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POSTER ABSTRACTS

311.DISORDERS OF PLATELET NUMBER OR FUNCTION: CLINICAL AND EPIDEMIOLOGICAL

Genetic Variants in Canonical Wnt Signaling Pathway Associated with Pediatric ITP

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Introduction : Pediatric immune thrombocytopenia (ITP) is thought to develop when a triggering event inappropriately activates an autoimmune anti-platelet response in the context of predisposing genetic factors. Inborn errors of immunity are increasingly being identified in cases of chronic, refractory autoimmune cytopenias. We sought to identify genetic variants associated with predisposition to 1) primary or secondary pediatric ITP of any disease duration versus healthy controls and 2) chronic ITP (cITP) versus disease that spontaneously resolves in < 1 year (sr-ITP).

Methods : DNA and clinical data were derived from 8 sites from the Pediatric ITP Consortium of North America's (ICON) biorepository. Samples were genotyped using the Illumina Global Screening Array BeadChip. Genotypes were imputed using the Michigan Imputation Server HRC reference panel. Genetic variants that passed standard quality metrics and had a MAF ≥1% were retained. Control samples (n=8,372) were obtained from the National Longitudinal Study of Adolescent to Adult Health (Add Health) cohort. Logistic regression models were used to estimate adjusted odds ratios (aORs) comparing (1) ITP and control cohorts and (2) cITP and sr-ITP cohorts. Models assumed additive allelic effects and accounted for the top 3 principal components. Genome-wide significance was defined as $P < 5 \times 10^{-8}$ and suggestive of genome-wide significance, $P < 1 \times 10^{-5}$.

Results : Six-hundred ten unique patient samples were genotyped. Nineteen (3.1%) did not pass quality control, leaving 591 for analysis. This cohort included 307 (52.0%) cITP patients, 209 (35.4%) sr-ITP patients, and 75 (12.7%) individuals without complete follow-up data to allow for classification of cITP or sr-ITP. The ITP cohort was 50.1% male, 50.1% non-Hispanic (NH) white, 29.4% Hispanic, 6.1% NH Black, 3.1% NH Asian, and 11.3% Other/Unknown.

Compared with healthy controls, we identified 6 loci associated with ITP at genome-wide significance (Figure 1). Located within the intronic region of *SLC24A4* rs75650997 was associated with an increased risk of ITP compared with controls (aOR: 2.38, P=3.9x10^{-8}). An intronic variant, rs2165798, in *NAV2* was inversely associated with ITP (aOR: 0.52, P=3.2x10^{-11}). A variant in *NKD1* rs4785216, was inversely associated with ITP (aOR: 0.43, P=8.86x10^{-15}).Another intergenic variant, rs4785426, in close proximity to *NKD1* was also inversely associated with ITP (aOR: 0.48, P=1.84x10^{-16}) . An additional 20 variants met suggestive of genome-wide significance. When comparing sr-ITP and cITP patients, no SNVs (single nucleotide variant) reached genome-wide significance, but one variant, rs117609649, in *ABCC4* met suggestive of genome-wide significance (aOR: 0.26, P=4.49x10^{-7}).

Discussion **:** This is the largest, unbiased genetic study of pediatric ITP patients. The analysis comparing ITP versus healthy controls identified 20 suggestive SNVs and 6 which met genome-wide significance. Several of the top SNVs identified in this study affect Wnt/β-catenin signaling. Wnt-signaling impacts the development and regulation of immune cell populations including dendritic cells, macrophages, NK cells, B cells, and T cells. *NAV2* activates Wnt/β-catenin signaling. *NAV2* variants have been implicated in autoimmune conditions including Celiac disease and rheumatoid arthritis. *NKD1* inhibits the canonical Wnt/β-catenin signaling pathway. The cumulative impact of these variants on Wnt activity in ITP should be evaluated in the future.

No genetic variants met genome-wide significance in a comparison of sr-ITP and cITP patients. Collectively, these findings suggest there may be genetic variants implicated in ITP risk, but those genetic features are not specific to sr-ITP or cITP. A focused analysis of 632 genes that cause inborn errors of immunity (IEI) is ongoing. This includes gene burden testing and analysis of pathogenic variants within this gene subset. Variants in IEI genes will also be evaluated in a sub-population of patients with Evans syndrome.

Conclusion **:** ITP is highly heterogenous in its presentation, disease course, and response to therapy. Mirroring its clinical behavior, the genetic contribution to ITP development is complex. This study identified potential SNVs associated with ITP, but not specific to sr-ITP or cITP. Variants in genes that affect the canonical Wnt-signaling pathway may play a role in ITP risk.

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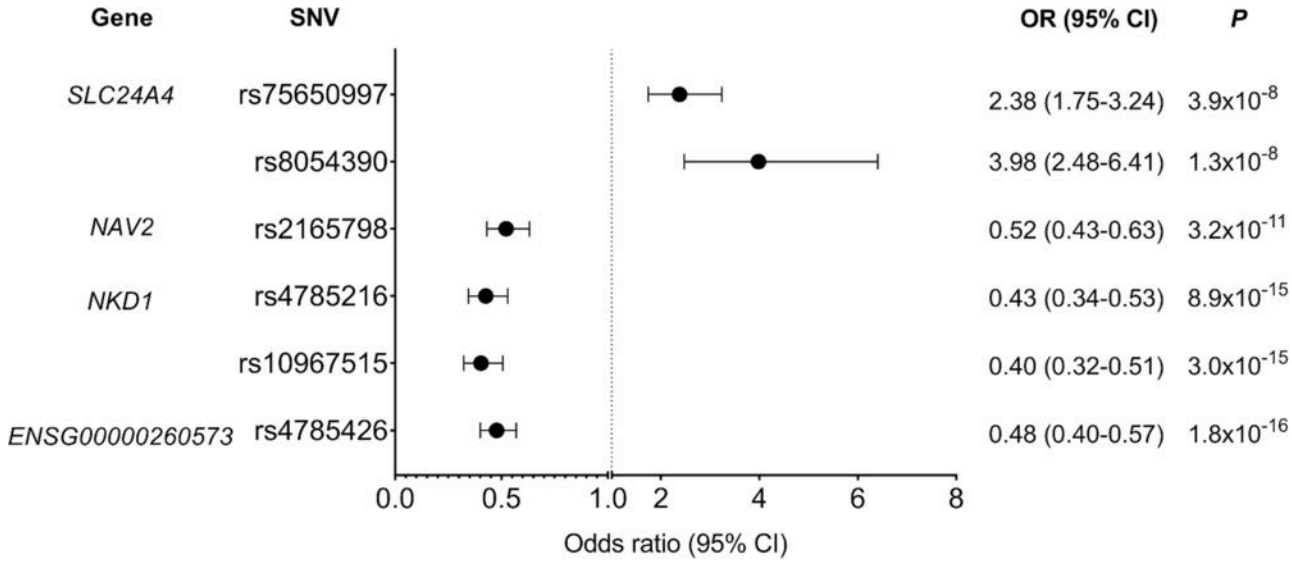

Figure 1

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