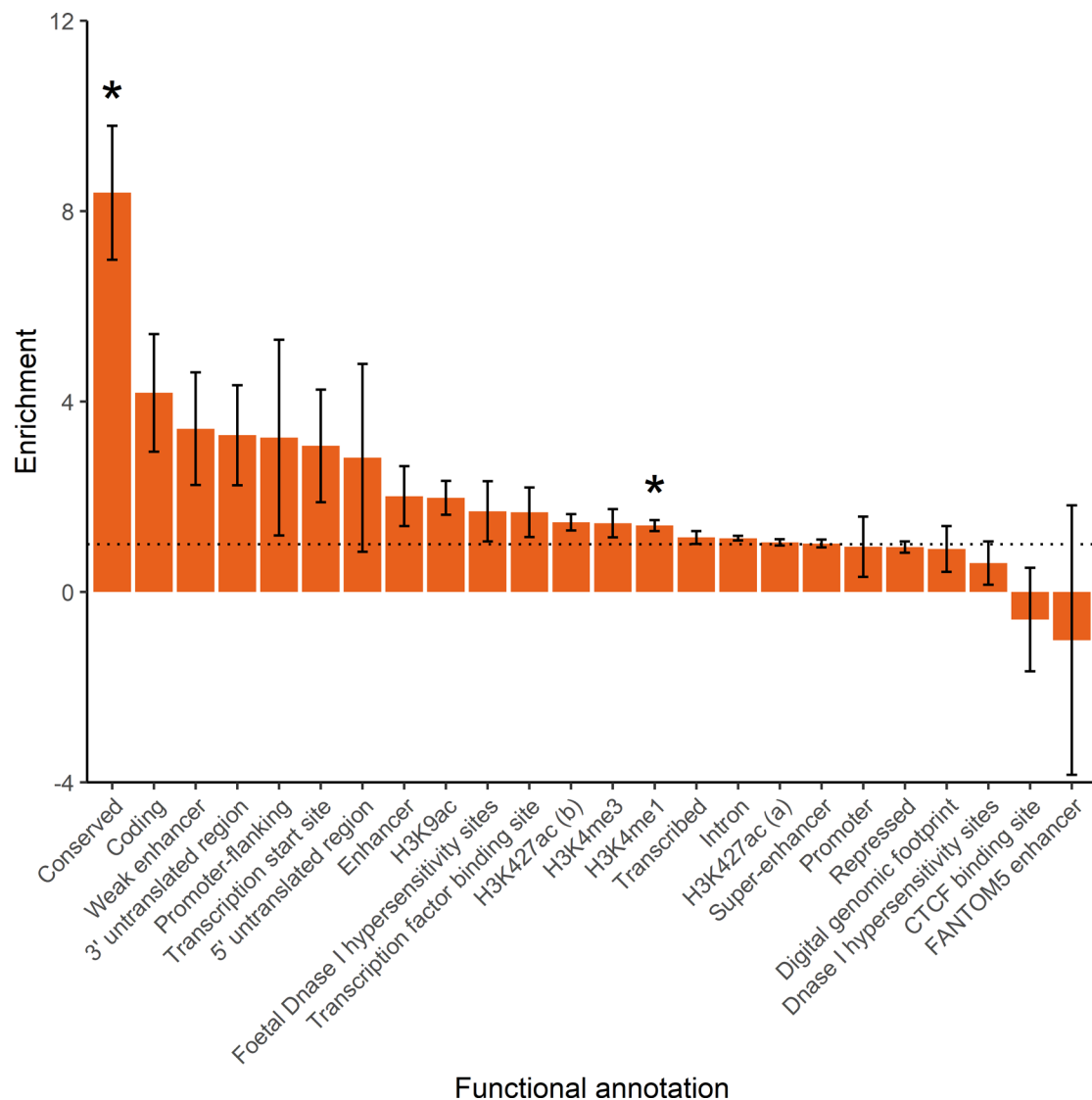
Consequences (all)



