ASSOCIATION BETWEEN MUSCULOSKELETAL STATUS AND GENETIC MUTATIONS IN PATIENTS WITH HEMOPHILIA A

Fitri Primacakti[1,2], Pustika A. Wahidiyat[2], Damayanti R. Sjarif[2,3], Novie A. Chozie[2], Naura A. Candini[2], Joedo Prihartono[4], Ninik Sekartini[5], Nadhifa T. Ramadhani[3], Bidasari Lubis[6]

[1]Doctoral Program in Medical Sciences Faculty of Medicine Universitas Indonesia1, [2]Pediatric Hematology–Oncology Division, Department of Child Health, Dr. Cipto Mangunkusumo Hospital, Faculty of Medicine, Universitas Indonesia 2, [3]Human Genetic Research Cluster-Institute of Medical Education and Research in Indonesia (HGRC-IMERI), [4]Department of statistics, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia [5]Department of Pathology Clinic, Dr. Cipto Mangunkusumo Hospital, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia, [6]Department of statistics, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia[4]Pediatric Hematology–Oncology Division, Department of Pediatrics, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia,

eISSN: 2828-4070
https://doi.org/10.69951/proceedingsbookoficeonimeri.v9i-.316
Proceedings ICE on IMERI. 2025.
Received: November 9th, 2025
Accepted: December 22nd, 2025
Published online: February 6th, 2026

Corresponding Author
Name : Fitri Primacakti
Email : f_primacakti@yahoo.co.id/fitri.primacakti01@ui.ac.id

Abstract

Introduction: Hemophilia A is an inherited bleeding disorder caused by mutations in the factor VIII (FVIII) gene. These mutations result in either reduced FVIII synthesis (null variants) or loss of FVIII function (non-null variants). Null variants are typically associated with more severe FVIII deficiency and recurrent joint bleeding, which may adversely affect musculoskeletal health. –**Objective:** To evaluate the relationship between musculoskeletal status and genetic mutations in patients with hemophilia A. **Methods:** A cross-sectional study was conducted at the Faculty of Medicine Universitas Indonesia-Dr. Cipto Mangunkusumo Hospital from June 2024 to March 2025. Genetic analysis was performed at the Human Genetic Research Center using inverse-shifting PCR and Sanger sequencing. Mutations were classified as null variants (intron-22 inversion, intron-1 inversion, large deletion, and nonsense mutations) and non-null variants (missense and non-conserved splice mutation). Musculoskeletal status was assessed by the presence of target joints and the Hemophilia Joint Health Score (HJHS), which evaluates global gait and joint function of the elbows, knees, and ankles. Higher HJHS scores indicate worse joint health. **Results:** Sixty patients were included in this study, of which 39 had severe, 15 had moderate, and the remaining 6 had mild hemophilia A. The median age was 9.5 years (range 2-18). Null variants were identified in 45/60 patients and non-null variants in 15/60 patients. The most common target joints were the knees in patients with null variants and the ankles in those with non-null variants. The median HJHS was 4 (Q1-Q3: 2-13.5) in the null variant group and 2 (Q1-Q3: 1-11) in the non-null variant group. No significant association was observed between the target joint and the HJHS and genetic mutations. Further subgroup analysis showed no difference in HJHS between mutation groups among patients receiving prophylaxis (p=0.366) or on-demand treatment (p=0.458).—**Conclusion:** No association was found between genetic mutation type and musculoskeletal status in patients with Hemophilia A. HJHS did not differ between mutation groups regardless of treatment regimens.

Keywords: Musculoskeletal, HJHS, target joint, hemophilia, genetic mutation

Introduction

The factor VIII (FVIII) gene is a large, complex gene located on the Xq28 region of the X chromosome. It spans approximately 186 kb, consists of 26 exons and 25 introns, and encodes a protein of 2,332 amino acids. Mutations in the FVIII gene result either in reduced FVIII synthesis, known as null variants, or impaired FVIII function, known as non-null variants.[1–5] Null variants arise from the absence or disruption of a functional FVIII protein, most commonly due to intron 22 inversion, with some attributable to intron 1 inversion, nonsense, and large deletion mutations. In contrast, non-null variants are typically caused by missense mutations or splice-site alterations.[4-6]

