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Prevalence Of Factor V Leiden In Down Syndrome Children With And Without Congenital Heart Disease

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Abstract

Down Syndrome (DS) is the most prevalent trisomy, linked to a higher risk of thromboembolic events, such as stroke, especially among those with congenital heart defects (CHD). Factor V Leiden (FVL) is a functional variant (F5:c.G1691A, rs6025) which is associated with increased thromboembolic complications. In the present study, we investigated the prevalence of this variant in DS patients with or without CHD. A total of 75 DS patients and 30 age- and sex-matched healthy controls were assessed for this variant using Sanger sequencing. Interestingly FVL frequency was higher in DS patients than in controls. In stratified analysis, this variant was overrepresented in DS patients with CHD at both phenotypic (p=0.037) and allelic (p=0.013) levels suggesting a possibly significant role in this subgroup which needs to be further explored.

Keywords: Down syndrome, Congenital Heart Defect, FVL, Sanger sequencing

1. Introduction

Down syndrome (DS) is the most common trisomy, primarily caused by an extra copy of chromosome 21. It occurs in approximately 1 in 800–1,000 live births, with higher maternal age being a significant risk factor **[1, 2]**. Clinically, DS individuals presents distinct physical features and predisposed to complications like intellectual disability, Congenital Heart Defects (CHD), and various health conditions, including elevated risk of stroke, and Moyamoya disease. Additionally, a higher incidence of thrombosis is observed among DS patients than in healthy controls in various studies **(Supplementary Table 1)**.

Factor V Leiden (FVL) is a mutation involving a G1691A nucleotide substitution, first identified by a Dutch scientist in Leiden. This missense variant leads to an amino acid substitution from (Arginine) R to(Glutamine) Q at position 506, resulting in a reduced anticoagulant response to activated protein C (APC) leading to a pro thrombotic state **(Figure 1)**. Various studies have linked FVL with different thromboembolic complications like Venous thromboembolism (VTE), stroke, pulmonary embolism, Moya moya syndrome, Deep vein thrombosis **[3-7]**. Since FVL is associated with thrombotic conditions, understanding its relationship with DS—where stroke, thrombosis, and Moyamoya syndrome are already prevalent—could provide valuable genetic insights and inform medical management tailored to DS patients. This study's aim is to explore if any association exists between the FVL variant and CHD in DS patients. CHD is a common comorbidity in DS, with an incidence of 54–66% in DS infants **[8]**. CHD frequently involves the shunting of systemic blood to the pulmonary circulation, potentially leading to thromboembolic complications **[9-13]**. Therefore, this study was designed to analyze the prevalence of this variant in DS children with and without CHD. The findings could have important implications for improving early screening, preventive strategies, and personalized management in DS patients with CHD.

