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Investigating the interplay between prematurity and genetic variation in the context of rare developmental disorders

Olivia Wootton[1†], Patrick Campbell[2†], Sarah Richardson[3], Sarah J. Lindsay[1], Qin Qin Huang[1], Erwan Delage[1], Sana Amanat[1], Hilary S. Wong[4], Helen V. Firth[1,4], Matthew E. Hurles[1], Michael A. Simpson[2], Elizabeth J. Radford[1,5†] and Hilary C. Martin[1*†]

Abstract

Background Rare damaging genetic variation accounts for a substantial proportion of the risk of rare developmental disorders (DDs), but common genetic variants as well as environmental factors, including prematurity, also contribute. Little is known about the interplay between prematurity and genetic variation in influencing phenotypic outcomes in DDs, nor about how genetic factors may contribute to risk of preterm birth in DDs.

Methods We leveraged phenotypic and genetic data from 21,712 patients with DDs recruited for clinical sequencing, 16% of whom were born prematurely. Using multivariable regression models, we compared phenotypic features and the prevalence of diagnostic genetic variation in specific genes between preterm and term individuals with DDs. We tested whether the fraction of cases attributable to de novo mutations differed between term and preterm probands. Additionally, we assessed whether associations between common variant contributions to education-related traits and prematurity are explained by direct genetic effects.

Results Prematurity was associated with more severe clinical phenotypes among these DD patients, including more affected organ systems and more delayed developmental milestones. Prematurity and the presence of a monogenic diagnosis contributed additively to severity. We found that genes associated with fetal anomalies were enriched for diagnostic mutations among preterm individuals ($p = 7.83 \times 10^{-5}$). We also demonstrated an exome-wide enrichment of de novo mutations (DNMs) in both term and preterm probands; the fraction of cases explained by DNMs in known DD-associated genes was higher in term than preterm cases (25% versus 20%) but DNMs in as-yet-undiscovered genes likely contribute approximately equally to both groups (14% versus 13%). Finally, we showed that the positive association between polygenic predisposition to education-related traits and gestational duration is likely to be the result of genetically influenced parental traits or confounders, rather than direct genetic effects in the child, and that a monogenic diagnosis modifies this association.

Conclusions Our findings emphasise the importance of considering environmental factors like prematurity in understanding outcomes in DDs suspected to have a genetic component, and motivate further exploration of the role that genetic variation plays in influencing prematurity.

†Olivia Wootton and Patrick Campbell contributed equally to this work.

Elizabeth J. Radford and Hilary C. Martin jointly supervised this work.

*Correspondence:
Hilary C. Martin
hcm@sanger.ac.uk
Full list of author information is available at the end of the article

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Keywords Prematurity, Genomics, Neurodevelopmental conditions, Monogenic, De novo mutations

Background

Understanding how the interplay of genetics and environment influences phenotype is an enduring question in biology. In the context of rare developmental disorders (DDs), there is evidence that both rare [1] and common [2, 3] genetic variation as well as environmental factors contribute to aetiology [4]. DDs are a group of conditions that arise in embryonic life or during early development and alter the developmental trajectory. Research over the past decade has had considerable success in identifying the rare genetic variation that causes many of these conditions. At present, a diagnostic rare variant is found in 25–45% of individuals with DDs who are referred for exome or genome sequencing [5–7]. One environmental factor likely to also contribute to phenotypes among these individuals is prematurity, given that premature delivery occurs in 9.9% of births [8] and a common sequelae is developmental delay [9]. This hypothesis is supported by recent work from the Deciphering Developmental Disorders (DDD) study, a large cohort of children with DDs, which demonstrated that preterm infants (who were enriched in the cohort, comprising 16% of probands) were less likely to receive a monogenic diagnosis than term infants [5]. To date, however, there has been limited investigation into the role of prematurity among children with DDs with a suspected genetic component.

The impact of prematurity on phenotypic presentation of DDs is important from a clinical perspective. It is well established that individuals with pathogenic variants in more than one Mendelian-acting gene can have composite phenotypes that reflect the combined effects of the individual genes [10–12]. Similarly, an individual with a pathogenic variant who is also born prematurely may have a composite phenotype. Consistent with this, recent research has found that in autism, a common neurodevelopmental condition with genetic contributions, individuals diagnosed with the condition have more comorbidities if born prematurely than if born at term [13]. In rare DDs, teasing apart the phenotypic impact of prematurity from that of underlying monogenic diagnoses could provide clinicians and families with a more complete explanation of an individual's clinical features and facilitate more accurate prediction of developmental outcomes.

Preterm birth arises from a range of often overlapping causes, including fetal, maternal, placental, and iatrogenic factors, and the complex pathways leading to early delivery remain an active area of investigation [14, 15]. A growing body of evidence shows that premature birth is influenced by genetic variation, both maternal and fetal [16, 17]. Studies have found higher rates of de novo variants in preterm infants, linking affected genes to fetal brain development [18], and have implicated structural variants that are known to cause developmental delay [19]. Additionally, the clinical synopsis of several DDs in Online Mendelian Inheritance in Man include premature birth as a feature (e.g. MIM: #619488 #618737 #620155). However, given the small number of cases these data are drawn from [20–22], the extent to which rare pathogenic variants in these genes are robustly associated with an increased risk of prematurity is unknown. Furthermore, genetic variation that contributes to prematurity may affect developmental trajectories in children with DDs. Recent work has found that common genetic variant predisposition to preterm birth is negatively genetically correlated with years in education (educational attainment; EA) and positively genetically correlated with risk of neurodevelopmental conditions [3]. Consistent with these findings, preterm probands in the DDD study were found to have a polygenic predisposition to lower EA compared to term probands [3]. It is unclear whether polygenic predisposition for lower EA has a direct genetic effect on an individual's risk of being born prematurely (i.e. the effects of genetic variants in an individual on that individual's own phenotype), as opposed to an indirect genetic effect that may be mediated through parental behaviours or the prenatal environment. Regardless, previous studies suggest that genetic risk for prematurity and developmental disorders may overlap and that common and rare genetic variation associated with prematurity may confound associations between prematurity and phenotypic outcomes in DDs.

Here, we use data from large cohorts of individuals with developmental disorders recruited for clinical sequencing ($N=21{,}712$) to investigate three questions. First, we assess the phenotypic impact of prematurity on clinical features and developmental outcomes. Second, we test whether there are DD-associated genes and disease-associated gene sets in which diagnostic variants are enriched among individuals with DDs born prematurely, and we evaluate the overall contribution of de novo variation to DDs in term and preterm probands. Third, we explore whether established associations between common variant predisposition to education-related traits and gestational duration are modified by the presence of a monogenic diagnosis and whether these associations are mediated through direct

genetic effects. In addressing these questions, this work aims to improve our scientific and clinical understanding of the interplay between genetic variation and prematurity on rare DDs.

Methods

Sample overview

Deciphering Developmental Disorders

This study includes 13,401 probands from the Deciphering Developmental Disorders (DDD) study, which aimed to identify molecular diagnoses for families and patients with previously genetically undiagnosed DDs that were thought likely to be of genetic origin [1]. Enrolment occurred between 2011 and 2015 from 24 clinical genetics units in the UK and Ireland. The DDD cohort is described in detail elsewhere [1, 5, 23, 24].

Genomics England 100,000 Genomes Project

This study uses data from the rare disease programme of the 100,000 Genomes Project (100kGP), an initiative by the UK Department of Health and Social Care to whole-genome sequence individuals from the National Health Service with rare conditions and cancer [25, 26]. We restricted our analysis to probands with phenotypes similar to those recruited into DDD with information on gestational duration (DDD-like, $N=9310$). DDD-like probands from the 100,000 Genomes projects are defined as individuals who:

1) were recruited into the same disease model as GEL probands who had previously been enrolled in DDD, or
2) had one of the top five human phenotype ontology (HPO) [27] terms used in DDD and their descendants, including HP:0000729 (autistic behaviour); HP:0001250 (seizure); HP:0000252 (microcephaly); HP:0000750 (delayed speech and language development); and HP:0001263 (global developmental delay).

Probands with an age of onset > 16 years were excluded, as well as probands recruited into the neurodegenerative disorders subcategory or recruited into a disease subcategory for which the mean age of probands was > 16 years. Lastly, we excluded any participants who were also recruited into DDD and/or who were related to DDD participants, leaving 8311 probands for analysis.

Description of phenotypes

For DDD probands, demographic, gestational duration, birthweight, and HPO [27] terms were recorded by the recruiting clinical geneticists in DECIPHER [28] and additional phenotypic information including on developmental milestones was collected using a bespoke online questionnaire collected via DECIPHER. See Additional File 1: Supplementary Note 1 for a description of developmental milestone data and quality control procedures.

For 100kGP probands, HPO terms were recorded by the recruiting clinicians. Gestational duration and birthweight data in 100kGP was gathered for all rare disease probands using three data sources (Additional File 1: Figure S1). First, about 1000 probands had this data clinically ascertained during recruitment. Second, the 100kGP has linked electronic healthcare data including admitted patient care episodes. Gestation and birthweight are recorded at birth in this dataset in the 'gestat' and 'birtweit' columns in episodes relating to both the child and mother, providing two potential data sources [29]. The *z*-scores for birthweight were then calculated using 'British 1990 reference data, reanalysed 2009' [30]. Individuals with a birthweight more than five standard deviations from the mean for their gestational duration and sex were removed (Additional File 1: Figures S2–3). The data was then limited to DDD-like probands ($N=8311$). This data is available to share within the Genomics England Research Environment upon request.

Preterm birth was defined as delivery before 37 completed weeks of gestation and was further categorised according to the World Health Organisation definitions: extreme (< 28 weeks), very (28 to < 32 weeks), and moderate (32 to < 37 weeks) [8, 31]. We selected antenatal factors available in both cohorts (including abnormalities on antenatal ultrasound scan, multiple pregnancy, maternal diabetes during pregnancy, and a history of previous pregnancy loss), birthweight, and HPO terms for analysis. We also considered a list of medically relevant HPO terms curated for their relevance to DDs [2], including abnormal speech or language, any craniofacial cleft, atypical behaviour, hearing or visual impairment, hypotonia, abnormal head circumference, seizure, and short stature. We counted the number of probands with an abnormality of an organ system or organ and with medically relevant HPO terms by conducting a search of a particular term and its daughter nodes [32]. We determined the number of distinct affected organ systems in each proband, following the methodology outlined in Niemi et al. [2], which accounts for overlapping terms to avoid redundancy across multiple organ systems. Additional File 2: Table S1 provides an overview of the phenotypic measures from DDD and 100kGP included in this study.

Genetic data preparation

DDD

DDD probands were genotyped using the Illumina HumanCoreExome chip (CoreExome), the Illumina OmniChipExpress (OmniChip), and the Illumina Infinium Global Screening Array (GSA). A subset of probands were genotyped using more than one array. For this

study, we used CoreExome and OmniChip data for analysis of the probands and the GSA and OmniChip data for analyses involving trios. Quality control procedures for the genotype data are described in detail elsewhere [2, 3]. WES data was used for the analysis of rare variants. Quality control and processing of the exome sequencing data are described in Huang et al. [3].

100kGP

Whole genome sequencing of 100kGP participants was performed with 150 bp paired-end reads using Illumina HiSeqX. This study used the 78,195 germline genomes from the aggregated variant calls released by the 100kGP team. Quality control and processing of the whole-genome sequencing data are described in Huang et al. [3].