Null variants are predominantly associated with severe hemophilia A and lead to markedly reduced FVIII levels, predisposing patients to recurrent spontaneous or trauma-related joint bleeding. Repeated hemarthrosis causes progressive cartilage and bone damage, ultimately impairing musculoskeletal function.[4,5] The synovial membrane has limited capacity to clear blood after an isolated incident of joint bleed; with recurrent bleeding, blood breakdown products accumulate within the joint space. Iron, a key component of hemoglobin, plays a major part in synovial inflammation by promoting the production of pro-inflammatory cytokines. This process leads to synovial hypertrophy, increased vascularity, and recruitment of inflammatory cells, creating a self-perpetuating cycle that progressively damages cartilage and results in hemophilic arthropathy.[5–7] Consequently, patients harboring null variants are hypothesized to have worse musculoskeletal outcomes compared with those with non-null variants.

Bleeding severity in hemophilia A is influenced by multiple factors beyond the underlying FVIII mutation, including polymorphism in inflammatory genes, coinheritance of other bleeding or clotting disorders, variability in factor VIII pharmacokinetics, physical activity patterns, and treatment regimens.[8] Nevertheless, determining the FVIII genotype remains clinically relevant, as it may help predict bleeding patterns and guide individualized management. However, evidence regarding the impact of genotype on joint health has been inconsistent. One study found no association between genetic mutations and joint deterioration in hemophilia patients,[9] whereas another study reported that patients with inversion, nonsense, and deletion mutations had worse joint outcomes. Those genotypes had 4-5 times higher risk of severe phenotype.[10] Given these conflicting data, this study aimed to evaluate the relationship between musculoskeletal status and genetic mutations in patients with hemophilia A.

Materials & Methods

A cross-sectional study was conducted at the Faculty of Medicine Universitas Indonesia-Dr. Cipto Mangunkusumo Hospital from June 2024 to March 2025. The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the

Ethics Committee of Dr. Cipto Mangunkusumo Hospital, Faculty of Medicine, University of Indonesia (approval number: KET-490/UN2.F1/ETIK/PPM.00.02/2024). Written informed consent was obtained from the parents or legal guardians of all participants prior to enrollment.

Unrelated pediatric patients with confirmed hemophilia A who attended the hospital regularly for treatment were included. Clinical information, including age, FVIII level, target joints, and treatment regimen (prophylaxis or on-demand), was collected from medical records and structured interviews. Patients received treatment according to clinical indications and were categorized into prophylaxis and on-demand treatment. Prophylaxis was defined as regular administration of therapeutic products aimed at maintaining hemostasis to prevent bleeding episodes, especially joint hemorrhages, which would lead to arthropathy and disability. Meanwhile, on-demand treatment was defined as an episodic administration of clotting factor concentrates only at the time of bleeding.[2]

Genetic testing was performed at the Human Genetic Research Center – Indonesian Medical Education Research Institute. Genomic DNA was extracted from 3 mL of venous EDTA blood using Geneaid Biotech Ltd kit, New Taipei City, Taiwan.[11] Inverse-shifting PCR was used to identify inversions in introns 22 and 1. Samples negative for inversion underwent Sanger sequencing to identify other variants. All detected variants were interpreted according to the recommendations of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology.[12] The mutations were categorized as null variants and non-null variants. The null variants included intron-22 inversion, intron-1 inversion, large deletion, and nonsense, while the non-null variants included missense and non-conserved splice-site mutations.

Musculoskeletal status was evaluated based on the presence of target joints and the Hemophilia Joint Health Score (HJHS). A target joint was defined as more than three joint bleeding episodes occurring in the same joint within a 6-month period.[13] The musculoskeletal function was assessed by a physical rehabilitation doctor using HJHS 2.1. It evaluated joint conditions of the elbows, knees, and ankles, as well as global gait. The tool measures 8 items: swelling, duration of swelling, muscle atrophy and strength, crepitus, mobility, and joint pain. Each joint is scored from 0 to 20 points, and the global gait score ranges from 0 to 4, resulting in a total HJHS score from 0 to 124 points. Higher scores indicate worse joint health.[14]

Results

Sixty patients with hemophilia A were included in this study: 39 with severe disease, 15 with moderate disease, and 6 with mild hemophilia A. The median age was 9.5 years (range 2-18). Genetic mutations were identified in all patients, with null variants and non-null variants found in 45/60 and 15/60 patients, respectively. The most prevalent mutation was

INV22 among null variants, and missense mutations were the most prevalent among non-null variants.