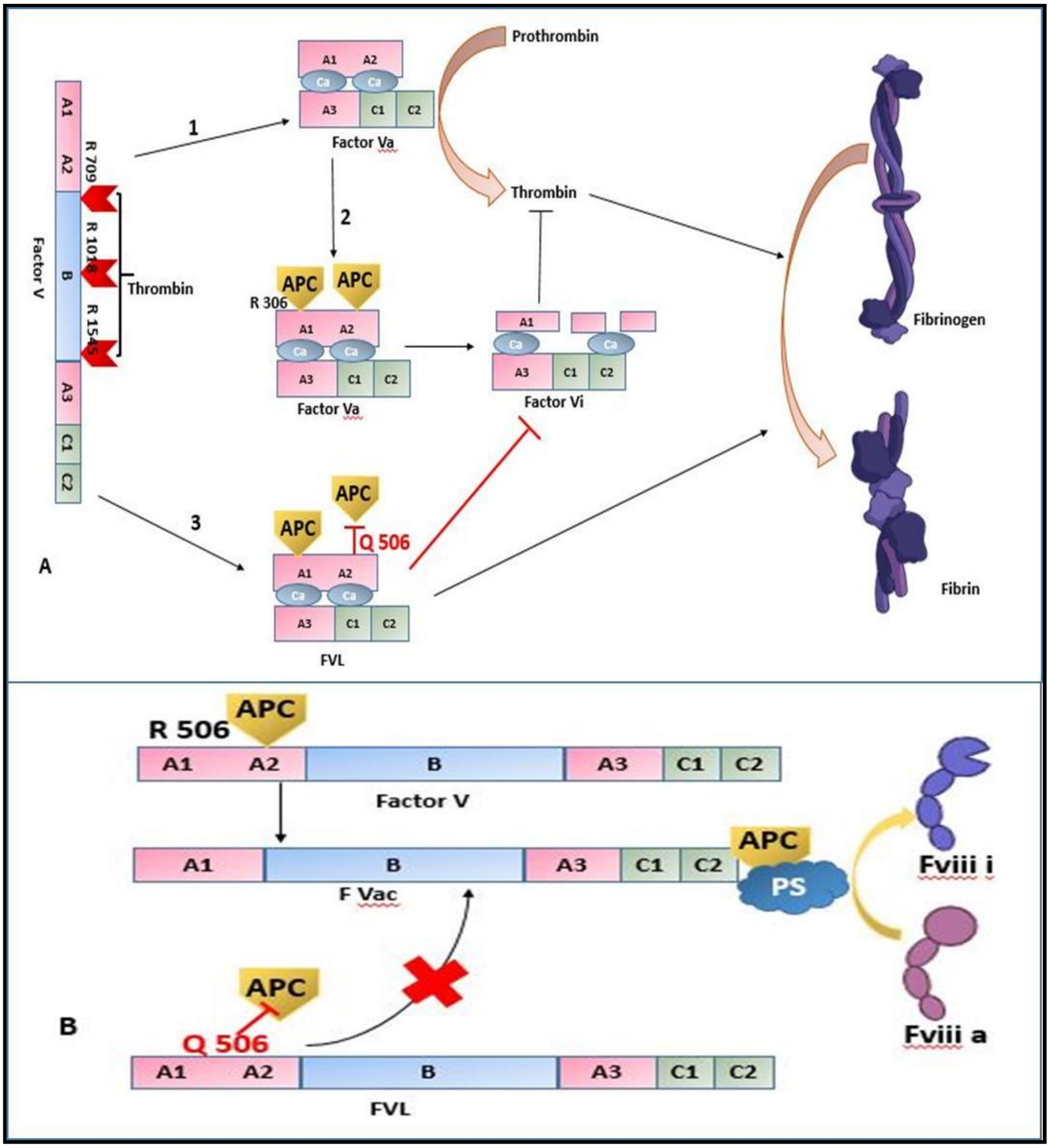

Figure 1: Mechanism of Action of Factor V Leiden (FVL).

(A) 1. Factor V is cleaved by thrombin at specific arginine residues (R709, R1018, and R1545) in the B domain, resulting in the formation of activated Factor Va. This complex along with Factor Xa, forms the prothrombinase complex, which facilitates the conversion of prothrombin to thrombin. Thrombin subsequently catalyzes the transformation of fibrinogen into fibrin, which polymerizes to form a blood clot. **2** Activated Protein C (APC) inactivates Factor Va by cleaving it at R306 and R506, producing inactivated Factor V (Factor Vi), which cannot convert prothrombin to thrombin, reducing clot formation. **3.** FVL mutation provides resistance to APC-mediated inactivation, leading to a prolonged half-life of Factor Va in plasma and increased thrombin generation, and a heightened risk of thrombophilia.

(B) (i) In some cases, APC cleaves Factor V at R506 before thrombin, producing Factor Vac, which acts as an anticoagulant by aiding APC in the inactivation of Factor VIIIa. **(ii)**The FVL mutation disrupts this process, reducing Factor Vac's anticoagulant activity.

The FVL mutation promotes thrombosis through two mechanisms: a gain of function that enhances fibrin formation and a loss of anticoagulant activity by impairing Factor Vac’s role in Factor VIIIa inactivation.

2. Material and Methods

Seventy-five DS patients and thirty age-and-sex-matched healthy control children were enrolled from Genetic Clinic of PGIMER **(Table 1)**. This study was approved by Institutional Ethics Committee (IEC) (NK/7949/PhD/784) and followed ICMR ethical guidelines. Informed consent was taken from the parents in line with the Declaration of Helsinki.