Genetic ancestry inference

We restricted our analysis to individuals of genetically inferred British ancestry (GBR-ancestry) defined by genetic similarity to British individuals from the 1000 Genomes Project [33]. The process of identifying GBR-ancestry samples in DDD and GEL was described previously [2, 3]. Briefly, a set of LD-pruned overlapping SNPs from DDD and 100kGP with MAF > 5% from a subset of unrelated individuals were projected onto 1000 Genomes phase 3 individuals [33]. Another principal component analysis was performed with the European ancestry subset and a homogeneous subgroup with GBR-ancestry was identified for each cohort.

Identification of related participants

We used KING [34] to identify up to third-degree relatives (kinship coefficient > 0.0442) in each cohort and used a subset of unrelated individuals (i.e. those more distantly related than third-degree) for genetic analyses (N_{DDD} = 7052; N_{100kGP} = 4781). For analyses of trios, we further restricted our analysis to probands whose parents were unrelated to other parents in the cohort ($N_{DDD\ trios}$ = 3101; $N_{100kGP\ trios}$ = 2989).

Genotype imputation

For DDD probands, imputation was performed separately for samples from each genotype array using the maximum number of available variants after QC and removal of palindromic SNPs. The HRC r1.1 reference panel [35] was used for imputation of samples genotyped on the CoreExome array [2] and the TOPMed r2 reference panel [36] was used for imputation of GSA and Omnichip samples [3]. Well-imputed SNPs (Minimac4 $R^2 > 0.8$) with minor allele frequency (MAF) > 1% present in the GEL 100kGP data were retained for further analysis (N = 5,699,435).

De novo variant calling

DNM calling and quality control procedures for 9858 trios from the DDD study are described in detail elsewhere [37]. For this analysis, DNM calling was carried out for 13,381 trios from 100kGP following the same quality control procedures; 5991 trios met the inclusion criteria for this study (Additional File 1: Supplementary Methods).

Defining a monogenic diagnosis

DDD

Potentially clinically relevant rare variants were identified from WES data and chromosome microarray data using a variant analysis pipeline described in Wright et al. [5]. Briefly, the study team identified rare damaging variants that fit an appropriate inheritance pattern from a set of genes known to be causal for DDs (DDG2P, https://www.deciphergenomics.org/ddd/ddgenes). Candidate diagnostic variants were uploaded to DECIPHER [28], and the pathogenicity was annotated by the patients' referring clinician. 'Diagnosed' probands were defined as those with at least one variant with a clinical annotation of pathogenic/likely pathogenic in DECIPHER, or with a predicted classification of pathogenic/likely pathogenic using autocoded ACMG diagnoses [5]. All remaining probands were classified as 'undiagnosed'.

100kGP

For the 100kGP genomes, diagnostic rare variant and copy number tiering was performed as previously described [26, 38, 39]. We categorised the diagnostic status of all probands included in the Genomic Medicine Service exit questionnaire. This questionnaire required the referring clinician to classify the pathogenicity of candidate variants identified by 100kGP's variant analysis pipeline and an overall diagnostic classification for the family. We defined 'diagnosed' probands as those with a variant that is annotated as pathogenic or likely pathogenic and the family classified as being 'solved' or 'partially solved' by the referring clinician. We also classified probands who have a variant prioritised by the 100kGP Clinical Research Team, and awaiting clinical review, in the 'Diagnostic Discovery data' as 'diagnosed' due to the high reported probability of these variants being later classified as disease-causing [40]. All other probands were classified as 'undiagnosed'.

Calculation of polygenic scores

Polygenic scores (PGS) were calculated using summary statistics from the latest genome-wide association studies (GWAS) for gestational duration [16], EA [41], and the cognitive and non-cognitive components of EA [42].

The non-cognitive component captures factors such as personality traits and socioeconomic status that may influence EA independently of cognitive ability [42], and is relevant to this study as some of these factors are correlated with gestational duration [43–47]. PGS were calculated using genotype array data for DDD participants and genome sequence data for 100kGP participants. PGS were estimated using LDpred2-auto [48] for a set of 1,444,196 HapMap3+variants [49] that pass quality control in 100kGP aggV2 samples, have a MAF > 1%, and are well imputed in all genotyping arrays used in DDD (Minimac4 $R^2 > 0.8$) ($N_{SNPs} = 1{,}001{,}592–1{,}039{,}890$). The recommended LD reference panel generated using HapMap3+[49] variants was used for PGS calculations. PGS for each individual were estimated using PLINK v1.9 [50], which uses the weights generated by LDpred2 to calculate the weighted sum of genotypes across a set of SNPs for each individual.

Calculation of rare variant burden scores

Sequence data from parents and probands from DDD and 100kGP was annotated with the Ensembl Variant Effect Predictor (VEP) [51] and variants with the 'worst consequence' annotation across transcripts were retained. Autosomal heterozygous protein-truncating variants (PTVs) defined as high confidence by LOFTEE [52] and 'missense' variants (defined as missense, stop lost, start lost, inframe insertion, inframe deletion, and loss-of-function variants annotated as low-confidence by LOFTEE [52]) were extracted. Rare variants with a $MAF < 1 \times 10^{-5}$ in each gnomAD [52] super-population and $MAF < 1 \times 10^{-4}$ in the respective cohorts were retained for analysis. A deleterious rare variant burden score (RVBS) was calculated by summing the number of high confidence PTVs and missense variants (MPC ≥ 2 [53]) in loss-of-function-intolerant genes (pLI > 0.9), restricting to inherited variants in children.

Data analysis

All data analysis was performed using R v4.3.1 [54] unless otherwise specified. The analysis plan was pre-registered [55] and deviations from the analysis plan are described in Additional File 1: Supplementary Methods.

Associations between prematurity and phenotypic outcomes

We used multivariable logistic regression models to assess the association between degree of prematurity and binary phenotypic measures listed in Additional File 2: Table S1, and multivariable linear regression models for continuous phenotypic measures, excluding developmental milestone attainment (see the 'Time-to-event analysis' section). For count-based outcomes, such as 'Number of Affected Organ Systems', we used multivariable negative binomial regression models. In all models, each degree of prematurity, 'moderate', 'very', or 'extreme', was compared to being born at term. The baseline models were estimated in the entire sample and regressed the phenotypic measure on degree of prematurity while controlling for relevant covariates.

$$Antenatal\ Outcome \sim prematurity + maternal\ age\ at\ birth$$

$$Phenotypic\ Outcome \sim prematurity + proband's\ age\ at\ assessment + proband's\ sex$$

where *phenotypic outcome* refers to all other phenotypic measures besides the antenatal outcomes listed in Additional File 2: Table S1.

To test if the presence of a diagnostic variant modified the association between prematurity and neurodevelopmental outcomes, an additional set of models was fitted to adjust for genetic diagnosis and an interaction between prematurity and a genetic diagnosis.

$$Antenatal\ Outcome \sim prematurity + maternal\ age\ at\ birth + diagnosis + prematurity * diagnosis$$

$$Phenotypic\ Outcome \sim prematurity + proband's\ age\ at\ assesment + proband's\ sex + diagnosis + prematurity * diagnosis$$

To test whether our findings were robust to treating gestational duration as a continuous measure, we re-estimated all models with gestational duration as a continuous predictor. In these models, gestational duration was standardised (mean = 0, sd = 1) within each cohort so each coefficient in the regression represents the change in log-odds (for binary outcomes) or mean outcome (for continuous outcomes) per one-SD change in gestational duration.

Finally, to assess the influence of other factors on the relationship between prematurity and phenotypic outcomes, we re-estimated all models, each time including only one additional factor. Specifically, we adjusted for either a deprivation index (available in 100kGP only) or genetic scores that showed a significant association with gestational duration.

We applied the Bonferroni correction for 522 tests (29 phenotypes × 3 levels of prematurity × 6 models per phenotype) and considered $p < 9.58 \times 10^{-5}$ significant. Regression models were estimated in DDD and 100kGP separately; and effect size estimates were meta-analysed using an inverse-variance weighted approach for phenotypes assessed in both cohorts.

Time-to-event analysis

Kaplan–Meier survival analysis with log-rank tests was performed to test for differences in the time taken to achieve a developmental milestone (social smile, sitting independently, walking independently, and first words) across gestational age groups. Analysis was performed for a subsample of participants from the DDD study with data on developmental milestone attainment ($n = 5692$–11,726). We also estimated Cox proportional hazards for developmental milestone attainment for each category of prematurity, relative to being born at term. The Cox models were adjusted for proband's age, sex, genetic diagnostic status, and an interaction between genetic diagnosis and degree of prematurity. We applied the Bonferroni correction for multiple testing, $p < 0.05/4$ (1 log-rank test for 4 milestones) and $p < 0.05/24$ ([3 degrees of prematurity + 3 interaction terms] for 4 milestones) were considered significant for Kaplan–Meier analysis and Cox models respectively.

Testing for enrichment of monogenic diagnoses in specific genes and gene sets

Logistic regression analyses were used to test for an association between prematurity, encoded as a binary variable, and the presence of monogenic diagnoses in selected genes in diagnosed probands with single gene diagnoses from DDD and 100kGP ($n = 7581$). Based on power calculations, we conducted association testing for 44 genes with at least 30 observed diagnostic variants in our dataset (Additional File 1: Supplementary Methods) and applied Bonferroni correction to account for the 44 tests.

Fisher's exact tests with post hoc pairwise comparisons were conducted to test for an enrichment of monogenic diagnoses in four gene sets associated with adverse pregnancy outcomes (fetal anomalies, prematurity, stillbirth, and intrauterine growth restriction) (Additional File 1: Supplementary Methods) across the gestational age groups in diagnosed probands from DDD and 100kGP. Tests that pass the Bonferroni correction ($\alpha = 0.05/(4$ gene sets tested $\times$ 4 tests per gene set); $p < 3.13 \times 10^{-3}$) were considered significant.

Estimating excess DNMs and the attributable fraction

We compared the observed number of DNMs to the expected count predicted by a null mutational model [56] for each consequence class, across the exome as well as in genes with and without a known association with DDs according to DDG2P [57]. We conducted Poisson tests to assess differences in the observed and expected nonsynonymous DNM counts and applied a Bonferroni multiple testing correction to account for 18 tests (2 gestational age groups × 3 proband groups × 3 gene sets).

We also estimated the attributable fraction, the proportion of DD cases attributable to nonsynonymous DNMs using the following formula:

$$Attributable\ Fraction = \frac{O_{nonsynonymous} - \lambda E_{nonsynonymous}}{Nprobands}$$

where O_{DMN} is the observed number of nonsynonynous DNMs, E_{DNM} is the expected number calculated using the model from [56], and λ is a correction factor calculated as $\frac{O_{synonymous}}{E_{synonymous}}$ among all probands.

The attributable fraction was estimated for probands in each gestational age group (N preterm = 2,169; N term = 11,857), both overall and stratified by diagnostic status, across the exome and for genes with and without known DD associations [57]. We compared the attributable fraction between gestational age groups for each gene set using z-tests and applied a Bonferroni correction to account for nine tests (3 proband groups × 3 gene sets).