Among the 60 subjects, 35 had target joints. Of these, 28/35 had single-joint involvement while 7/35 had multiple target joints. All patients with multiple joint involvement were older than 12 years; two were receiving on-demand treatment, and five were on tertiary prophylaxis. In patients with null variants, the most common target joint was the knee (21/45), followed by the ankle (7/45) and elbow (6/45). In the non-null variant group, the ankle was the most frequently targeted joint (4/15), followed by the knee (3/15) and the elbow (2/15). Patients' demographic characteristics are presented in **Table 1.** No association was found between genetic mutation type and the presence of target joints (**Table 2**).

Table 1. Demographic Characteristics

Characteristic	**N (60)**
Age, median (range), years	9.5 (2-18)
Severity, n (%)	
Mild	6 (10%)
Moderate	15 (25%)
Severe	39 (65%)
Genetic mutations, n (%)	
Null variants	
Intron 22 inversion	27 (45%)
Intron 1 inversion	9 (15%)
Large deletion	6 (10%)
Nonsense	3 (5%)
Non-null variants	
Missense	12 (20%)
Non-conserved splice site	3 (5%)
Target joints, n (%)	
No target joint	25 (41.7)
Single-joint involvement	28 (46.7%)
Multiple-joints involvement	7 (11.6%)
Treatment regimens	
Prophylaxis	27 (45%)
On-demand	33 (55%)

Table 2. Association between Genotype and Target Joints

Genotype	***Target Joint***		**P value**	**OR (95%CI)**
	Yes (n=35)	**No (n=25)**		
Null variants	28	17	0.369	1.88 (0.58-6.13)
Non-null variants	7	8		

The median HJHS was 4 (Q1-Q3: 2-13.5) among null variants and 2 (Q1-Q3: 1-11) in those with non-null variants, with no significant difference between groups (p=0.237) (**Fig. 1a**). Overall, 27 patients were receiving regular prophylaxis treatment (null variants and non-null variants: 22 vs 5), while 33 were on on-demand treatments for bleeding episodes (null variants and non-null variants: 23 vs 10). The median age of patients receiving prophylaxis treatment was 12 years (Q1-Q3: 7-15), and the median age in the on-demand group was also 12 years (Q1-Q3: 6-14). In the prophylaxis group, the median HJHS score for null variants and

non-null variants was 4 (Q1-Q3: 2-13.75) and 1 (Q1-Q3: 1-5), respectively. In the on-demand group, the median HJHS was 5 (Q1-Q3: 1.5-11.5) for null variants and 2.5 (Q1-Q3: 1.25-10.25) for non-null variants. Further analysis revealed no significant difference in HJHS between genetic mutation groups among patients receiving prophylaxis (p=0.366) or on-demand treatment (p=0.458). (**Fig. 1b and c**).