Table 1: Basic clinical features in DS children enrolled in the present study

	Down syndrome patients	**Healthy controls**
Participants enrolled	75	30
Males	51 (68%)	20 (66.7%)
Females	24 (32%)	10 (33.3%)
Age (years) Mean ± SD	4.61 ± 3.77	4.0 ±3.63
Weight (kg) Mean ± SD	14.40±10.90	20 ± 15.23
Height (cm) Mean ± SD	89.38 ±25.95	120.46± 48.65
CHD (+)	44(58.6%)	
CHD (-)	31 (44.4%)	30 (100%)
Hypothyroidism (+)	33 (44%)	
Hypothyroidism (-)	42 (56%)	30 (100%)
FVL +ve (Phenotypic frequency)	0.106 (10.6%)	0%
FVL -ve (Phenotypic frequency)	0.894 (89.4%)	1 (100%)
FVL +ve (Allelic frequency)	0.053 (5.3%)	0 (0%)
FVL -ve (Allelic frequency)	0.947 (94.7%)	1 (100%)

SD: Standard Deviation; CHD: Congenital Heart Defect: FVL: Factor V Leiden

Sample Collection:

From December 2020 to July 2023, 2-3 ml of venous blood was collected from each participant in EDTA vacutainers. DNA was extracted using Qiagen kits and assessed both qualitatively and quantitatively using 0.8% agarose gel and a Nanodrop. Primers were designed using Primer Blast: Forward: CCCACAGAAAATGATGCCCAG; and Reverse TCTCCTGGCTAAATAATGGGGC (Primer Blast) for Sanger sequencing for analyzing the FVL variant with the help of Finch TV software. Direct counting was used for calculating allelic and phenotypic frequency. Statistical comparisons were done using Fisher's Exact test with a significance determined at $p< 0.05$.

3. Results

Among the 75 DS patients, the FVL variant was identified in 8 individuals **(Figure 2)**, while 67 displayed only the wild-type allele. None of the healthy controls exhibited the FVL variant. Although a higher frequency of the FVL variant was observed in DS patients compared to controls, this was not statistically significant at the phenotypic (p-value = 0.101) or allelic level (p-value = 0.110). Moreover, none of the study participants exhibited an FVL variant in the homozygous state, which is in concordance with population data of this variant from the Indian subcontinent **(Supplementary Table 2).**

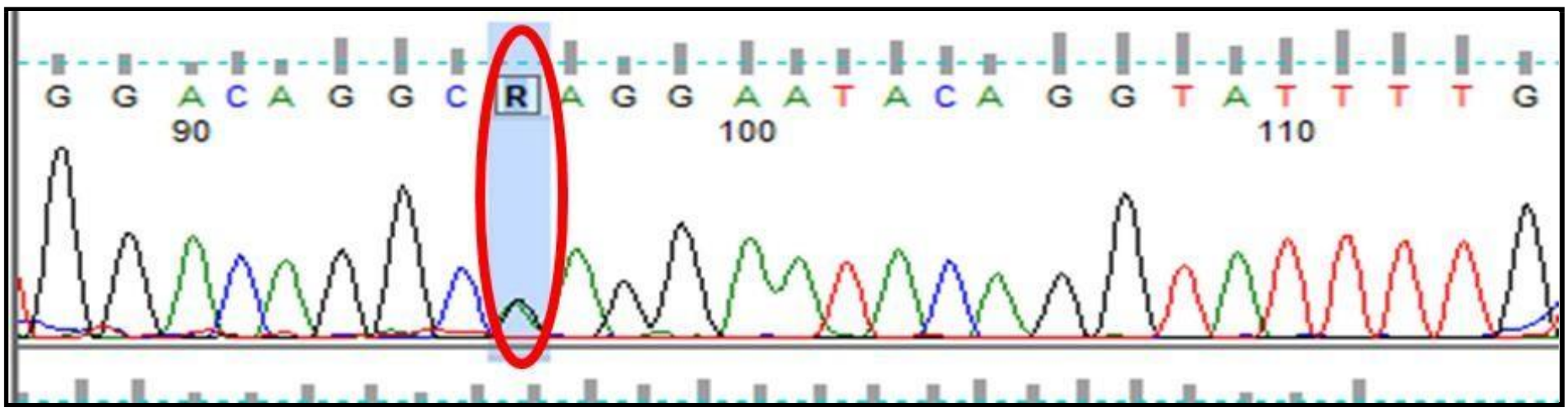

Figure 2: Sanger sequencing chromatogram of the F5 variant (FVL) in DS patients, with the variant position marked by a dark circle.

