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GENOTYPE–PHENOTYPE RELATIONSHIPS IN PRETERM BIRTH: INSIGHTS FROM FETAL GENOMIC VARIATION

Svetlana DAUENGAUER-KIRLIENE¹, Laura PRANCKENIENE², Austėja LETUKIENE², Faustas PUZERAS², Ingrida DOMARKIENE², Alina URNIKYTE²

¹Department of Human and Medical Genetics, Institute of Biomedical Sciences, Faculty of Medicine, Vilnius University, Vilnius, Lithuania

²Populational Genomics Laboratory, Translational Health Research Institute, Faculty of Medicine, Vilnius University, Vilnius, Lithuania

Contact e-mail: svetlana.dauengauer-kirliene@mf.vu.lt

Background and Aim: Preterm birth (PTB) remains incompletely explained, partly due to limited understanding of how fetal genomic variation contributes to heterogeneous clinical phenotypes. We aimed to investigate whether prematurely born neonates harbour distinct fetal genomic signals associated with PTB by integrating analyses of inherited PTB-associated variants, rare variants, de novo variants (DNVs), relative fitness, and quantitative neonatal phenotyping.

Materials and Methods: We analysed parent–offspring trios comprising 71 preterm cases, including 23 trios in the final DNV analysis, and 25 term-born controls. Genomic data were generated using SNP arrays and short-read whole-genome sequencing. Variants were prioritised and analysed for biological pathways and relative fitness profiles. A quantitative Major Neonatal Outcome (MNO) score was incorporated to support genotype–phenotype analyses.

Results: Preterm neonates and their mothers demonstrated distinct rare variant profiles compared with term-born controls, with no overlap across curated PTB-associated loci. Relative fitness analysis identified contrasting genomic signatures: term-born controls were enriched for rare or population-absent variants, whereas preterm genomes were characterised predominantly by more common non-coding variation. A total of 147 DNVs were identified across 23 preterm neonates, of which 74.3% were non-coding. No significant association was observed between total DNV burden and clinical severity. However, variant-level analyses identified rare coding and regulatory variants co-occurring with clinically relevant phenotypes. Pathway enrichment analyses suggested involvement of neurodevelopmental and extracellular signalling pathways, although the associations attenuated after multiple-testing correction.

Conclusions: These findings suggest that the genomic architecture of PTB reflects heterogeneous combinations of rare and regulatory fetal variants rather than overall mutational burden alone. Integrating quantitative neonatal phenotypes may improve the interpretation of genotype–phenotype relationships in PTB and support more refined fetal genomic studies.

Keywords: de novo variants, fetal genomics, genotype–phenotype associations, preterm birth, rare variants