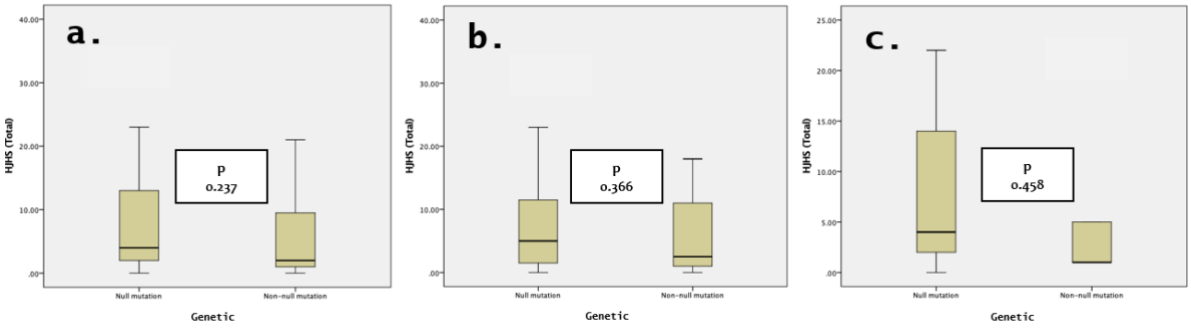

Figure 1. (a) Comparison of HJHS scores between hemophilia A genotypes, **(b)** HJHS scores in patients with null versus non-null variants receiving prophylaxis treatment **(c)** HJHS scores in patients with null versus non-null variants receiving on-demand treatment.

Discussion

This study successfully identified genetic mutations in all patients. Null variants were more prevalent, with intron 22 inversion being the most common mutation, identified in nearly half of the cohort (27/60) and predominantly affecting patients with severe hemophilia A (22/27). These findings are consistent with reports from other ASEAN countries, including Malaysia (53%)[8], Thailand (30.6%)[9], and Vietnam (44%), which also demonstrated a higher prevalence of intron 22 inversion among patients with severe hemophilia A.[15–17] Our findings were also similar to previous reports regarding non-null variants, in which the missense mutation was more frequently observed in hemophilia A.[18,19]

Musculoskeletal function remains a primary outcome measure in patients with hemophilia. Recurrent hemarthrosis leads to the accumulation of hemosiderin, synovial inflammation, cartilage degradation, and ultimately joint destruction, collectively termed hemophilic arthropathy.[14,20] Severe hemophilia is associated with a higher risk of joint damage compared with mild or moderate disease.[21] Genetic mutations influence FVIII deficiency severity, thereby contributing to recurrent hemarthrosis and joint destruction, leading to hemophilia arthropathy.[7,21] However, only a limited number of studies have examined the relationship between genetic mutation and joint health.

Joint health is a key contributor to the quality of life in patients with hemophilia. To evaluate joint health, patients in this study were assessed for the presence of target joints and HJHS. In this study, 35 subjects (58.3%) had target joints, most commonly affecting the

knees and ankles, which are weight-bearing joints and therefore more susceptible to bleeding. This observation aligns with previous data showing that approximately 80% of bleeding episodes occur in the knees, elbows, and ankles. Recurrent bleeding and target joint formation may prevent joints from regaining their range of motion, muscle strength, and appearance. These changes can be permanent from the bleeding cycle, leading to joint damage.[2,13,12]

Our study demonstrated that all patients with multiple joint involvement were over 12 years old. Most of them were on tertiary prophylaxis, which means they were started on prophylaxis after joint damage was already established. Our analysis revealed that the risk of having a target joint was higher in the null variant group. However, this association was not statistically significant (OR 1.88; p: 0.369), likely due to the limited sample size. To our knowledge, this is the first study evaluating the correlation between target joints and hemophilia genotype.

Previous studies have shown that null variants, which result in severe FVIII deficiency, are associated with recurring bleeding and increased joint damage.[5,6] Patients with severe molecular defects have a 4.1-fold increased risk for severe phenotype compared with other mutations, predisposing them to hemarthrosis and arthropathy.[10] Despite this, our study found no significant association between HJHS and genetic mutation type. Median HJHS was 4 (Q1-Q3: 2-13.5) in the null-variant group, while the non-null variant group was 2 (Q1-Q3: 1-11).

In addition to FVIII gene mutations, some studies found that polymorphisms in inflammatory genes were associated with arthropathy. Some patients develop serious arthropathy even with a moderate number of bleeds, while others maintain good joints despite many bleeds. Jayandharan et al.[10] hypothesized that differences in inflammatory and vascular responses would determine this heterogeneity.

Polymorphisms or genetic variation in coagulation-related genes, such as Factor VII (FVII), influence bleeding severity (phenotype) in hemophilia patients, even with similar FVIII levels, explaining why some patients with severe mutations, such as null variants, have milder bleeding and subsequently less joint damage. These variations, along with immune or inflammatory gene polymorphisms, modify the overall bleeding tendency and long-term joint outcomes, creating diverse clinical presentations beyond just the main FVIII mutation. Higher frequency of certain alleles is more prevalent in the severe phenotypes, and polymorphisms of the immune response genes have been suggested to be contributing determinants on the inhibitor risk, which may cause a higher risk for bleeding and non-response to treatment, further causing joint damages.[10, 22–25] Unfortunately, the polymorphism of the inflammatory gene was not evaluated in our study.