Data from gnomAD database **(Figure 3)** revealed the highest allelic frequency of FVL variant in the Amish population (0.093), and the lowest in East Asians (0.00006) **[14].** In our study, the allelic frequency was 0.053 in DS patients, which is higher compared to all general populations except the Amish.

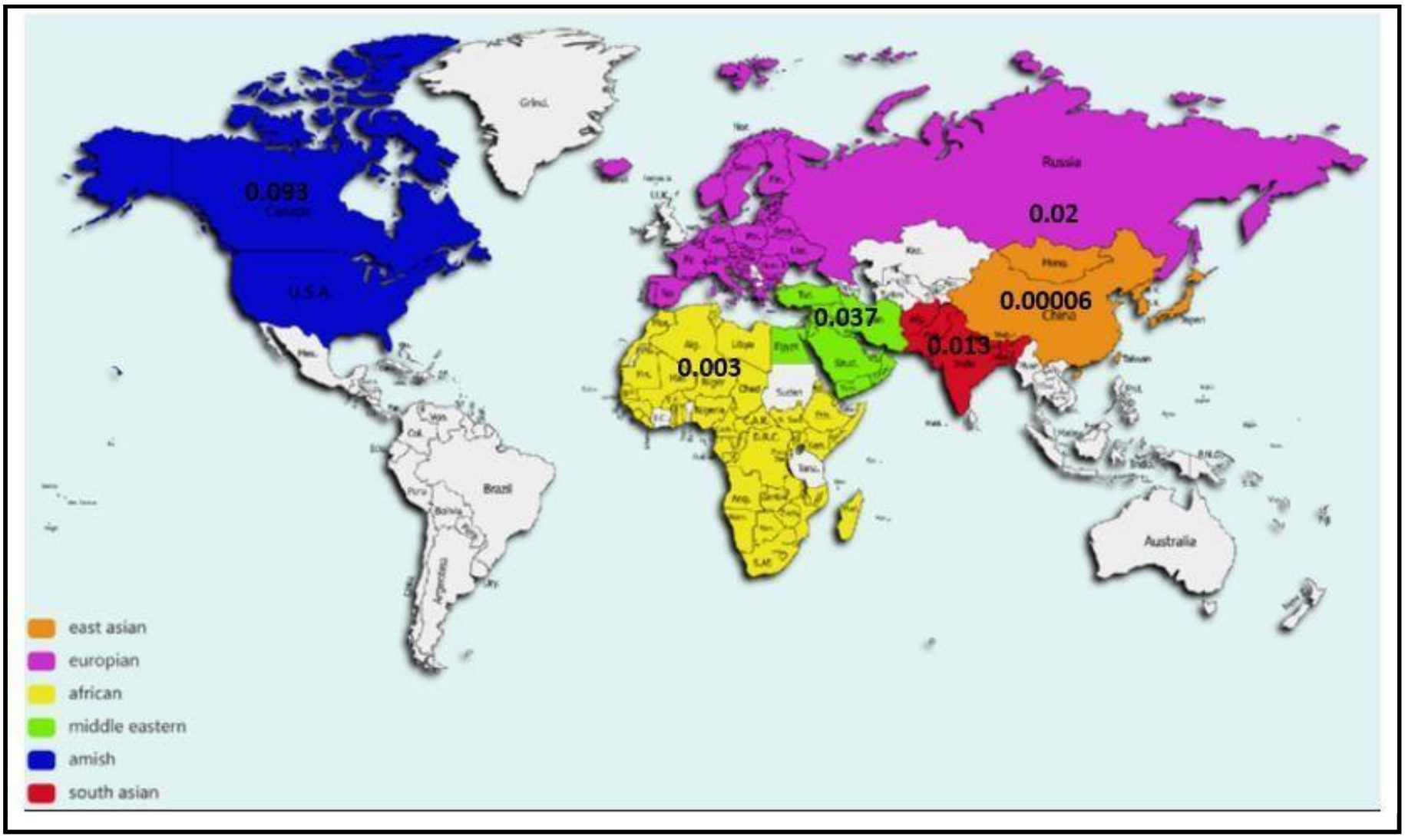

Figure 3: Global distribution of the FVL variant allelic frequency across different populations. The highest FVL frequency is observed in the Amish population in the United States (0.093), while the lowest frequency is noted in the East Asian population (0.00006). Other frequencies include 0.02 in Europeans, 0.013 in South Asians, 0.003 in Africans, and a 0.037 in the Middle Eastern population. This map illustrates the variation in FVL prevalence worldwide, highlighting an elevated frequency in the DS children of this study (0.053), which surpasses the FVL frequencies observed in most populations represented here.