Coding consequences

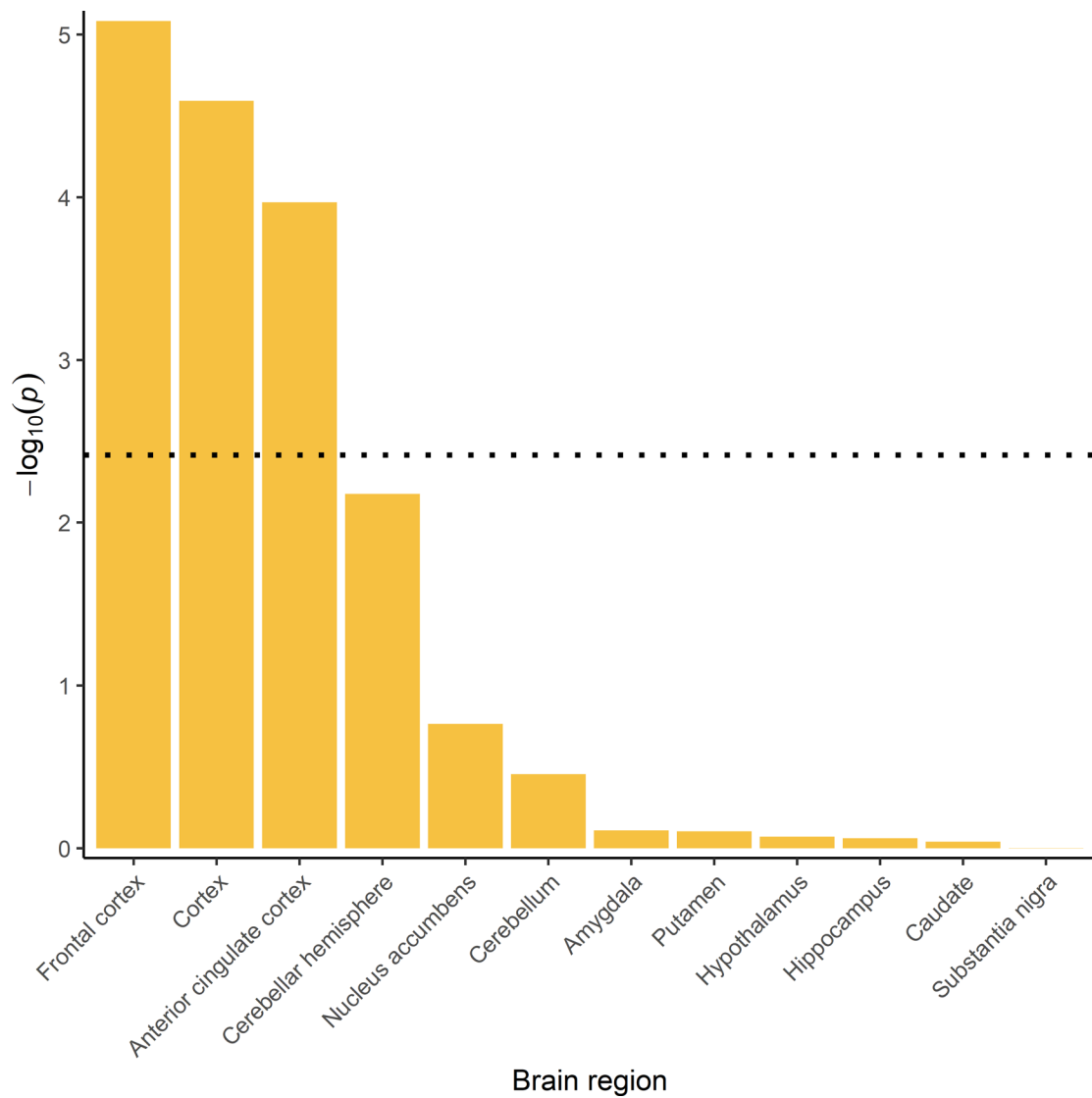


Extended Data Fig. 4 | Variant effect predictor summary for the credible set of variants significantly associated with dyslexia. Summary information is output from the online variant effect predictor in ENSEMBL (release 104). All our variants were present in the 1000 Genomes reference panel so are considered existing, and no pre-filtering (for example, on MAF; consequence type) was done.