Various factors may influence the frequency and severity of joint damage and subsequent musculoskeletal function, including treatment regimen, timing of prophylaxis, physical activity, nutritional status, and daily self-care measures.[26] Because the development of hemophilic arthropathy is complex, a comprehensive therapeutic approach is necessary to effectively prevent it in patients with hemophilia. Bleeding frequency in hemophilia is reduced by regular prophylaxis, thereby reducing articular damage, preventing hemophilia arthropathy, and preserving musculoskeletal function. For countries with resource constraints, the World Federation for Hemophilia (WFH) has endorsed a low-dose regimen to ensure the availability of prophylaxis for all patients.[2]

Following this, we performed subsequent analysis to identify the role of prophylaxis. Further evaluation revealed no significant difference in HJHS between the two genetic mutations in patients in the prophylaxis or on-demand groups. The policy to provide prophylaxis with FVIII in Indonesia began in 2022. The median age of our patients was above 9.5 years, meaning that before the policy was initiated, patients had been receiving on-demand treatment since their diagnosis of hemophilia. This might be a potential risk factors that influence the extent of joint damage in these patients. However, we did not measure other risk factors of hemophilia arthropathy, such as nutritional status or daily activity patterns, in our study.

Tools for diagnosing and monitoring hemophilic arthropathy are critical for detecting early joint damage, enabling management to be adjusted accordingly. MRI is currently the gold standard for identifying hemophilic arthropathy and soft-tissue changes by detecting synovial hypertrophy and joint effusions which are commonly found at all stages of joint disease. It is recommended to combine HJHS and MRI or ultrasound to generate a more detailed analysis of joints. However, MRI is often limited by high costs, the need for sedation in children, and the inability to differentiate active from inactive synovium.[7,21] In this study, we did not perform any imaging evaluation. Thus, further study is needed to analyze these factors.

Our study has several limitations. The small number of subjects might influence significancy of the results. Other risk factors for joint health, including gene polymorphisms, were not assessed in this study. Nevertheless, the results of this study showed that genetic mutations may play a role in musculoskeletal function. Further studies should be performed with a larger sample size, with a complete joint assessment including MRI or Ultrasound, and should also evaluate other risk factors.

Conclusion

No association was observed between genetic mutation type and musculoskeletal status, and HJHS did not differ across mutation groups within treatment regimens. Nevertheless, the bleeding tendency inherent to severe genotypes should not delay early prophylaxis. Instead, genotype should heighten clinical vigilance and guide proactive management.

Competing Interests

The authors declare that they have no conflicts of interest.