Associations between genetic measures and gestational duration

We tested for an association between gestational duration and four PGS (gestational duration and three PGS for educational attainment) as well as RVBS by fitting linear regression models in unrelated probands of genetically inferred GBR ancestry. The sample size for the PGS analysis was 11813 ($N_{DDD} = 7032$; $N_{100kGP} = 4781$). For the RVBS analysis, the sample size was 6592 ($N_{DDD} = 5184$; $N_{100kGP} = 1408$), as we assessed only inherited rare variants so the cohort was restricted to trios. Since gestational duration was non-normally distributed, we applied a rank-based inverse normal transformation. Proband's sex and the first 20 genetic principal components (PCs) were included as covariates in the models. We ran the model using data from all probands, as well as separately for diagnosed and undiagnosed probands.

$$Gestational\ Duration \sim PGS + proband's\ sex + PC1 + \cdots + PC20$$

$$Gestational\ Duration \sim RVBS + proband's\ sex + PC1 + \cdots + PC20$$

To formally test whether the association differed between diagnosed and undiagnosed probands, we additionally fitted interaction models that included diagnostic status (coded 0 = undiagnosed, 1 = diagnosed) and an interaction term:

$$Gestational\ Duration \sim PGS + diagnostic\ status + PGS * diagnostic\ status + proband's\ sex + PC1 + \cdots + PC20$$

$$Gestational\ Duration \sim RVBS + diagnostic\ status + RVBS * diagnostic\ status + proband's\ sex + PC1 + \cdots + PC20$$

Power calculations for detecting an interaction effect are described in Additional File 1: Supplementary Methods.

We applied a Bonferroni correction for fifteen tests (five genetic measures and three proband groups—all, diagnosed, and undiagnosed probands). All models were estimated in DDD and 100kGP separately. The effect size estimates from the two cohorts were meta-analysed using an inverse-variance weighted approach.

Lastly, we extended the baseline model in fully genotyped trios ($N_{DDD} = 3101$; $N_{100kGP} = 2989$) to control for parental PGS to test if maternal and paternal non-transmitted common alleles are associated with offspring gestational duration (Additional File 1: Supplementary Methods).

Results

Our analysis included probands with data on gestational age at birth from the DDD study ($N = 13{,}401$) as well as DDD-like probands from the rare disease programme of the 100,000 Genomes Project ($N = 8311$). Table 1 provides an overview of the basic demographic and clinical characteristics of probands from each cohort.

Premature birth affects clinical features among individuals with developmental disorders suspected to have a genetic component

We first sought to test whether premature birth influences phenotypic presentation in children with DDs and whether additional genetic factors, such as diagnostic variants and polygenic predisposition, also contribute. The results for this analysis were generally consistent for probands from DDD and 100kGP; thus, results from the meta-analysis are presented below (see Additional File 1: Figures S4–6 for cohort-specific results).

We started by estimating the association between degree of prematurity and selected antenatal factors, recapitulating established associations observed in the general population [58–61]. Specifically, we found that premature delivery was more likely for mothers with a history of previous pregnancy loss, diabetes during pregnancy, an abnormal antenatal ultrasound scan, and in multifetal pregnancies (Additional File 1: Figure S4). Multifetal pregnancy showed a strong, significant association with all categories of prematurity with the greatest odds observed for extremely preterm delivery (OR = 14.03, $p = 7.32 \times 10^{-36}$). Maternal diabetes was associated with

Table 1 Descriptive statistics of the datasets combined

	DDD (*N* = 13,401)	100kGP (*N* = 8311)
Gestational age group (%)		
Term (37 + weeks)	11,246 (83.9%)	7042 (84.7%)
Moderately premature (32–36 weeks)	1753 (13.1%)	998 (12%)
Very premature (28–31 weeks)	291 (2.2%)	205 (2.5%)
Extremely premature (< 28 weeks)	111 (0.8%)	66 (0.8%)
Number diagnosed (%)	5493 (41%)	2383 (28.7%)
Term	4750 (42.2%)	2092 (29.7%)
Moderately premature	627 (35.8%)	243 (24.3%)
Very premature	91 (31.3%)	41 (20%)
Extremely premature	25 (22.5%)	7 (10.6%)
Age at recruitment in years (mean ± SD)	7.32 ± 6.13	7.87 ± 5.14
Number in trios (%)	9829 (73.4%)	5585 (67.2%)
Birthweight in grammes (mean ± SD)	3,047 ± 772	3,114 ± 732
Number of organ systems affected[a]	4.14 ± 2.06	3.52 ± 2.34

[a] As terms may be associated with multiple organ systems, the number of distinct affected organ systems was calculated using the approach outlined in Niemi et al. to assign each HPO term to just one organ system [2]

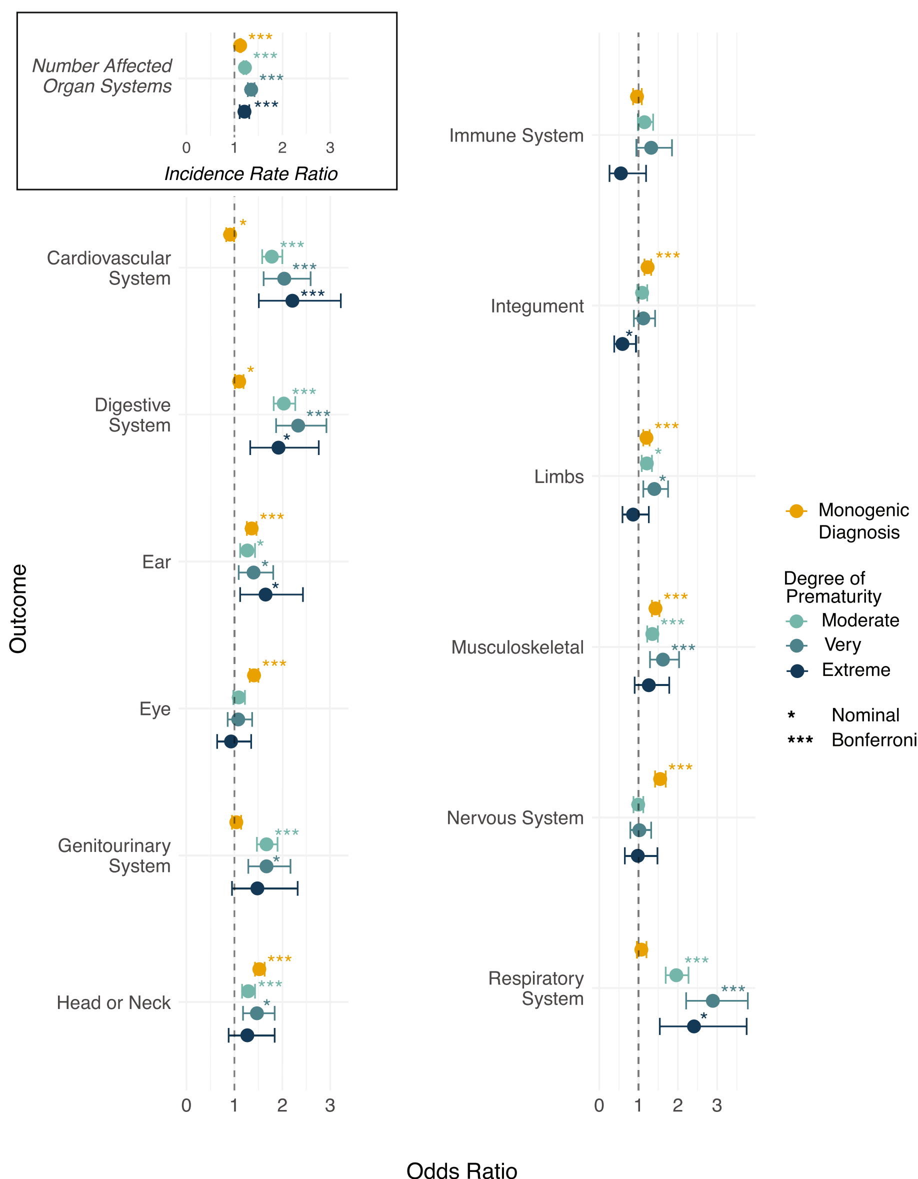

Fig. 1 Associations between phenotypic abnormalities, degree of prematurity (blue circles), and the presence of a monogenic diagnosis (yellow circles), estimated from a joint model. For each HPO term describing an abnormality of an organ or organ system, the figure shows the odds of being assigned the term, or any of its descendant terms, for probands in each category of prematurity compared to those born at term, and for probands with a monogenic diagnosis compared to those without. For these binary phenotypes (non-italicised), odds ratios are presented. For the count variable, number of affected organ systems (box, top left), the incidence rate ratio is shown, representing the relative change in the expected number of affected organ systems for each prematurity category or diagnostic group compared to their respective reference. Associations were estimated using models regressing each phenotype on degree of prematurity and monogenic diagnosis. Error bars represent 95% confidence intervals

a significantly increased likelihood of moderate prematurity (OR = 2.10, $p = 1.78 \times 10^{-16}$), but not very or extreme prematurity. We found that a genetic diagnosis does not change the relationship between prematurity and these antenatal factors (Additional File 2: Table S2).

Next, we assessed associations between preterm birth and phenotypes recorded for probands from both cohorts, including HPO terms describing affected organs and/or organ systems and the severity of intellectual and/or developmental delay. On average, premature probands across all categories of prematurity were more likely to have lower birth weight ($p < 3.23 \times 10^{-7}$) and had more affected organ systems than term probands ($p < 1.78 \times 10^{-6}$) (Additional File 1: Figures S5).

Reassuringly, we found significantly increased odds of being assigned the HPO term, 'abnormality of prenatal development or birth', for all categories of prematurity, with the odds increasing as the degree of prematurity increased (OR = 3.48–10.79, $p < 2.75 \times 10^{-45}$). All categories of premature birth were significantly associated with increased odds of being assigned an HPO term related to abnormality of the cardiovascular and digestive systems ($p < 6.90 \times 10^{-5}$) (Fig. 1; Additional File 1: Figures S6). For these organ systems, very preterm children had higher odds than moderately preterm children. However, we did not observe increased odds for extremely preterm children relative to other categories of prematurity. The confidence intervals for the extremely preterm estimates were wide, likely due to the small number of extremely preterm probands in the analysis. We found no significant associations between any category of prematurity and severity of intellectual disability or developmental delay or abnormalities of the ears, eyes, immune system, integument, limbs, and nervous system (Additional File 1: Figures S4–5).

In an extended model that aimed to test if the presence of a monogenic diagnosis modified phenotypic associations with prematurity, we found that the organ systems impacted by prematurity differed from those associated with diagnostic variants (Fig. 1). For instance, while the presence of a diagnostic variant did not increase the likelihood of abnormalities in the cardiovascular or digestive systems, it significantly increased the odds of abnormalities in the nervous system, eyes, ears, and integument (Fig. 1). No significant interactions were detected between any category of prematurity and the presence of a monogenic diagnosis, suggesting that preterm birth and diagnostic variants independently and additively influence clinical features in developmental disorders (Additional File 2: Table S3).

We then considered two additional sets of HPO terms for this analysis: a set of prematurity-associated HPO terms chosen by clinicians (e.g., retinopathy of prematurity, intraventricular haemorrhage, and necrotising enterocolitis) and a curated set of medically relevant HPO terms selected for their relevance to neurodevelopmental disorders [2]. We found that few to no probands in these cohorts were assigned the prematurity-associated HPO terms; thus, we did not conduct the association analysis (Additional File 1: Figure S7). When analysing the medically relevant HPO terms, we observed few significant associations between prematurity and the phenotypes (Additional File 1: Figure S8). Two exceptions were that the likelihood of short stature was significantly higher for children born across all categories of prematurity compared to those born at term ($p < 8.98 \times 10^{-7}$), and that moderate prematurity was associated with significantly reduced odds of being assigned an HPO term for seizures (OR = 0.75, $p = 5.38 \times 10^{-7}$) (Additional File 1: Figure S8). There were no significant interactions between degree of prematurity and the presence of a monogenic diagnosis for any of the medically relevant HPO terms (Additional File 2: Table S3).