The association between different subgroups of individuals with DS and FVL was examined by categorizing DS individuals based on various comorbidities. In our stratified analysis, 7 out of 44 DS patients (15.9%) with CHD had the FVL variant, while it was absent in healthy controls (p=0.037, **Figure 4**). On the other hand, no association was observed between hypothyroidism and FVL in DS patients as well as compared to healthy controls. Conversely, a significant association was found between FVL and congenital heart disease (CHD) alone, as well as the combined presence of CHD and hypothyroidism in DS patients (p-value < 0.05) **(Table 2)**. Thus there a positive association between FVL and CHD in DS children.

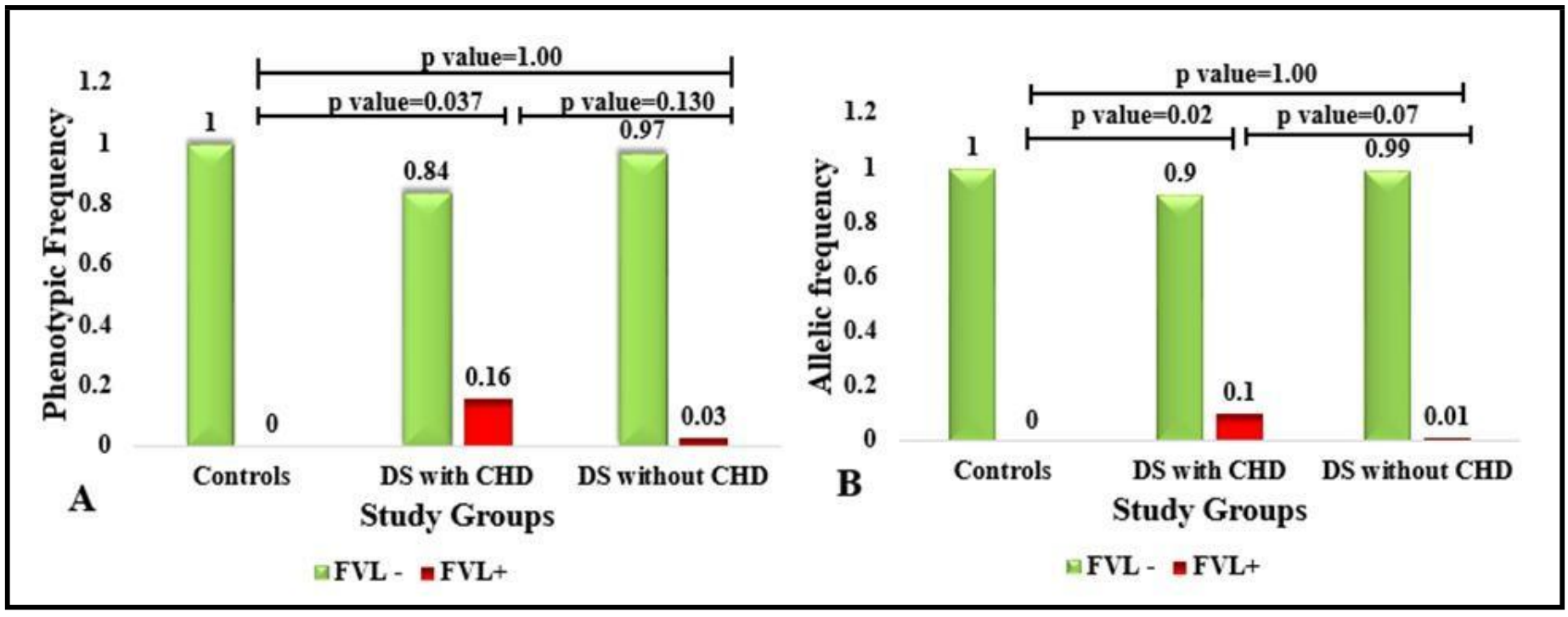

Figure 4: Distribution of FVL variation phenotypic and allelic frequency among controls and children with DS with and without CHD. FVL negative (FVL-) individuals are shown in green, FVL positive (FVL+) individuals are shown in red. Statistical analysis using Fishers Exact test.