References

1. Payne AB, Miller CH, Kelly FM, Michael Soucie J, Craig Hooper W. The CDC Hemophilia A Mutation Project (CHAMP) mutation list: a new online resource. Hum Mutat [Internet]. 2013 [cited 2025 Oct 25];34(2):E2382–92. Available from: https://pubmed.ncbi.nlm.nih.gov/23280990/
2. Srivastava A, Santagostino E, Dougall A, Kitchen S, Sutherland M, Pipe SW, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. Haemophilia [Internet]. 2020 Aug 1 [cited 2025 Oct 25];26 Suppl 6(S6):1–158. Available from: https://pubmed.ncbi.nlm.nih.gov/32744769/
3. Santacroce R, Acquila M, Belvini D, Castaldo G, Garagiola I, Giacomelli SH, et al. Identification of 217 unreported mutations in the F8 gene in a group of 1,410 unselected Italian patients with hemophilia A. J Hum Genet [Internet]. 2008 Mar [cited 2025 Oct 25];53(3):275–84. Available from: https://pubmed.ncbi.nlm.nih.gov/18217193/
4. Oldenburg J, Pezeshkpoor B, Pavlova A. Historical review on genetic analysis in hemophilia A. Semin Thromb Hemost [Internet]. 2014 Nov 6 [cited 2025 Oct 25];40(8):895–902. Available from: https://pubmed.ncbi.nlm.nih.gov/25377322/
5. Pezeshkpoor B, Oldenburg J, Pavlova A. Insights into the Molecular Genetic of Hemophilia A and Hemophilia B: The Relevance of Genetic Testing in Routine Clinical Practice. Hamostaseologie [Internet]. 2022 Dec 1 [cited 2025 Oct 25];42(6):390–9. Available from: https://pubmed.ncbi.nlm.nih.gov/36549291/
6. Oldenburg J, El-Maarri O. New insight into the molecular basis of hemophilia A. Int J Hematol [Internet]. 2006 Feb [cited 2025 Oct 25];83(2):96–102. Available from: https://pubmed.ncbi.nlm.nih.gov/16513526/
7. Knobe K, Berntorp E. Haemophilia and joint disease: pathophysiology, evaluation, and management. J Comorb [Internet]. 2011 Jan [cited 2025 Dec 10];1(1):51. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC5556421/
8. Carcao MD, Van Den Berg HM, Ljung R, Mancuso ME. Correlation between phenotype and genotype in a large unselected cohort of children with severe hemophilia A. Blood [Internet]. 2013 May 9 [cited 2025 Oct 25];121(19):3946–52. Available from: https://pubmed.ncbi.nlm.nih.gov/23482934/
9. Khanum F, Bowen DJ, Kerr BC, Collins PW. Joint health scores in a haemophilia A cohort from Pakistan with minimal or no access to factor VIII concentrate: correlation with thrombin generation and underlying mutation. Haemophilia [Internet]. 2014 [cited 2025 Dec 11];20(3):426–34. Available from: https://pubmed.ncbi.nlm.nih.gov/24354535/

10. Jayandharan GR, Nair SC, Poonnoose PM, Thomas R, John J, Keshav SK, et al. Polymorphism in factor VII gene modifies phenotype of severe haemophilia. Haemophilia [Internet]. 2009 Nov 1 [cited 2025 Dec 6];15(6):1228–36. Available from: /doi/pdf/10.1111/j.1365-2516.2009.02080.x
11. Rossetti LC, Radic CP, Larripa IB, De Brasi CD. Genotyping the hemophilia inversion hotspot by use of inverse PCR. Clin Chem [Internet]. 2005 [cited 2025 Oct 25];51(7):1154–8. Available from: https://pubmed.ncbi.nlm.nih.gov/15860568/
12. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genetics in Medicine [Internet]. 2015 May 8 [cited 2025 Oct 25];17(5):405–24. Available from: https://pubmed.ncbi.nlm.nih.gov/25741868/
13. Mulder K, Llinás A. The target joint. Haemophilia, Supplement [Internet]. 2004 Oct [cited 2025 Dec 6];10(4):152–6. Available from: /doi/pdf/10.1111/j.1365-2516.2004.00976.x
14. Kuijlaars IAR, van der Net J, Feldman BM, Aspdahl M, Bladen M, de Boer W, et al. Evaluating international Haemophilia Joint Health Score (HJHS) results combined with expert opinion: Options for a shorter HJHS. Haemophilia [Internet]. 2020 Nov 1 [cited 2025 Dec 6];26(6):1072. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC7821332/
15. Zahari M, Sulaiman SA, Othman Z, Ayob Y, Karim FA, Jamal R. Mutational Profiles of F8 and F9 in a Cohort of Haemophilia A and Haemophilia B Patients in the Multi-ethnic Malaysian Population. Mediterr J Hematol Infect Dis [Internet]. 2018 [cited 2025 Oct 25];10(1):e2018056. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC6131101/
16. Trirut C, Sosothikul D, Ittiwut R, Ittiwut C, Pongsewalak S, Songthawee N, et al. F8 variants and their genotype-phenotype correlations in Thai patients with haemophilia A: a nationwide multicentre study. J Clin Pathol [Internet]. 2024 [cited 2025 Oct 25]; Available from: https://pubmed.ncbi.nlm.nih.gov/38981663/
17. Thi Nguyen BS, Thi Le XT, Huynh N, Nguyen HH, Nguyen CMT, Nguyen BH. Determining common variants in patients with haemophilia A in South Vietnam and screening female carriers in their family members. J Clin Pathol [Internet]. 2023 May 1 [cited 2025 Oct 25];76(5):339–44. Available from: https://pubmed.ncbi.nlm.nih.gov/34844950/
18. Labarque V, Mancuso ME, Kartal-Kaess M, Ljung R, Mikkelsen TS, Andersson NG. F8/F9 variants in the population-based PedNet Registry cohort compared with locus-specific genetic databases of the European Association for Haemophilia and Allied Disorders and the Centers for Disease Control and Prevention Hemophilia A or Hemophilia B Mutation Project. Res Pract Thromb Haemost [Internet]. 2023 Jan 1 [cited 2025 Oct 25];7(1). Available from: https://pubmed.ncbi.nlm.nih.gov/36798899/
19. McVey JH, Rallapalli PM, Kemball-Cook G, Hampshire DJ, Giansily-Blaizot M, Gomez K, et al. The European Association for Haemophilia and Allied Disorders (EAHAD) Coagulation Factor Variant Databases: Important resources for haemostasis clinicians