Given the prevalence of prematurity-associated HPO terms was far below expected given the number of premature infants in our sample, we were concerned that potentially biased selection of HPO terms by clinicians may be influencing our findings. Therefore, we conducted a sensitivity analysis using diagnoses from hospital admissions available for a subset of probands from 100kGP ($N = 6474$; Additional File 1: Supplementary Note 2). These data are unbiased by HPO recording practices used when enrolling patients for genetic testing. The results of this analysis support the hypothesis that these practices result in under-reporting phenotypes related to complications of prematurity (Additional File 1: Figures S9–10). However, the findings also reinforce our primary conclusion that premature probands in these cohorts, on average, have a higher number of affected organ systems and that aspects of their phenotype reflect the known sequelae of prematurity (Additional File 1: Figure S11).

Finally, to confirm that our conclusions hold when treating gestational duration as a continuous rather than discrete measure, we re-estimated all associations with gestational duration (in weeks) as a continuous predictor (Additional File 2: Tables S4–5). Overall, these analyses supported our primary conclusions: shorter gestational duration was associated with a higher likelihood of antenatal complications (Additional File 2: Tables S4–5), and with an increased number of affected organ systems, with the highest odds observed for abnormalities of the respiratory, cardiovascular, and digestive system (Additional File 1: Figure S12). We also detected associations with abnormalities of the limbs, ears, and genitourinary systems — phenotypes that were not significantly associated with all categories of prematurity in previous models. In models including diagnostic status, the interaction term between continuous gestational duration and diagnostic variant remained nonsignificant for all outcomes (Additional File 2: Table S5), consistent with the conclusion that gestational duration and the presence of a genetic diagnosis independently influence phenotypic outcomes.

Attainment of developmental milestones

In the analysis described above, we did not detect an association between degree of prematurity and severity of developmental delay or intellectual disability. However, this analysis relied on clinical reports of

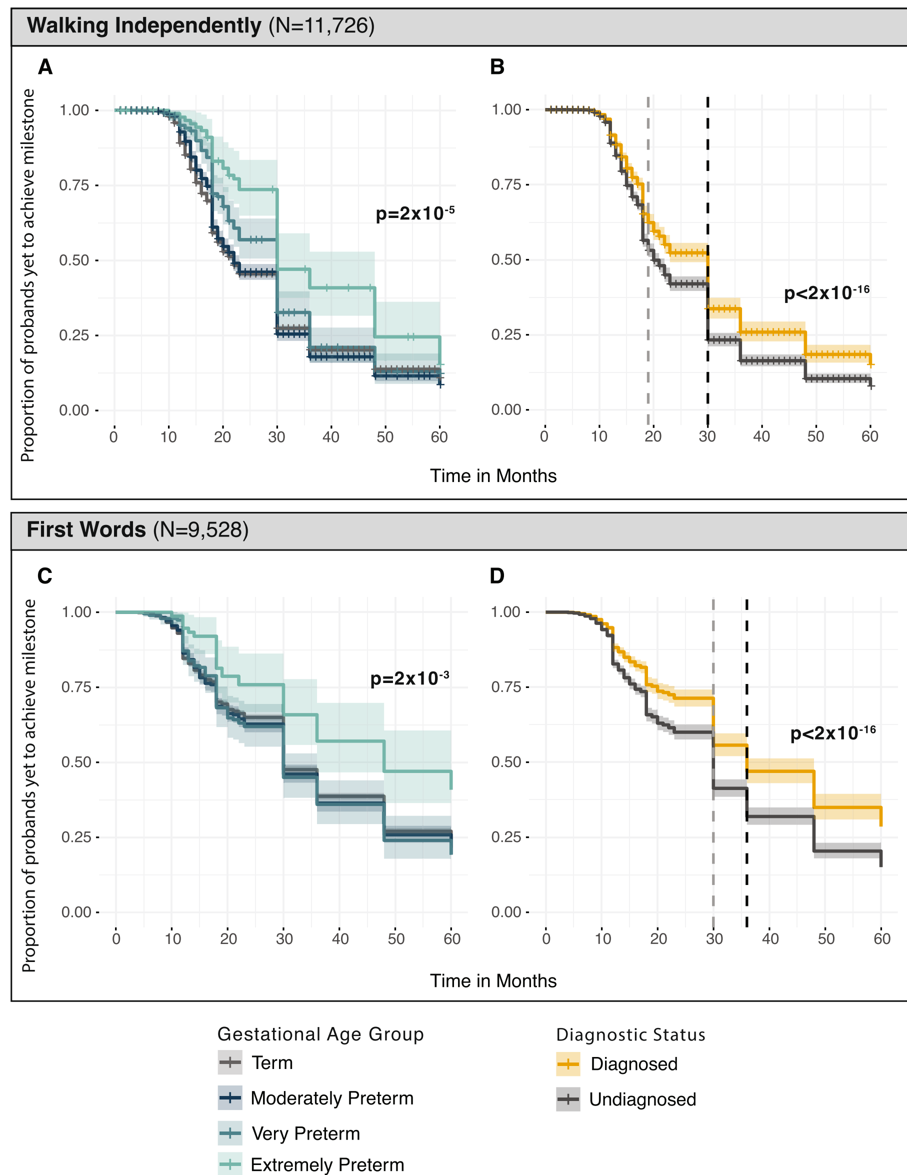

Fig. 2 Developmental milestone attainment by gestational age and genetic diagnosis in DDD. Survival curves illustrate time from birth (time 0) to attainment of the developmental milestone. *x*-axis denotes time in months, and the *y*-axis shows the proportion of probands who have not achieved the developmental milestone at each time point. Shaded ribbons depict 95% confidence interval. Panels **A** and **C** show Kaplan–Meier curves comparing time taken (in months) to walking independently (**A**) and first words (**C**) across gestational age groups. Colour corresponds to gestational age group, *p*-values are from log-rank tests comparing differences between groups. Panels **B** and **D** show survival curves estimated from Cox regression models comparing time to milestone attainment for preterm probands with and without a genetic diagnosis. Dashed vertical line shows median time to achieve milestone for diagnosed term probands (black) and undiagnosed term probands (grey). *p*-values are from Cox regression models. See Additional File 1: Figure S13 for corresponding plots for the milestones, social smile, and sitting independently

severity, which were missing for 75% of probands. To address this limitation, we utilised developmental milestone data, available in DDD probands, to reexamine the impact of prematurity and genetic variation on neurodevelopment. We first compared time taken to achieve a developmental milestone (social smile, sitting independently, walking independently, and first words) across gestational age groups using Kaplan–Meier survival analysis with log-rank tests. Gestational age group was significantly associated with variation in the time taken to achieve all assessed developmental milestones (log rank test $p<2\times10^{-3}$) (Fig. 2; Additional File 1: Figure S13; Additional File 2: Table S6). Extremely preterm probands consistently

achieved all milestones later than other groups. Term probands achieved the developmental milestones of 'social smile' and 'sitting independently' significantly earlier than probands from the preterm gestational age groups (Additional File 2: Table S6). A similar trend was seen for age of walking and age of first words, but only extremely preterm probands showed a significant delay compared to term probands ($p < 1.73 \times 10^{-4}$). We extended this analysis with Cox regression models to explore how the presence of a diagnostic variant influenced the time taken to achieve these developmental milestones. In these models, the presence of a genetic diagnosis was associated with increased time to milestone attainment across the gestational age groups for all developmental milestones ($p < 0.04$) (Fig. 2; Additional File 1: Figure S13). However, there was no evidence of an interaction between a monogenic diagnosis and gestational age at birth on the time to milestone attainment (Additional File 2: Table S7). These findings are consistent with the findings of our phenotype association analysis whereby prematurity and the diagnostic variant act additively as opposed to multiplicatively to influence outcomes in DDs.

Differential enrichment of monogenic diagnoses in specific genes and gene sets in premature probands

We next investigated if diagnostic variants in any specific genes or gene sets were associated with prematurity in an analysis of 7581 diagnosed probands (986 preterm) with single gene diagnoses across both DDD and 100kGP.

We identified four genes, *EP300* (OR = 2.7, $p = 2.34 \times 10^{-3}$), *KMT2A* (OR = 1.9, $p = 5.54 \times 10^{-3}$), *NSD1* (OR = 2.2, $p = 4.96 \times 10^{-2}$), and *NF1* (OR = 2.4, $p = 1.81 \times 10^{-2}$), in which a diagnostic mutation was associated with an increased likelihood of prematurity at nominal significance, and one gene, *MECP2* (OR = 0.1, $p = 2.24 \times 10^{-2}$), in which the likelihood was reduced (Additional File 2: Table S8). After correction for multiple testing, no associations remained significant. After limiting the analysis to probands with diagnostic variants that had been clinically annotated as pathogenic or likely pathogenic (6223 probands, 791 premature), we found that all identified genes except *NF1* remained nominally significantly associated with prematurity and that the association with *EP300* passed multiple testing correction (Additional File 2: Table S9).

Next, we tested for differences in the proportion of diagnosed probands with a diagnostic mutation in four gene sets, prioritised for their relevance to prematurity, across the categories of gestational duration. We observed significant differences in the proportion of term, moderately preterm, and very or extremely preterm probands with diagnostic mutations in the fetal anomalies gene set ($p = 3.33 \times 10^{-5}$) (Additional File 2: Table S10). Post hoc analysis indicated that moderately preterm probands had a significantly higher enrichment of mutations in the fetal anomalies gene set compared to term probands (OR = 1.36, $p = 7.83 \times 10^{-5}$), while very or extremely preterm probands exhibited a nominal enrichment of these mutations compared to term probands (OR = 1.54, $p = 1.92 \times 10^{-2}$) (Fig. 3). We saw a nominal enrichment of diagnostic mutations in premature probands in the gene sets associated with IUGR and prematurity ($2.11 \times 10^{-2} < p < 0.05$) (Fig. 3). Post hoc comparisons demonstrated a nominal difference in the proportion of moderately preterm probands with mutations in these gene sets when compared to term probands ($8.53 \times 10^{-3} < p < 0.05$) (Fig. 3).

In summary, we find some evidence that monogenic diagnoses in certain genes and gene sets differ in prevalence between term and preterm probands in this sample. However, these enrichments could have several possible interpretations, as discussed below.

