Genome-Wide Association Study to Identify Novel Genetic Variants Associated with Primary Budd-Chiari Syndrome

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BACKGROUND AND AIMS

Primary Budd-Chiari syndrome (BCS) is a rare hepatic vascular disorder characterised by hepatic venous outflow obstruction involving the hepatic veins and/or inferior vena cava secondary to thrombosis or intrinsic vascular abnormalities.[1-5] Predisposing factors include inherited procoagulant states (factor V Leiden gene [G1691A] mutation, prothrombin gene [G20210A] mutation, protein C/S deficiency, antithrombin-III deficiency, and hyperhomocysteinaemia), or acquired procoagulant states including myeloproliferative disorders (polycythemia vera with *JAK2* [V617F] mutation).[6] Marked geographic variation in vascular anatomy and prothrombotic profile suggests an underlying genetic predisposition.[7] This study aimed to identify genetic variants associated with primary BCS using genome-wide association study and to characterise implicated biological pathways.

MATERIALS AND METHODS

This case-control study was conducted at the All-India Institute of Medical Sciences, New Delhi, a tertiary care centre in India between June 2020–May 2022. Consecutive adults (≥18 years) with primary BCS attending the outpatient department were prospectively enrolled after informed consent. A total of 310 adults with primary BCS and 312 age- and sex-matched healthy controls were recruited. Genotyping was performed using the Illumina Inc. (San Diego, California, USA) bead array-based high-density whole-genome single nucleotide polymorphism (SNP) genotyping kit (catalogue number: 20030773). Genotype calling, normalisation, and clustering were carried out using GenomeStudio (Illumina Inc., San Diego, California, USA) 2.0 software. After quality control, 262 cases and 265 controls were included. SNPs were mapped to genes and assessed using gene ontology (GO), pathway, and tissue-expression analyses. Quantile-quantile plots and Manhattan plots were produced by using the PLINK software (version 1.09).[8] GO and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway plots were produced using the SRplot tool.[9]

RESULTS

Genome-wide SNP data quality was assessed by a quantile-quantile plot demonstrating minimal inflation (λ=1.048) and high-quality data. Overall, 778,783 high-quality SNPs were analysed; 1,549

were associated with BCS at p<0.05 and 340 lead SNPs at p<0.001. Fifteen top SNPs ($p<5\times10^{-5}$) were predominantly intronic, intergenic, or regulatory and mapped to loci including rs13164180, rs6883351, rs1558294, rs2656107, rs1413229, rs2903138, rs4919217, rs11948339, rs6936121, rs62218439, rs12966305, rs1609245, rs965428, rs697957, and rs34176204. GO enrichment analyses showed significant associations for biological processes including cell junction assembly, regulation of small guanosine triphosphatase (GTPase)-mediated signal transduction, and calcium ion sequestration and release. Molecular function enrichments included calcium/sodium/cation channel activity, extracellular matrix constituent, and GTPase regulator/activator activities. The adult Genotype-Tissue Expression (GTEx) analysis using GTEx version 8 in FUMA (Functional Mapping and Annotation) GENE2FUNC platform indicated significant expression of 340 lead SNP-associated genes in blood vessels and liver with no overlap between lead SNPs and canonical hypercoagulable genes (protein C/S, antithrombin III, factor V, JAK2, calreticulin). Survival and restenosis were evaluated as per the genotypes of the top 15 SNPs using Kaplan–Meier analysis in BCS cases. For rs1558294, the heterozygous genotype was associated with significantly lower survival than the other genotypes (p=0.001), whereas for rs11948339, the wild-type homozygous genotypes were associated with lower survival (p=0.019). rs11948339 was also significantly associated with case status on Fisher's exact test (p=0.015). The homozygous wild type of rs2903118 was associated with a significantly higher restenosis (p=0.038). Our findings suggest distinct genetic underpinnings beyond known thrombophilic states and support a shift in focus from purely somatic coagulation defects to vascular structural remodelling in the pathogenesis of BCS.[10,11]

CONCLUSION

This genome-wide association study in primary BCS identifies novel germline loci predominantly in non-coding and regulatory regions, implicating extracellular matrix remodelling, vascular tone, and cell-adhesion pathways rather than classical thrombophilia genes, and supports further functional studies to refine genetic risk stratification.

References

1. Kumar S et al. Genome-wide association study to identify novel genetic variants associated with primary Budd-Chiari syndrome. Abstract THU-299. EASL Congress, 26-30 May, 2026.
2. Aydinli M, Bayraktar Y. Budd-Chiari syndrome: etiology, pathogenesis and diagnosis. World J Gastroenterol. 2007;13(19):2693-6.
3. Li Y et al. Epidemiology of Budd-Chiari syndrome: a systematic review and meta-analysis. Clin Res Hepatol Gastroenterol. 2019;43(4):468-74.
4. Xu PQ et al. Surgical treatment of 1360 cases of Budd-Chiari syndrome: 20-year experience. Hepatobiliary Pancreat Dis Int. 2004;3(3):391-4.
5. Garcia-Pagán JC, Valla DC. Primary Budd-Chiari syndrome. N Engl J Med. 2023;388(14):1307-16.
6. Hernández-Gea V et al. Current knowledge in pathophysiology and management of Budd-Chiari syndrome and non-cirrhotic non-tumoral splanchnic vein thrombosis. J Hepatol. 2019;71(1):175-99.
7. Gavriilidis P et al. State of the art, current perspectives, and controversies of Budd-Chiari syndrome: a review. J Clin Med Res. 2022;14(4):147-57.
8. Purcell S et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. Am J Hum Genet. 2007;81(3):559-75.
9. Tang D et al. SRplot: a free online platform for data visualization and graphing. PLoS One. 2023;18(11):e0294236.
10. Adam F et al. Apelin: an antithrombotic factor that inhibits platelet function. Blood. 2016;127(7):908-20.
11. Stark K, Massberg S. Interplay between inflammation and thrombosis in cardiovascular pathology. Nat Rev Cardiol. 2021;18(9):666-82.