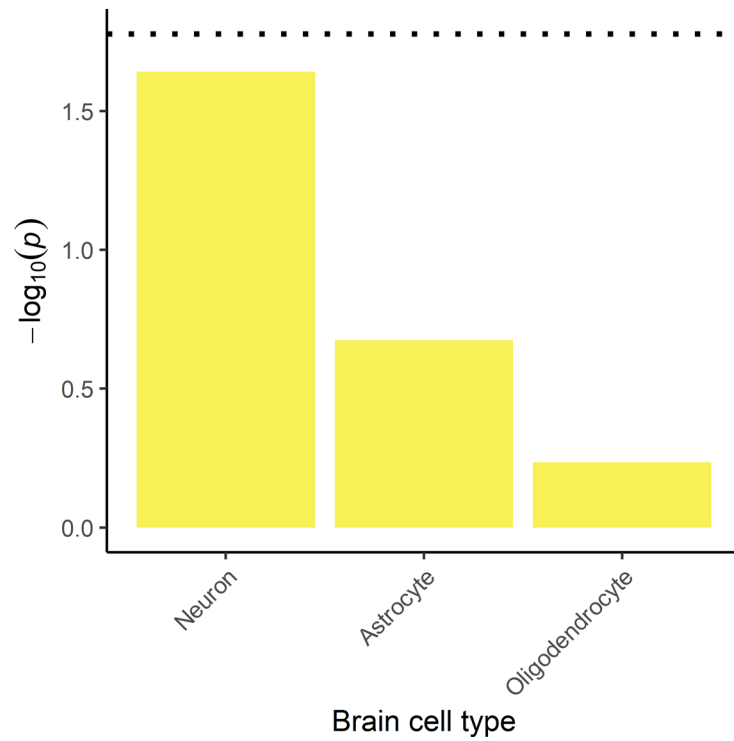


Extended Data Fig. 5 | Enrichment estimates for major functional annotations. The 24 major functional annotations were defined by Finucane et al.³⁹. Enrichment is the proportion of h^2 /proportion of SNPs. The horizontal dotted line indicates no enrichment (where proportion of h^2 /proportion of SNPs

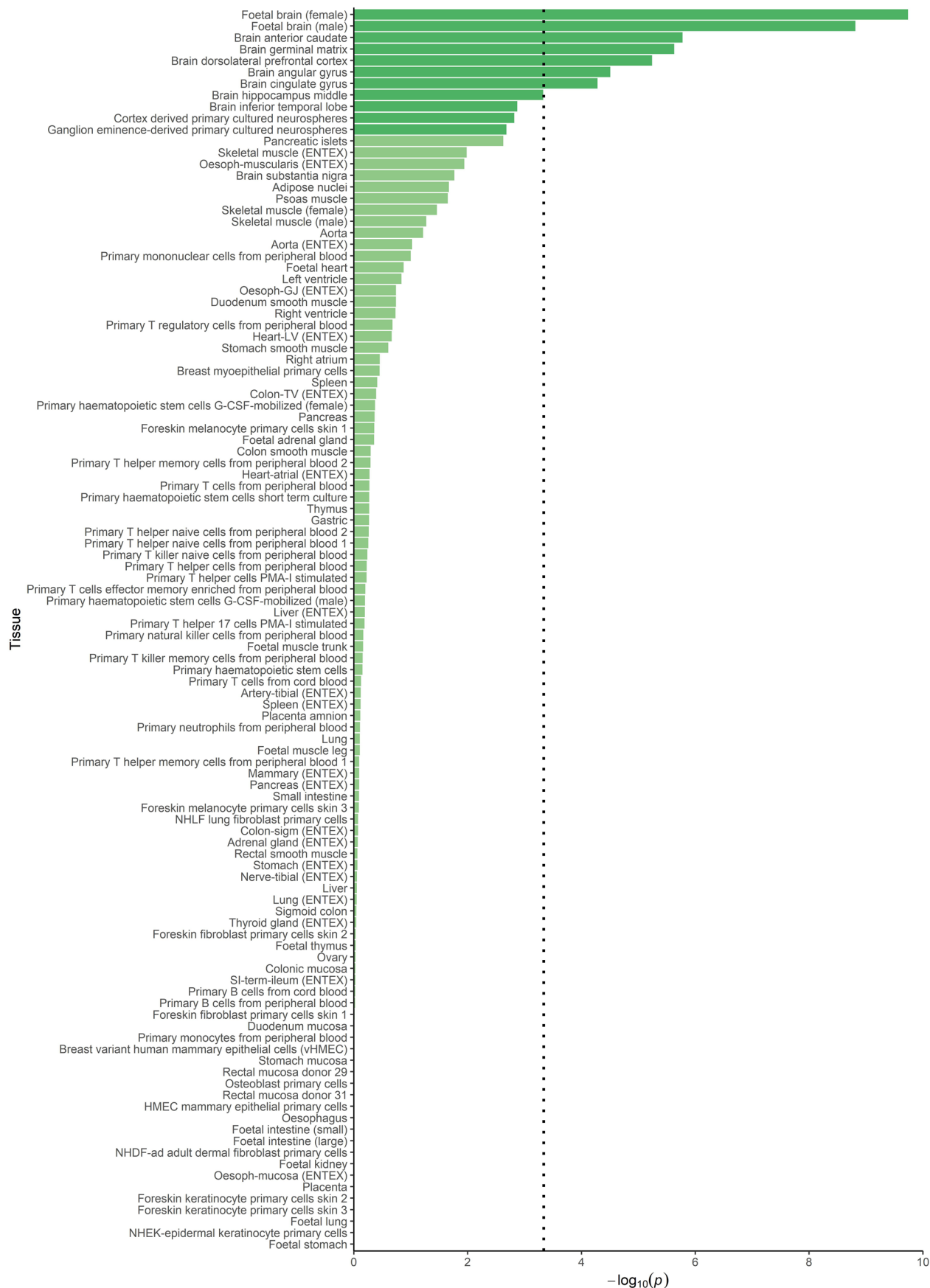
= 1). Error bars represent standard errors of the enrichment estimates. Asterisks indicate enrichment estimates are significant based on a Bonferroni-derived P value of $< 2.08 \times 10^{-3}$ (for 24 tests). Exact values of enrichment statistic, standard error, and P value can be found in Supplementary Table 16.