The relationship between de novo variation and gestational age in developmental disorders

As DNMs account for the majority of genetic diagnoses among DDs [5, 64], we sought to compare the fraction of diagnoses attributable to DNMs and the genes enriched for DNMs between preterm ($N = 2169$) and term ($N = 11857$) probands. Overall, both preterm and term groups carried significantly more nonsynonymous DNMs than expected under a null mutational model ($p < 4.38 \times 10^{-63}$) (Fig. 4; Additional File 2: Table S11). We previously observed that term probands were more likely to have a genetic diagnosis than preterm probands in DDD [5], reflecting a liability threshold model; consistent with this, the attributable fraction across all genes was nominally significantly higher for term probands than preterm probands (39% [95% CI 37–41%] versus 33% [29–37%]; *z*-test *p*-value = 0.01) (Fig. 4; Additional File 2: Table S12). We then further compared attributable fractions between DD-associated genes and all other genes. Term infants had a higher attributable fraction than preterm among known DD-associated genes (25% [95% CI 24–26%] versus 20% [95% CI 18–23%]; *z*-test *p*-value = 1.28×10^{-4}) but there was no difference between these groups in genes with no known DD-associations (14% [95% CI 12–15%] versus preterm 13% [95% CI 9–16%]; *z*-test *p*-value = 0.62) (Fig. 4). Among undiagnosed probands across all genes, DDG2P genes and non-DDG2P genes, there was no difference in the attributable fraction between the term and preterm probands, but both groups were enriched for non-synonymous mutations ($p < 1.68 \times 10^{-10}$) (Additional File 2: Table S12). Overall, these findings suggest that while premature probands are less likely to have genetic

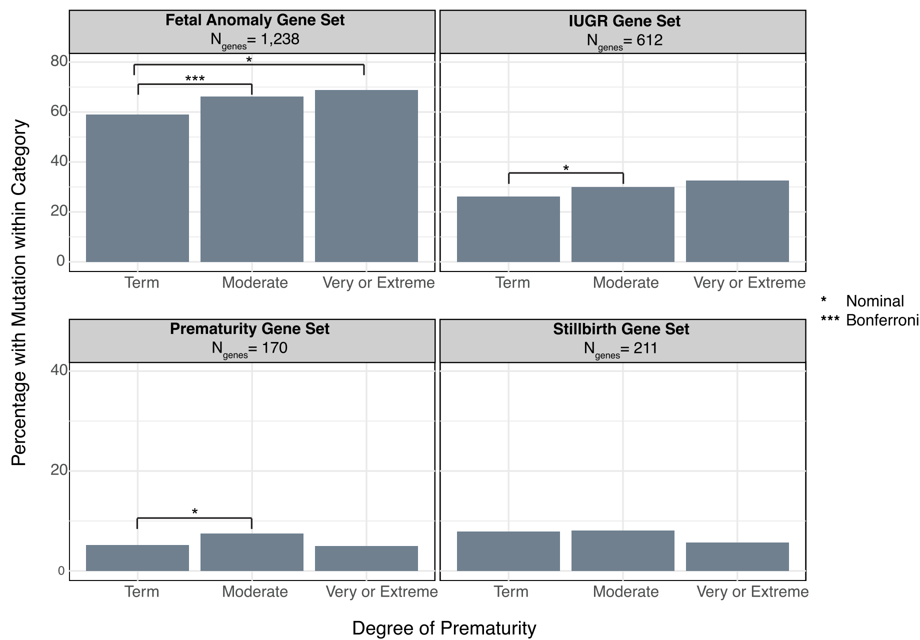

Fig. 3 Gene set enrichment analysis. Bar chart showing the proportion of diagnosed probands within each gestational age group with a diagnostic mutation in gene from a given gene set. The fetal anomaly [62] and stillbirth [63] gene sets are curated by experts. Gene sets associated with prematurity and IUGR were derived by the HPO team from a combination of OMIM data mining and manual curation [27]

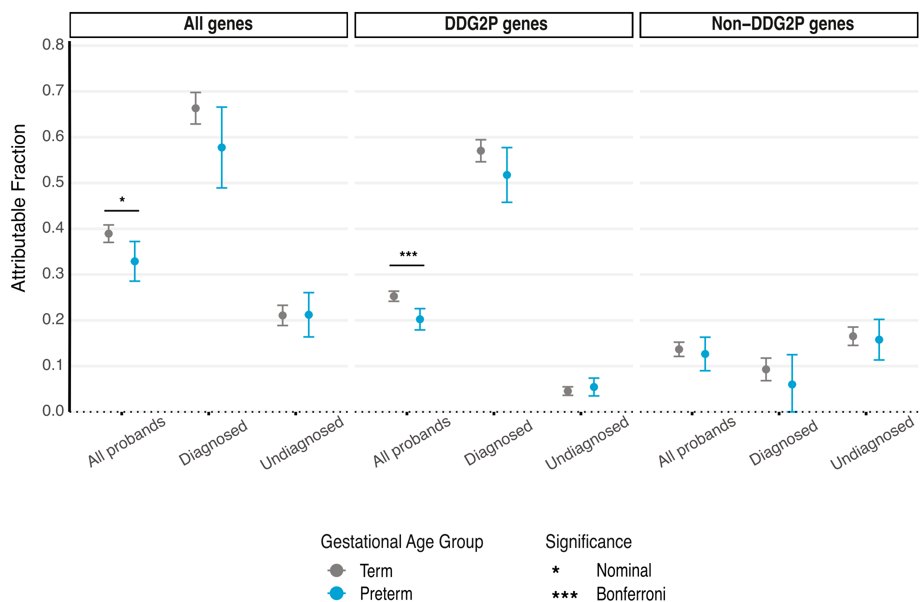

Fig. 4 Attributable fraction of preterm and term developmental disorder cases due to de novo variation. The *y*-axis depicts the attributable fraction of cases accounted for by nonsynonymous DNMs, shown separately for term and preterm probands, both overall and stratified by diagnostic status. The figure presents the attributable fraction across all genes as well as for genes with and without known DD associations (DDG2P and non-DDG2P, respectively). Asterisks indicate the significance of *z*-tests comparing the fraction between each group of term and preterm probands. Error bars represent 95% confidence intervals

diagnoses than term probands in these cohorts, there are still diagnoses to be made in both known and novel DD-associated genes among both preterm and term undiagnosed probands.

Characterising the association between polygenic scores for educational attainment and gestational duration

Since genetic variation may confound associations between epidemiological factors such as prematurity

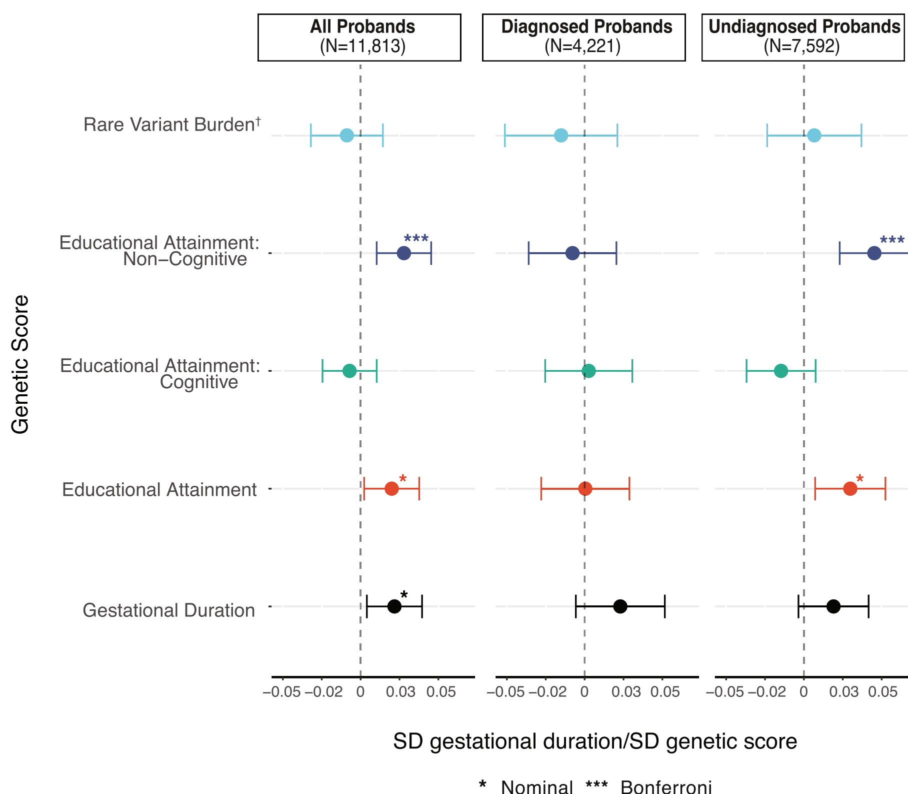

Fig. 5 Associations between genetic measures and gestational duration. Standardised effect of proband's genetic measure on gestational duration. Gestational duration was rank-based inverse normal transformed (RINT). The effect size should be interpreted as change in standard deviation of RINT gestational duration per standard deviation change in genetic score. Panels show effect size estimates from a meta-analysis of regression results from DDD and 100kGP. Errors bars represent 95% confidence intervals. † The sample size for the RVBS analysis is 6592 ($N_{Diagnosed}$=3171 and $N_{Undiagnosed}$ = 3421) as it is limited to trios

and clinical outcomes in DDs, in this work, we aimed to investigate whether genetic background influences the relationship between gestational age at birth and phenotypic outcomes in DDs. Prior to testing this hypothesis, we first sought to replicate and further explore associations between common variant predisposition to education-related traits and prematurity that were observed in probands with neurodevelopmental conditions in DDD [3], across DDD probands (N=7032), and DDD-like probands from 100kGP (N=4781). We considered PGSs for three education-related traits: educational attainment (PGS_{EA}) [41], and its cognitive (PGS_{CogEA}) and non-cognitive components ($PGS_{NonCogEA}$) [42].

As expected, the proportion of variance in gestational age at birth explained by the child's PGS was small in both cohorts (incremental R^2=0.01–0.26%), though the significance of associations varied between them (Additional File 2: Table S13). In DDD, associations were consistent with observed genetic correlations [3] and were generally stronger than in 100kGP, possibly due to the larger sample size (Additional File 1: Figure S14). In the cross-cohort meta-analysis of all probands, gestational duration was nominally significantly associated with the PGS_{EA} (β=0.02, p=0.03) and significantly associated with $PGS_{NonCogEA}$ (β=0.03, $p=1.83\times10^{-3}$). This suggests that probands with a higher common variant predisposition to the non-cognitive components of EA were more likely to be born at later gestational ages (Fig. 5). When stratifying the probands by diagnostic status, we only observed an association between $PGS_{NonCogEA}$ and gestational duration in undiagnosed probands (β=0.05, $p=6.82\times10^{-5}$; also nominally significant in both cohorts), implying that the presence of a diagnostic variant attenuates the effect of $PGS_{NonCogEA}$ on gestational duration (Fig. 5). We formally tested for an interaction between each PGS and diagnostic status and only observed a nominally significant interaction for $PGS_{NonCogEA}$ ($\beta= -0.05$, $p=4.57\times10-3$), consistent with the attenuation of the association in diagnosed probands (Additional File 1: Figure S15). No association was observed between the number of inherited damaging coding variants in loss-of-function-intolerant genes, captured as a rare variant burden score, and gestational duration, although these rare variants are also known

to be associated with lower EA [65–68] (Additional File 1: Supplementary Note 3). As a sanity check, we tested whether PGS for gestational duration [16] was associated with this phenotype, and found that it was in the meta-analysis of all probands ($\beta = 0.02$, $p = 1.62 \times 10^{-2}$) (Fig. 5).

We next tested whether associations between a proband's PGS for education-related traits and gestational duration are driven by direct genetic effects and whether there was any evidence for these associations being driven by parental alleles which presumably act by affecting the prenatal environment (i.e. indirect genetic effects). To test this, we fitted a trio model [69] (Additional File 1: Supplementary Methods), in which the coefficient on the child's PGS represents the direct genetic effect, and the coefficient on the parents' PGSs represents the association between non-transmitted parental alleles and the child's phenotype, which could reflect either indirect genetic effects or confounders [69–71]. We found no evidence of a direct genetic effect of probands' $PGS_{NonCogEA}$ on gestational duration (Additional File 1: Figure S16). In contrast, we detected a nominal significant positive association between maternal and paternal non-transmitted alleles for $PGS_{NonCogEA}$ and PGS_{EA} and gestational duration. These findings suggest that the observed association between the proband's PGS for EA and its non-cognitive component may reflect the influence of parental polygenic predisposition to these traits on gestational duration, rather than a direct effect of the proband's genotype. However, we cannot rule out that this is driven by confounders such as parental assortment or uncontrolled population stratification [3, 69, 71, 72]. See Additional File 1: Supplementary Note 4 for further discussion of the trio analysis.