and researchers. Haemophilia [Internet]. 2020 Mar 1 [cited 2025 Dec 11];26(2):306–13. Available from: https://pubmed.ncbi.nlm.nih.gov/32166871/

20. Ay C, Mancuso ME, Matino D, Strike K, Pasta G. The haemophilia joint health score for the assessment of joint health in patients with haemophilia. Haemophilia [Internet]. 2024 Nov 1 [cited 2025 Dec 6];30(6):1265–71. Available from: /doi/pdf/10.1111/hae.15116
21. Gooding R, Thachil J, Alamelu J, Motwani J, Chowdary P. Asymptomatic Joint Bleeding and Joint Health in Hemophilia: A Review of Variables, Methods, and Biomarkers . J Blood Med [Internet]. 2021 Apr 1 [cited 2025 Dec 6];12:209–20. Available from: https://www.dovepress.com/asymptomatic-joint-bleeding-and-joint-health-in-hemophilia-a-review-of-peer-reviewed-fulltext-article-JBM
22. Pavlova A, Delev D, Lacroix-Desmazes S, Schwaab R, Mende M, Fimmers R, et al. Impact of polymorphisms of the major histocompatibility complex class II, interleukin-10, tumor necrosis factor-α and cytotoxic T-lymphocyte antigen-4 genes on inhibitor development in severe hemophilia A. Journal of Thrombosis and Haemostasis [Internet]. 2009 Dec 1 [cited 2025 Dec 10];7(12):2006–15. Available from: https://www.sciencedirect.com/science/article/pii/S1538783622134318
23. Gualtierotti R, Solimeno LP, Peyvandi F. Hemophilic arthropathy: Current knowledge and future perspectives. Journal of Thrombosis and Haemostasis [Internet]. 2021 Sep 1 [cited 2025 Dec 11];19(9):2112. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC8456897/
24. López-Jiménez J de J, Ortega-Cervantes R, Luna-Záizar H, Fletes-Rayas AL, Beltrán-Miranda CP, Troyo-Sanromán R, et al. Genetic biomarkers related to hemarthrosis, inflammation, and cartilage structure in pediatric patients with hemophilic arthropathy. Mol Genet Genomic Med [Internet]. 2019 Nov 1 [cited 2025 Dec 11];7(11):e979. Available from: /doi/pdf/10.1002/mgg3.979
25. Gomperts ED, Schwarz J, Donfield SM, Lail AE, Astermark J, Keith Hoots W, et al. The importance of genetic factors for the development of arthropathy: a longitudinal study of children and adolescents with haemophilia A. Thromb Haemost [Internet]. 2016 [cited 2025 Dec 11];117(2):277. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC8058627/
26. Bladen M, Main E, Hubert N, Koutoumanou E, Liesner R, Khair K. Factors affecting the Haemophilia Joint Health Score in children with severe haemophilia. Haemophilia [Internet]. 2013 Jul 1 [cited 2025 Dec 7];19(4):626–31. Available from: /doi/pdf/10.1111/hae.12108