Extended Data Fig. 6 | Heritability of dyslexia partitioned by brain tissue gene expression. The $-\log_{10}P$ value of the enrichment estimates for heritability of dyslexia for genes expressed in 12 brain regions. The horizontal dotted line indicates significance after Bonferroni correction for 12 tests ($P < 4.17 \times 10^{-3}$).

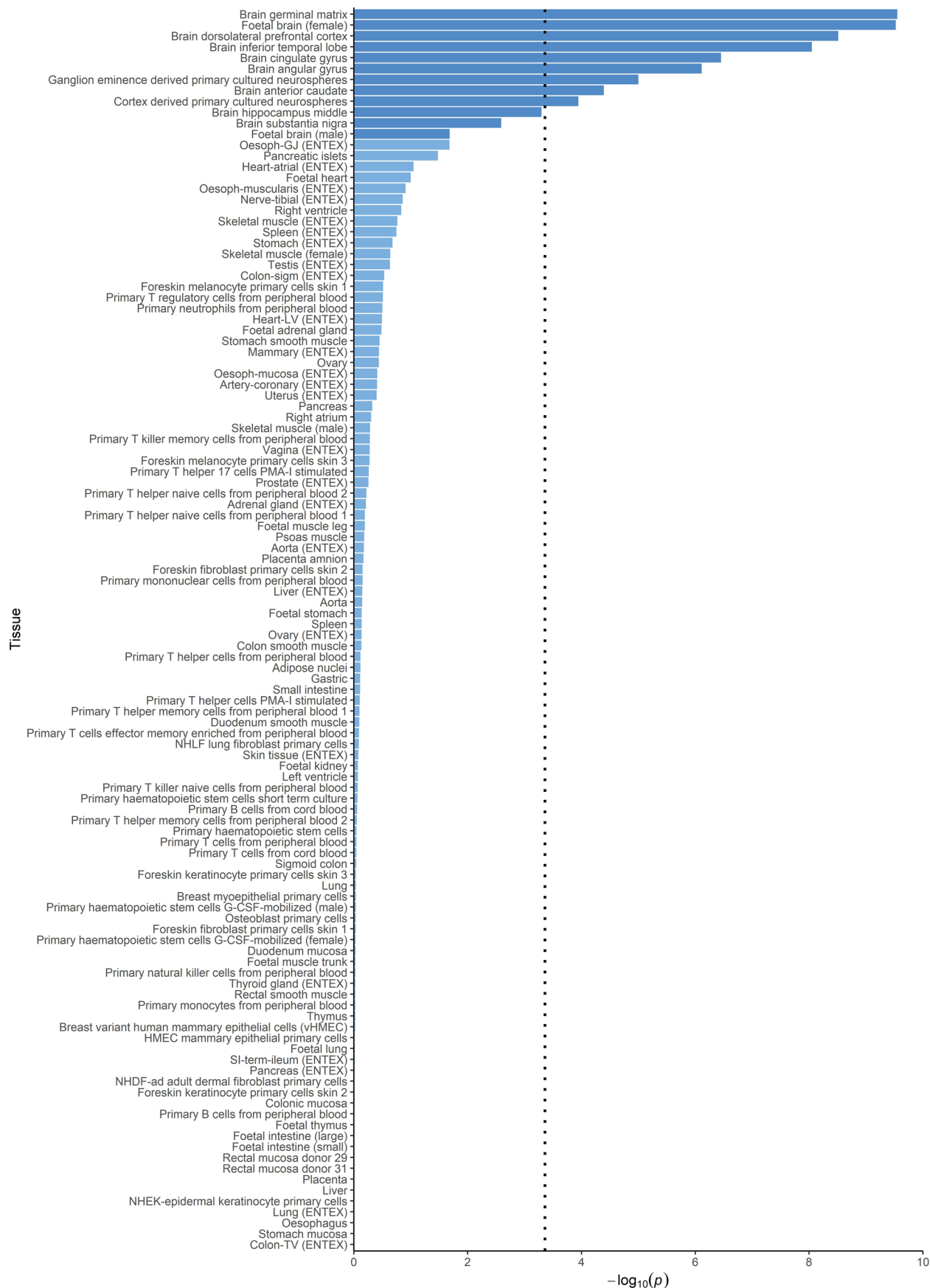


Extended Data Fig. 7 | Heritability of dyslexia partitioned by brain cell type. The $-\log_{10} P$ value of the enrichment estimates for heritability of dyslexia for brain cell types. The horizontal dotted line indicates significance after Bonferroni correction for three tests ($P < 1.67 \times 10^{-2}$).



Extended Data Fig. 8 | Heritability of dyslexia partitioned by cell-type specific H3K4me1. The $-\log_{10}P$ value of the enrichment estimates for heritability of dyslexia for variants located within H3K4me1 peaks of different tissues.

Central nervous systems tissues are represented in dark green and other tissues are represented in light green. The vertical dotted line indicates significance after Bonferroni correction for 114 tests ($P < 4.39 \times 10^{-4}$).



Extended Data Fig. 9 | Heritability of dyslexia partitioned by cell-type specific H3K4me3. The $-\log_{10}P$ value of the enrichment estimates for heritability of dyslexia for variants located within H3K4me3 peaks of different tissues.

Central nervous systems tissues are represented in dark blue and other tissues are represented in light blue. The vertical dotted line indicates significance after Bonferroni correction for 114 tests ($P < 4.39 \times 10^{-4}$).

Reporting Summary

Nature Portfolio 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 Portfolio policies, see our [Editorial Policies](#) and the [Editorial Policy Checklist](#).

Statistics

For all statistical analyses, confirm that the following items are present in the 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
- A statement on 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 statistical parameters 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

Our web collection on [statistics for biologists](#) contains articles on many of the points above.

Software and code

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

Data collection

Data analysis

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 and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio [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 description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our [policy](#)

The full summary statistics for each dyslexia GWAS presented in this paper will be made available through 23andMe to qualified researchers under an agreement with 23andMe that protects the privacy of the 23andMe participants. Interested investigators should email dataset-request@23andme.com and reference this paper for more information.