Finally, we assessed whether the observed association between $PGS_{NonCogEA}$ and prematurity might confound the relationship between prematurity and clinical outcomes in DDs. We repeated the phenotype association analysis while controlling for $PGS_{NonCogEA}$ and observed no significant change in the associations between degree of prematurity and any antenatal factors or tested phenotypic outcomes in either cohort (Additional File 2: Table S14). Given that $PGS_{NonCogEA}$ may capture aspects of socioeconomic status, we conducted a similar analysis adjusting for the Index of Multiple Deprivation [73] and again we observed no significant change in associations (Additional File 2: Table S15). Therefore, the association between prematurity and these phenotypes is unlikely to be confounded by socioeconomic status or common variants associated with the non-cognitive component of EA.

Discussion

Using data from two large cohorts of individuals with DDs recruited for clinical sequencing, we investigated genetic influences on premature birth, and associations between prematurity and phenotypic outcomes. We demonstrated that prematurity, in addition to the presence of a monogenic diagnosis, impacts the clinical features and developmental trajectories of these individuals. We identified developmental disorder genes and relevant gene sets associated with an elevated risk of preterm delivery among individuals with DDs, motivating future research aimed at understanding the relationship between prematurity and genetic variation in DDs. Our analysis of de novo variation demonstrated that a higher proportion of probands are attributable to DNMs in known disease-genes in term than in preterm probands, but for both groups, there is a similar proportion of probands accounted for by DNMs in as-yet-undiscovered developmental disorder genes. Finally, we show that individuals with higher common variant predisposition to the 'non-cognitive' component of EA are, on average, less likely to be born premature, but that this association is not driven by direct genetic effects on the child.

Our work shows that prematurity expands the spectrum of clinical features experienced by individuals with DDs ascertained for clinical sequencing. Specifically, prematurity was associated with an increased number of affected organ systems. We identified organ systems related to common complications of prematurity—in particular respiratory [74], cardiovascular [75], and digestive systems [74]—to be more frequently affected among premature probands; this held even after accounting for the presence of a monogenic diagnosis (Fig. 1). These findings align with recent work in autism [13] which showed that individuals born prematurely had more comorbidities than those born at term. Although both prematurity and the presence of a monogenic diagnosis [5] are associated with neurodevelopmental impairment [76–84], we did not find an increased rate of neurodevelopmental abnormalities among premature probands in our analysis of HPO terms [9, 85]. We suspect that this discrepancy may reflect cohort ascertainment: nearly all probands have an HPO term related to abnormal neurodevelopment, reducing our power to see any effect of prematurity on this. Our milestone analysis does provide support for an additive impact of prematurity and monogenic diagnoses on neurodevelopment. Premature probands with a monogenic diagnosis experience greater delays than those without a monogenic diagnosis in attaining certain developmental milestones, including sitting and walking independently and first words (Fig. 2). Although we found that the presence of any monogenic diagnosis acts additively with prematurity in influencing certain phenotypic outcomes, given the large-scale genetic heterogeneity of DDs, monogenic diagnoses in individual genes could still interact with prematurity to influence phenotypic severity. Additionally, our analyses tested only for

multiplicative interactions, and we therefore cannot rule out the possibility of additive interactions. Larger sample sizes, together with deeper and longitudinal phenotyping [86, 87], will be required to partition the relative contributions of environment and genetics on longer-term neurodevelopmental outcomes.

For our analysis of the role of rare genetic variation, we hypothesised that premature individuals with DDs may have proportionally more diagnostic variants in genes with links to fetal anomalies, IUGR, prematurity, and stillbirth than term individuals with DDs. We found an enrichment of diagnostic variants in genes from the fetal anomalies gene panel in moderate and very/extremely preterm individuals compared to term individuals (Fig. 3). This is unsurprising as congenital anomalies are found at an increased rate among individuals born premature [88]. However, there was no significant enrichment of diagnostic variants in genes linked to IUGR, prematurity, and stillbirth among preterm individuals. This may reflect the lack of a robust knowledge base of the rare genetic causes of these traits [17, 63]. These latter three lists are also smaller, reducing our power, and the preterm and IUGR gene sets were not curated by domain experts.

We then performed an analysis of odds of prematurity across individual disease genes in which 30 or more diagnostic variants were observed in our cohorts. Although we had adequate power to detect genes with an odds ratio of six or higher, no genes remained significant after correction for the number of individual genes tested. This suggests that the most common monogenic causes of DDs are not associated with a substantially higher prevalence of preterm birth among individuals already ascertained for DDs. At a nominal level of significance, we identified *EP300*, *KMT2A*, *NSD1*, and *NF1* as being associated with a higher prevalence of premature birth and *MECP2* with a lower prevalence. The association with EP300 reached statistical significance in a sensitivity analysis restricted to individuals with a clinically confirmed pathogenic variant. Fetuses with mutations in *EP300* are predisposed to IUGR, and their mothers are at increased risk of preeclampsia [89], both of which are indications for medical induction of preterm labour. While these results are exploratory, if replicated, there could be a case for reconsidering the comment in the recent consensus guideline for Rubinstein-Taybi syndrome, which stated that there is no increased risk of premature birth for individuals with variants in *EP300* [90]. In future, large datasets of preterm children, ideally ascertained for being born preterm rather than for having a DD, will be required to clarify the association between the genes identified in our study and prematurity risk.

Our analysis of the burden of de novo variation lends further support to a liability threshold model of DD aetiology and has potential clinical implications. We found that the attributable fraction of cases to nonsynonymous DNMs among all genes was nominally higher for term than preterm probands, and that among DDG2P genes alone this difference was significant after correcting for multiple testing. This is consistent with our previous findings which considered the rate of genetic diagnoses, and with a model in which an individual's total liability must exceed a certain threshold to manifest clinically recognisable DDs: those with a substantial environmental contribution require less or no genetic contribution [5]. This finding suggests that initial clinical genome sequencing analysing known disease genes will generally yield more de novo diagnoses if focused on term probands, while novel gene discovery efforts are likely to be equally helpful for diagnosing preterm and term probands. Interestingly, no difference in the rate of DNMs in neurodevelopmental disorder genes was observed between term and preterm probands in autism [13], perhaps due to its different genetic architecture and overall lower contribution from DNMs compared to the DDs studied here.

This work advances current understanding of the contribution of common genetic variation to preterm delivery in DDs in two key ways. First, we demonstrate that while common variants associated with the non-cognitive component of EA are positively associated with gestational age at birth across all DD probands, this association becomes null when the analysis is restricted to probands with a monogenic diagnosis (Fig. 5). This finding suggests that among diagnosed probands, it is the nature of the genetic diagnosis that has the largest effect on gestational timing, and this partly overrides the effect of any polygenic factors that might otherwise influence the likelihood of premature birth. Second, we show that the association between $PGS_{NonCogEA}$ and prematurity in probands is not explained by direct genetic effects (Additional File 1: Figure S16). Instead, parental non-transmitted alleles associated with the non-cognitive component of educational attainment are associated with the risk of preterm birth, likely due to effects on the prenatal environment or confounding factors like population stratification or assortative mating. Non-cognitive skills associated with higher EA, such as self-regulation and motivation, are negatively genetically correlated with substance use, risk-taking behaviours, and socioeconomic deprivation [42]. Maternal smoking and drug use have been identified as potential mediators of the established epidemiological association between maternal educational attainment and preterm delivery [44]. Given this context, our trio analysis supports the idea that

parental behaviours associated with the non-cognitive component of educational attainment may contribute to the risk of preterm birth in offspring.

Our analysis has several limitations. First, the phenotypic data for our main analyses consist primarily of HPO terms recorded at assessment, which are subject to clinician judgement and recruitment protocols. Our sensitivity analysis using Hospital Episodes Statistics (HES) suggests that this led to underreporting of the direct sequelae of prematurity (Additional File 1: Supplementary Note 2). Nonetheless, the HES analysis supports our primary conclusion that premature individuals in these cohorts have more affected organ systems, broadly reflecting the known clinical impacts of prematurity. Second, when we attempted to correct for gestational duration in the milestone analysis, this highlighted inconsistencies that suggested that the milestones for some but not all probands had been corrected for gestational age before data entry (see Additional File 1: Supplementary Note 1), which likely added noise in our analyses. Third, the modest sample size of extremely preterm infants may have limited our power to detect phenotype associations in this group.

The rare variant analysis has specific limitations that limit the generalisability and interpretation of the findings. The analysis is performed in individuals with DDs; thus, it is not informative about the effect of rare variants in a given gene on the chance of premature birth within the general population. Instead, it indicates whether variants in specific DD-associated genes are more likely to be seen in premature probands among this sample of DD patients recruited for clinical sequencing. Therefore, there may well be alternate reasons for gene and gene-set associations within the cohort that are not causal for prematurity. Premature probands are only likely to have been recruited if their clinical phenotype was disproportionate to the expected effects of their prematurity. This clinical threshold for inclusion could introduce correlations between variables that would not exist in a random, unascertained sample (i.e. collider bias). For example, if prematurity increases the severity of monogenic conditions, then genes with variable expressivity may be associated with prematurity within these cohorts because patients with variants in these genes were more likely to meet the clinical threshold for recruitment if they were also born prematurely. Finally, identified gene associations could reflect iatrogenic rather than biological mechanisms of preterm birth. For instance, genetic variants associated with constitutional small size may prompt clinician-initiated delivery before term.

Conclusions

In summary, we begin to tease apart the relative contributions and interplay of common and rare genetic variation and prematurity in developmental disorders. In future, the genetic and phenotypic characterisation of research cohorts ascertained for being born prematurely would provide more generalisable findings. Such cohorts would enable us to establish the fraction of premature babies likely to have a monogenic diagnosis, identify rare variants which increase the risk of being born prematurely, and investigate which clinical features indicate that a premature baby is likely to benefit from genetic investigations for a monogenic cause. Emphasis should be placed on sampling those at the lower extremes of gestational duration, who are most likely to experience health sequelae but are uncommon in the general population. This would allow us to understand the complex relationships between gestational duration, genetic variation, and health and development.

Abbreviations

100kGP	100,000 Genomes project
CoreExome	Illumina humancoreexome chip
DD	Developmental disorder
DDD	Deciphering Developmental Disorders
DDG2P	Developmental disorders genotype-to-phenotype database
DNMs	De novo mutations
EA	Educational attainment
GBR-ancestry	Genetically inferred British ancestry
GSA	Illumina infinium global screening array
GWAS	Genome-wide association studies
HES	Hospital episodes statistics
MAF	Minor allele frequency
OmniChip	Illumina omnichipexpress
PCs	Principal components
PGS	Polygenic score
PGS_{CogEA}	Polygenic score for the cognitive component of educational attainment
PGS_{EA}	Polygenic score for educational attainment
$PGS_{NonCogEA}$	Polygenic score for the non-cognitive component of educational attainment
PTV	Protein-truncating variants
RINT	Rank-based inverse normal transformed
RVBS	Rare variant burden score
VEP	Ensembl Variant Effect Predictor

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13073-025-01560-3.

Additional file 1: Supplementary methods, supplementary notes 1–4, and supplementary Figs. 1–20.

