

## NEONATAL GENOMIC SCREENING ENABLES PRE-SYMPTOMATIC DIAGNOSIS AND PREVENTIVE MANAGEMENT OF HEMOPHILIA

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**Background and Aims.** Haemophilia A and B are X-linked bleeding disorders caused by factor VIII or IX deficiency. In newborns without a known family history, diagnosis is often delayed until a bleeding event occurs, exposing infants to potentially severe complications, including intracranial haemorrhage. Although genomic newborn screening programmes are rapidly expanding, evidence regarding their role in inherited bleeding disorders remains limited. We evaluated the feasibility, diagnostic yield and clinical impact of including haemophilia in a population-based neonatal genomic screening programme.

**Materials and Methods.** Newborns born at Sant'Anna Hospital (Turin, Italy) between October 2023 and July 2024 were prospectively enrolled in the NeoGen study (IRB 278/2023). Whole-exome sequencing (WES) was performed on DNA extracted from dried blood spots. Infants carrying pathogenic or likely pathogenic variants in F8 or F9 underwent haematological assessment, genetic counselling, coagulation testing, molecular confirmation and family segregation studies. Parental psychological outcomes were evaluated using validated questionnaires.

**Results.** Among 4,054 screened newborns, 11 carried pathogenic or likely pathogenic variants in F8 or F9 (5 males, 6 females). Seven variants involved F8 and four F9. All three males carrying F9 variants were confirmed to have haemophilia B, including one infant with severe disease diagnosed before symptom onset who started primary prophylaxis before any major bleeding event. Two males carrying F8 variants had normal factor VIII levels and their variants were subsequently reclassified as variants of uncertain significance. All assessed female infants remained asymptomatic. Two premature twin boys with severe haemophilia A were not identified by WES but were investigated after prolonged bleeding following heel-prick sampling and subsequently diagnosed with F8 intron 1 inversion, a structural variant not detectable by short-read sequencing. Parents reported moderate distress but high levels of understanding of the information provided.

**Conclusions.** Neonatal genomic screening can identify children with haemophilia before clinical presentation and enable earlier preventive management. To our knowledge, this is the first reported case in which neonatal genomic screening led to initiation of primary prophylaxis before any major bleeding event. Our findings also highlight the limitations of short-read sequencing for detecting recurrent structural F8 rearrangements. Combining genomic screening with coagulation testing, targeted molecular analyses and emerging long-read sequencing technologies may overcome these limitations and improve diagnostic yield, supporting a shift from reactive to preventive haemophilia care.