Table 2: Distribution of FVL mutation among control and DS groups, with breakdown by CHD and hypothyroidism status.

	Controls	**DS**	**DS with CHD**	**DS without CHD**	**DS with hypo-thyroid**	**DS without hypo-thyroid**	**DS without both CHD and hypo - thyroid**	**DS with CHD and without hypo-thyroid**	**DS with hypo-thyroid and without CHD**	**DS with both CHD and hypo-thyroid**
N	30	75	44	31	33	42	15	27	16	17
FVL^+	0	8	**7***	1	5	3	0	4	1	**4****
FVL^-	30	67	37	30	28	39	15	24	15	13
FVL^+/FVL^+	0	0	0	0	0	0	0	0	0	0
FVL^+/FVL^-	0	8	7	1	5	3	0	3	1	4
FVL^-/FVL^-	30	67	37	30	28	39	15	24	15	13

FVL: Factor V Leiden, CHD: Congenital Heart Defect

The table presents the total number of individuals (N), FVL-positive (FVL+), FVL-negative (FVL−), and genotype combinations (FVL+/FVL+ and FVL+/FVL−) for each group.

* There was a significantly higher phenotypic and allelic frequency of FVL in DS children with CHD (*p-value=0.037 and 0.02*) compared to controls.

** There was a significantly higher phenotypic and allelic frequency of FVL in DS children with both CHD and hypothyroidism (*p-value=0.013and 0.020*) compared to controls.

4. Discussion

The findings of this study suggest that there is a significant association of FVL variant with DS individuals having CHD. FVL mutation being a key activator in the coagulation cascade, leads to a prothrombotic phenotype by elevating the production of thrombin. Research identifies VTE as the primary clinical manifestation associated with the FVL mutation, with heterozygous carriers had four to five times higher risk of VTE in lower extremities and six times higher risk of for thrombosis in upper extremities and superficial veins **[15, 16]**. Furthermore, FVL has been linked with an approximately 1.74-fold increased risk of ischemic stroke **[17]**. Additionally, previous research has also documented a higher risk of thrombosis in DS patients **(Supplementary Table 1)**, however the prevalence of FVL in DS is largely unknown. To this end, only one study i.e., by *Damar et al.*, reported a relatively higher prevalence of FVL among DS individuals (0.16) compared to a normal population database suggesting a potential additional genetic risk **[18]**. Similarly, we also observed a higher prevalence of FVL in DS children (0.106) compared to healthy controls **(Table 2)**. Incidentally, at the genotypic levels, homozygosity of this variant was not observed, which is in line with previous Indian studies **(Supplementary Table 2)**. Further, stratified analysis revealed that DS children with CHD had a significant overrepresentation of the FVL variant. These finding could plausible improve early screening protocols, devising preventive strategies, and tailoring management plans to mitigate thromboembolic risks in DS patients, particularly those with CHD. Larger-scale studies are warranted further to establish clinical relevance of FVL in families with DS children especially in those with CHD, which may have significant consequences for targeted screening and early preventive strategies and personalized monitoring.

5. Conclusion

To conclude, this study highlights a significant association between the Factor V Leiden variant and DS patients with CHD. These findings underscore the importance of early screening and personalized management strategies to mitigate high cardiovascular risks in this vulnerable population. Further large-scale studies are needed to establish actual clinical relevance and refine preventive interventions.

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Compliance With Ethical Standards

Research received the permission of Institute Ethics Committee (IEC) of PGIMER Chandigarh (IEC-02/2021-1893). Informed

written consent was obtained from the parents of all study participants and agreed to the Helsinki Declaration.