Additional file 2. Supplementary tables 1–17.

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100,000 Genomes Project: This research was made possible through access to data in the National Genomic Research Library, which is managed by Genomics England Limited (a wholly owned company of the Department of Health and Social Care). The National Genomic Research Library holds data provided by patients and collected by the NHS as part of their care and data collected as part of their participation in research.

Authors' contributions
OW and PC conducted most of the analyses, with the remainder being conducted by SJL and ED. QH, PC, OW, SA, and SJL carried out data preparation and quality control with supervision by HCM. EJR and HCM supervised the analyses and directed the study with key intellectual input from SR and MAS. OW, PC, EJR and HCM wrote the first draft of the manuscript, with input from SR. All authors read and approved the final manuscript.

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Data availability
The raw and post-QC genotype array data and exome sequence data from DDD are available through European Genome-phenome Archive (EGA; https://ega-archive.org/), under study ID EGAS00001000775. Clinically interpreted variants and associated phenotypes from DDD are available through DECIPHER (https://www.deciphergenomics.org/). Extended clinical data and photographs are not available to researchers outside of the DDD collaboration without specific consent from the family [1]. Whole-genome sequence data and phenotypic data from the 100,000 Genomes project can be accessed by application to Genomics England (https://www.genomicsengland.co.uk/research/academic/join-gecip) [26]. Birthweight and gestational age data, and relevant code, is available upon request in the 100kGP for registered users.

Declarations

Ethics approval and consent to participate
All data were collected with informed consent and in accordance with relevant guidelines and regulations. The authors declare that all procedures contributing to this work comply with the ethical standards of the Helsinki Declaration of 1975, as revised in 2008. The DDD study is approved by the UK Research Ethics Committee (10/H0305/83, granted by the Cambridge South Research Ethics Committee and GEN/284/12, granted by the Republic of Ireland Research Ethics Committee). The 100,000 genomes project was approved by the HRA Committee East of England – Cambridge South REC Ref 14/EE/1112. Data for the 100,000 Genomes Project is stored in the National Genome Research Library, which was approved by the East of England Cambridge Central Research Ethics Committee REC ref 20/EE/0035.

Consent for publication
Not applicable.

Competing interests
M.E.H. is a cofounder of, consultant to and holds shares in Congenica, a genetics diagnostic company, and is also a consultant to AstraZeneca Centre for Genomics Research. The remaining authors declare that they do not have any competing interests.

Author details
[1]Human Genetics Programme, Wellcome Sanger Institute, Wellcome Genome Campus, Hinxton, Cambridgeshire CB10 1SA, UK. [2]Department of Medical and Molecular Genetics, King's College London, London, UK. [3]Oxford Centre for Genomic Medicine, Oxford University Hospitals NHS Foundation Trust, Oxford, UK. [4]Cambridge University Hospitals Foundation Trust, Addenbrooke's Hospital, Cambridge, UK. [5]Department of Paediatrics, University of Cambridge, Cambridge Biomedical Campus, Cambridge, UK.

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References

1. Wright CF, Fitzgerald TW, Jones WD, Clayton S, McRae JF, van Kogelenberg M, et al. Genetic diagnosis of developmental disorders in the DDD study: a scalable analysis of genome-wide research data. Lancet. 2015;385(9975):1305–14.
2. Niemi MEK, Martin HC, Rice DL, Gallone G, Gordon S, Kelemen M, et al. Common genetic variants contribute to risk of rare severe neurodevelopmental disorders. Nature. 2018;562(7726):268–71.
3. Huang QQ, Wigdor EM, Malawsky DS, Campbell P, Samocha KE, Chundru VK, et al. Examining the role of common variants in rare neurodevelopmental conditions. Nature. 2024;20:1–8.
4. Huang J, Zhu T, Qu Y, Mu D. Prenatal, perinatal and neonatal risk factors for intellectual disability: a systemic review and meta-analysis. PLoS ONE. 2016;11(4):e0153655.
5. Wright CF, Campbell P, Eberhardt RY, Aitken S, Perrett D, Brent S, et al. Genomic diagnosis of rare pediatric disease in the United Kingdom and Ireland. N Engl J Med. 2023;388(17):1559–71.
6. Nurchis MC, Altamura G, Riccardi MT, Radio FC, Chillemi G, Bertini ES, et al. Whole genome sequencing diagnostic yield for paediatric patients with suspected genetic disorders: systematic review, meta-analysis, and GRADE assessment. Arch Public Health. 2023;81(1):93.
7. Slavotinek A, Rego S, Sahin-Hodoglugil N, Kvale M, Lianoglou B, Yip T, et al. Diagnostic yield of pediatric and prenatal exome sequencing in a diverse population. NPJ Genom Med. 2023;8(1):10.
8. Ohuma EO, Moller AB, Bradley E, Chakwera S, Hussain-Alkhateeb L, Lewin A, et al. National, regional, and global estimates of preterm birth in 2020, with trends from 2010: a systematic analysis. Lancet. 2023;402(10409):1261–71.
9. Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. Lancet. 2008;371(9608):261–9.
10. Smith ED, Blanco K, Sajan SA, Hunter JM, Shinde DN, Wayburn B, et al. A retrospective review of multiple findings in diagnostic exome sequencing: half are distinct and half are overlapping diagnoses. Genet Med. 2019;21(10):2199–207.
11. Posey Jennifer E., Harel Tamar, Liu Pengfei, Rosenfeld Jill A., James Regis A., Coban Akdemir Zeynep H., et al. Resolution of disease phenotypes resulting from multilocus genomic variation. N Engl J Med. 2017;376(1):21–31.
12. Ridsdale AM, Dickerson A, Chundru VK, Firth HV, Wright CF. Phenotypic spectrum of dual diagnoses in developmental disorders. Am J Hum Genet. 2024;111(11):2382–91. Available from: https://www.cell.com/ajhg/fulltext/S0002-9297(24)00335-5.
13. Zhang Y, Yahia A, Sandin S, Åden U, Tammimies K. Prematurity and genetic liability for autism spectrum disorder. Genome Med. 2025;17:108.
14. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. Lancet. 2008;371(9606):75–84.
15. Romero R, Dey SK, Fisher SJ. Preterm labor: one syndrome, many causes. Science. 2014;345(6198):760–5.
16. Solé-Navais P, Flatley C, Steinthorsdottir V, Vaudel M, Juodakis J, Chen J, et al. Genetic effects on the timing of parturition and links to fetal birth weight. Nat Genet. 2023;55(4):559–67.
17. Wadon M, Modi N, Wong HS, Thapar A, O'Donovan MC. Recent advances in the genetics of preterm birth. Ann Hum Genet. 2020;84(3):205–13.
18. Li J, Oehlert J, Snyder M, Stevenson DK, Shaw GM. Fetal de novo mutations and preterm birth. PLoS Genet. 2017;13(4):e1006689.
19. Wong HS, Wadon M, Evans A, Kirov G, Modi N, O'Donovan MC, et al. Contribution of de novo and inherited rare CNVs to very preterm birth. J Med Genet. 2020;57(8):552–7.
20. Bertoli-Avella AM, Kandaswamy KK, Khan S, Ordonez-Herrera N, Tripolszki K, Beetz C, et al. Combining exome/genome sequencing with data repository analysis reveals novel gene-disease associations for a wide range of genetic disorders. Genet Med. 2021;23(8):1551–68.
21. Mitani T, Punetha J, Akalin I, Pehlivan D, Dawidziuk M, CobanAkdemir Z, et al. Bi-allelic pathogenic variants in TUBGCP2 cause microcephaly and lissencephaly spectrum disorders. Am J Hum Genet. 2019;105(5):1005–15.