Field-specific reporting

Please select the one below that is 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/documents/nr-reporting-summary-flat.pdf](https://www.nature.com/documents/nr-reporting-summary-flat.pdf)

Behavioural & social sciences study design

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

Study description	This is a quantitative study that relies on self-report data. Replication analyses draw on cognitive test data.
Research sample	The research sample are customers of 23andMe, a consumer genetics company, who have agreed to participate in research. They are slightly selected in that there is over-representation of higher socio-economic position participants. The replication samples are from the general population and some are enriched from reading difficulties.
Sampling strategy	The sample were volunteer customers of 23andMe, who consented to the use of their DNA and survey results. The largest sample size available at the time of the study were used.
Data collection	Data collection for the main analysis was online survey collection. For replication samples it was mostly in-person cognitive testing.
Timing	The main sample data include customers who consented to participate up until late 2020. The replication sample cohorts vary in data collection times with some dating back to the 90s.
Data exclusions	No exclusions were made.
Non-participation	This is not a longitudinal study so there is no sample drop-out to report.
Randomization	There was no randomization but we controlled for age and sex in the analyses.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

Methods

n/a	Involved in the study
<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 and archaeology
<input checked="" type="checkbox"/>	<input type="checkbox"/> Animals and other organisms
<input type="checkbox"/>	<input checked="" type="checkbox"/> Human research participants
<input checked="" type="checkbox"/>	<input type="checkbox"/> Clinical data
<input checked="" type="checkbox"/>	<input type="checkbox"/> Dual use research of concern

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	See above.
Recruitment	Participants are customers of 23andMe, so are invited to participate in general research, our study uses data from a number of online questions. There is under-representation of low socio-economic position and all participants are over 18 years.
Ethics oversight	External AAHRPP-accredited IRB, Ethical & Independent Review Services.

Note that full information on the approval of the study protocol must also be provided in the manuscript.