22. Rabin R, Radmanesh A, Glass IA, Dobyns WB, Aldinger KA, Shieh JT, et al. Genotype-phenotype correlation at codon 1740 of SETD2. Am J Med Genet A. 2020;182(9):2037–48.
23. Deciphering Developmental Disorders Study. Large-scale discovery of novel genetic causes of developmental disorders. Nature. 2015;519(7542):223–8.
24. Deciphering Developmental Disorders Study. Prevalence and architecture of de novo mutations in developmental disorders. Nature. 2017;542(7642):433–8.
25. Turro E, Astle WJ, Megy K, Gräf S, Greene D, Shamardina O, et al. Whole-genome sequencing of patients with rare diseases in a national health system. Nature. 2020;583(7814):96–102.
26. Genomics England. National Genomic Research Library v5.1. figshare; 2020. Available from: https://figshare.com/articles/dataset/GenomicEnglandProtocol_pdf/4530893/7. Cited 2025 Mar 19.
27. Köhler S, Gargano M, Matentzoglu N, Carmody LC, Lewis-Smith D, Vasilevsky NA, et al. The human phenotype ontology in 2021. Nucleic Acids Res. 2021;49(D1):D1207–17.
28. DECIPHER: database of chromosomal imbalance and phenotype in humans using ensembl resources. Am J Hum Genet. 2009;84(4):524–33.
29. Herbert A, Wijlaars L, Zylbersztejn A, Cromwell D, Hardelid P. Data resource profile: hospital episode statistics admitted patient care (HES APC). Int J Epidemiol. 2017;46(4):1093–1093i.
30. Cole TJ, Freeman JV, Preece MA. British 1990 growth reference centiles for weight, height, body mass index and head circumference fitted by maximum penalized likelihood. Stat Med. 1998;17(4):407–29.
31 Blencowe H, Bhutta Z, Althabe F, Lawn J, Howson C. I044 born too soon: a global action report for 15 million preterm births. Int J Gynaecol Obstet. 2012;119(S3):S171-2.
32. Greene D, Richardson S, Turro E. ontologyX: a suite of R packages for working with ontological data. Bioinformatics. 2017;33(7):1104–6.
33. 1000 Genomes Project Consortium, Auton A, Brooks LD, Durbin RM, Garrison EP, Kang HM, et al. A global reference for human genetic variation. Nature. 2015;526(7571):68–74.
34. Manichaikul A, Mychaleckyj JC, Rich SS, Daly K, Sale M, Chen WM. Robust relationship inference in genome-wide association studies. Bioinformatics. 2010;26(22):2867–73.
35. McCarthy S, Das S, Kretzschmar W, Delaneau O, Wood AR, Teumer A, et al. A reference panel of 64,976 haplotypes for genotype imputation. Nat Genet. 2016;48(10):1279–83.
36. Taliun D, Harris DN, Kessler MD, Carlson J, Szpiech ZA, Torres R, et al. Sequencing of 53,831 diverse genomes from the NHLBI TOPMed Program. Nature. 2021;590(7845):290–9.
37. Kaplanis J, Samocha KE, Wiel L, Zhang Z, Arvai KJ, Eberhardt RY, et al. Evidence for 28 genetic disorders discovered by combining healthcare and research data. Nature. 2020;586(7831):757–62.
38. Genomics England. Genomics England Rare Disease Results Guide. Document key/version number: BIO-GUI-018/V5.0. 2021. Available from: https://re-docs.genomicsengland.co.uk/gel_rare_disease.pdf. Cited 2024 Oct 3.
39. 100,000 Genomes Project Pilot Investigators, Smedley D, Smith KR, Martin A, Thomas EA, McDonagh EM, et al. 100,000 genomes pilot on rare-disease diagnosis in health care - preliminary report. N Engl J Med. 2021;385(20):1868–80.
40. Walker S, Smith C, Brittain H, Cheng E, Ross A, Tavares AL, et al. Increasing the diagnostic yield in the 100,000 genomes project through diagnostic discovery. Abstracts from the 56th European society of human genetics (ESHG) conference: Oral presentations. Eur J Hum Genet. 2024;32(Suppl 1):62.
41. Okbay A, Wu Y, Wang N, Jayashankar H, Bennett M, Nehzati SM, et al. Polygenic prediction of educational attainment within and between families from genome-wide association analyses in 3 million individuals. Nat Genet. 2022;54(4):437–49.
42. Demange PA, Malanchini M, Mallard TT, Biroli P, Cox SR, Grotzinger AD, et al. Investigating the genetic architecture of noncognitive skills using GWAS-by-subtraction. Nat Genet. 2021;53(1):35–44.
43. Knudsen CK, Christesen AMS, Heuckendorff S, Fonager K, Johansen MN, Overgaard C. The risk of preterm birth in combinations of socioeconomic position and mental health conditions in different age groups: a Danish nationwide register-based cohort study. BMC Pregnancy Childbirth. 2021;21(1):696.
44. Granés L, Torà-Rocamora I, Palacio M, De la Torre L, Llupià A. Maternal educational level and preterm birth: exploring inequalities in a hospital-based cohort study. PLoS ONE. 2023;18(4):e0283901.
45. Dahlin S, Gunnerbeck A, Wikström AK, Cnattingius S, EdstedtBonamy AK. Maternal tobacco use and extremely premature birth - a population-based cohort study. BJOG. 2016;123(12):1938–46.
46. Liu B, Xu G, Sun Y, Qiu X, Ryckman KK, Yu Y, et al. Maternal cigarette smoking before and during pregnancy and the risk of preterm birth: a dose-response analysis of 25 million mother-infant pairs. PLoS Med. 2020;17(8):e1003158.
47. Broccia M, Munch A, Hansen BM, Sørensen KK, Larsen T, Strandberg-Larsen K, et al. Heavy prenatal alcohol exposure and overall morbidities: a Danish nationwide cohort study from 1996 to 2018. Lancet Public Health. 2023;8(1):e36-46.
48. Privé F, Arbel J, Vilhjálmsson BJ. LDpred2: better, faster, stronger. Bioinformatics. 2021;36(22–23):5424–31.
49. Privé F, Albiñana C, Arbel J, Pasaniuc B, Vilhjálmsson BJ. Inferring disease architecture and predictive ability with LDpred2-auto. Am J Hum Genet. 2023;110(12):2042–55.
50. Chang CC, Chow CC, Tellier LC, Vattikuti S, Purcell SM, Lee JJ. Second-generation PLINK: rising to the challenge of larger and richer datasets. Gigascience. 2015;4(1):7.
51. McLaren W, Gil L, Hunt SE, Riat HS, Ritchie GRS, Thormann A, et al. The Ensembl variant effect predictor. Genome Biol. 2016;17(1):1–14.
52. Karczewski KJ, Francioli LC, Tiao G, Cummings BB, Alföldi J, Wang Q, et al. The mutational constraint spectrum quantified from variation in 141,456 humans. Nature. 2020;581(7809):434–43.
53. Samocha KE, Kosmicki JA, Karczewski KJ, O'Donnell-Luria AH, Pierce-Hoffman E, MacArthur DG, et al. Regional missense constraint improves variant deleteriousness prediction. bioRxiv. 2017. p. 148353. Available from: https://www.biorxiv.org/content/10.1101/148353. Cited 2023 Nov 7.
54. R Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2023. Available from: https://www.R-project.org/.
55. Wootton O, Campbell P, Richardson S, Huang QQ, Wong H, Simpson MA, et al. Investigating the interplay between prematurity and genetic variation in the context of neurodevelopmental conditions. Open Science Framework; 2024.
56. Samocha KE, Robinson EB, Sanders SJ, Stevens C, Sabo A, McGrath LM, et al. A framework for the interpretation of de novo mutation in human disease. Nat Genet. 2014;46(9):944–50.
57. Thormann A, Halachev M, McLaren W, Moore DJ, Svinti V, Campbell A, et al. Flexible and scalable diagnostic filtering of genomic variants using G2P with Ensembl VEP. Nat Commun. 2019;10(1):2373.
58. Ye W, Luo C, Huang J, Li C, Liu Z, Liu F. Gestational diabetes mellitus and adverse pregnancy outcomes: systematic review and meta-analysis. BMJ. 2022;25(377):e067946.
59. Wu CQ, Nichols K, Carwana M, Cormier N, Maratta C. Preterm birth after recurrent pregnancy loss: a systematic review and meta-analysis. Fertil Steril. 2022;117(4):811–9.
60. Blondel B, Macfarlane A, Gissler M, Breart G, Zeitlin J, PERISTAT Study Group. Preterm birth and multiple pregnancy in European countries participating in the PERISTAT project. BJOG. 2006;113(5):528–35.
61. Many A, Hill LM, Lazebnik N, Martin JG. The association between polyhydramnios and preterm delivery. Obstet Gynecol. 1995;86(3):389–91.
62. Lord J, McMullan DJ, Eberhardt RY, Rinck G, Hamilton SJ, Quinlan-Jones E, et al. Prenatal exome sequencing analysis in fetal structural anomalies detected by ultrasonography (PAGE): a cohort study. Lancet. 2019;393(10173):747–57.
63. Stanley KE, Giordano J, Thorsten V, Buchovecky C, Thomas A, Ganapathi M, et al. Causal genetic variants in stillbirth. N Engl J Med. 2020;383(12):1107–16.
64. Gilissen C, Hehir-Kwa JY, Thung DT, van de Vorst M, van Bon BWM, Willemsen MH, et al. Genome sequencing identifies major causes of severe intellectual disability. Nature. 2014;511(7509):344–7.
65. Gardner EJ, Neville MDC, Samocha KE, Barclay K, Kolk M, Niemi MEK, et al. Reduced reproductive success is associated with selective constraint on human genes. Nature. 2022;603(7903):858–63.
66. Kingdom R, Beaumont RN, Wood AR, Weedon MN, Wright CF. Genetic modifiers of rare variants in monogenic developmental disorder loci. Nat Genet. 2024;56(5):861–8.

67. Chen CY, Tian R, Ge T, Lam M, Sanchez-Andrade G, Singh T, et al. The impact of rare protein coding genetic variation on adult cognitive function. Nat Genet. 2023;55(6):927–38.
68. Ganna A, Genovese G, Howrigan DP, Byrnes A, Kurki M, Zekavat SM, et al. Ultra-rare disruptive and damaging mutations influence educational attainment in the general population. Nat Neurosci. 2016;19(12):1563–5.
69. Kong, Thorleifsson, Ml F, Bj V, Ai Y, Te T, et al. The nature of nurture: effects of parental genotypes. Yearb Pediatr Endocrinol [Internet]. 2018 Sep 11. https://doi.org/10.1530/ey.15.14.15
70. Young AI, Benonisdottir S, Przeworski M, Kong A. Deconstructing the sources of genotype-phenotype associations in humans. Science. 2019;365(6460):1396–400.
71. Balbona JV, Kim Y, Keller MC. Estimation of parental effects using polygenic scores. Behav Genet. 2021;51(3):264–78.
72. Young AS. Estimation of indirect genetic effects and heritability under assortative mating. bioRxivorg. 2023. p. 2023.07.10.548458. Available from: https://www.biorxiv.org/content/10.1101/2023.07.10.548458v1.abstract. Cited 2025 Jan 17.
73. Noble M, Wright G, Dibben C, Smith GAN, Mclennan D, Anttila C, et al. The English indices of deprivation 2004. 2004.
74. Tasker RC, McClure RJ, Acerini CL. Oxford Handbook of Paediatrics. OUP Oxford; 2013. 1072 p.
75. Chu PY, Li JS, Kosinski AS, Hornik CP, Hill KD. Congenital heart disease in premature infants 25–32 weeks' gestational age. J Pediatr. 2017;181:37-41.e1.
76. Potharst ES, van Wassenaer AG, Houtzager BA, van Hus JWP, Last BF, Kok JH. High incidence of multi-domain disabilities in very preterm children at five years of age. J Pediatr. 2011;159(1):79–85.
77. Joseph RM, O'Shea TM, Allred EN, Heeren T, Hirtz D, Jara H, et al. Neurocognitive and academic outcomes at age 10 years of extremely preterm newborns. Pediatrics. 2016;137(4). https://doi.org/10.1542/peds.2015-4343
78. Cheong JLY, Anderson PJ, Burnett AC, Roberts G, Davis N, Hickey L, et al. Changing neurodevelopment at 8 years in children born extremely preterm since the 1990s. Pediatrics. 2017;139(6). https://doi.org/10.1542/peds.2016-4086
79. Beauregard JL, Drews-Botsch C, Sales JM, Flanders WD, Kramer MR. Does socioeconomic status modify the association between preterm birth and children's early cognitive ability and kindergarten academic achievement in the United States? Am J Epidemiol. 2018;187(8):1704–13.
80. Wong HS, Edwards P. Nature or nurture: a systematic review of the effect of socio-economic status on the developmental and cognitive outcomes of children born preterm. Matern Child Health J. 2013;17(9):1689–700.
81. Lacalle L, Martínez-Shaw ML, Marín Y, Sánchez-Sandoval Y. Intelligence quotient (IQ) in school-aged preterm infants: a systematic review. Front Psychol. 2023;25(14):1216825.
82. Crump C, Sundquist J, Sundquist K. Preterm or early term birth and risk of attention-deficit/hyperactivity disorder: a national cohort and co-sibling study. Ann Epidemiol. 2023;86:119-25.e4.
83. Husby A, Wohlfahrt J, Melbye M. Gestational age at birth and cognitive outcomes in adolescence: population based full sibling cohort study. BMJ. 2023;18(380):e072779.
84. Allotey J, Zamora J, Cheong-See F, Kalidindi M, Arroyo-Manzano D, Asztalos E, et al. Cognitive, motor, behavioural and academic performances of children born preterm: a meta-analysis and systematic review involving 64 061 children. BJOG. 2018;125(1):16–25.
85. Kerstjens JM, de Winter AF, Bocca-Tjeertes IF, Bos AF, Reijneveld SA. Risk of developmental delay increases exponentially as gestational age of preterm infants decreases: a cohort study at age 4 years: decreasing gestational age and exponential risk of developmental delay. Dev Med Child Neurol. 2012;54(12):1096–101.
86. Pettinger KJ, Kelly B, Sheldon TA, Mon-Williams M, Wright J, Hill LJB. Starting school: educational development as a function of age of entry and prematurity. Arch Dis Child. 2020;105(2):160–5.
87. Jay MA, McGrath-Lone L, Gilbert R. Data resource: the National Pupil Database (NPD). Int J Popul Data Sci. 2019;4(1):1101.
88. Honein MA, Kirby RS, Meyer RE, Xing J, Skerrette NI, Yuskiv N, et al. The association between major birth defects and preterm birth. Matern Child Health J. 2009;13(2):164–75.
89. Cohen JL, Schrier Vergano SA, Mazzola S, Strong A, Keena B, McDougall C, et al. EP300-related Rubinstein-Taybi syndrome: highlighted rare phenotypic findings and a genotype-phenotype meta-analysis of 74 patients. Am J Med Genet A. 2020;182(12):2926–38.
90. Lacombe D, Bloch-Zupan A, Bredrup C, Cooper EB, Houge SD, García-Miñaúr S, et al. Diagnosis and management in Rubinstein-Taybi syndrome: first international consensus statement. J Med Genet. 2024;61(6):503–19.

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