Author Contribution

The authors confirm contribution to the paper as follows: MG, GS, HSK, and IP were involved in drafting and finalization of the manuscript. MG was involved in the experimental work including Sanger Sequencing, GS, and HSK was involves in the statistical analysis and reviewing of the manuscript. IP was involved in diagnosis and clinical follow up of the patients. All authors have reviewed the results and approve the final manuscript.

Data Availability Statement

Data sharing not applicable to this article as no major datasets were generated during the current study.

Competing Interest: No conflicts of interest declared by authors.

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Supplementary

Supplementary Table 1: Literature and case reports on thromboembolic complications in DS patients.

S.No	Age/ Sex of DS patient	Major Clinical features	FVL	References
1.	10 months/F	Disappearing Venacava, Generalized thrombus in popliteal veins, small saphenous veins, superficial and deep femoral veins	Heterozygous FVL	Petik B et al. 2016 **[1]**
2.	19Y/ F	Sinus venous thrombosis, Moyamoya syndrome, Cardio embolism		Stöllberger C et al. 2012 **[2]**
3.	14 months/F	Deep Vein thrombosis, CHD	wild type (No FVL)	Alioğlu B et al. 2007 **[3]**
4.	10 Days/F	Giant thrombus in right ventricle, Severe respiratory distress		Caner I et al. 2006 **[4]**
5.	13Y/F	Deep Vein Thrombosis		Karow A et al. 2011 **[5]**
6.	14Y/M (N=2)	Case1: Hirschsprung disease, Hearing loss, Deep vein thrombosis in both the limbs and pulmonary embolism Case 2: Liver abscess, Deep vein thrombosis in both the limbs	Case1 wild type (No FVL), Case 2: Not tested	Kurokami T et al. 2018 **[6]**
7.	36Y/F	Epilepsy, COVID 19, Cerebral venous thrombosis	**Not tested**	Robayo et al. **[7]**
8.	18Y/M	Pneumonia, Cerebral venous thrombosis		Lin Y et al. 2018 **[8]**
9.	3Y/F	Moyamoya, Saggital Sinus thrombosis		Del-Rio et al. 2001 **[9]**
10.	38Y/M	Seminoma, Deep Vein Thrombosis		Hengy M et al. 2022 **[10]**
11.	12Y/F	Broncho pneumonia, Choroid plexus thrombosis		Deshpande V et al. 1984 et al **[11]**
12.	25Y/M	Clonic Tonic Seizures, Deep vein thrombosis		Tarlaci S et al. 2001 **[12]**
13.	Neonate/M	Dural venous thrombosis, Aspiration pneumonia		Damam S et al. 2024 **[13]**
14	26Y/M	Mesentric vein thrombosis, Mild epilepsy, Fatty liver		Tateishi A et al. 2001 **[14]**
15	2Y/M	Hashimoto thyroiditis, Precious three episodes of thrombosis, Antiphospholipid syndrome, CHD		Hoxha A et al. 2008 **[15]**
16	15Y/M	COVID-19, History of recurrent pneumonia, Pulmonary embolism		Nuñez-P et al. 2023 **[16]**
17	34Y/M	Attention deficit disorder, Deep vein thrombosis		Medina G et al. 2009 **[17]**
18	15Y/F	Hypothyroidism, Hidradenitis suppurativa, Superior saggital sinus thrombosis		Williams ML et al. 2003 **[18]**
19	20Y/F	ALL, Bilateral internal juglar vein thrombosis		Manghat N et al. 2004 **[19]**
20.	11Y/NA	Venous sinus thrombosis		Worley G et al. 2004 **[20]**
21	32Y/M	Extensive actute thrombosis of portal vein, splenic vein, and superior mesenteric vein		Agarwal A et al. 2012 **[21]**
22	13Y/M	Thrombocytopenia, Aortic valve thrombus, Stroke AMPL (acute pro-myelocytic leukemia), CHD		Plant G et al. 2024 **[22]**
23.	39Y/M	Type 1 diabeties, Left axillary vein thrombosis, Epilepsy		Gill GV et al. 2006 **[23]**
24.	2Y/F	Antiphospholipid syndrome, Deep vein thrombosis CHD		Gru A et al. 2010 **[24]**
25.	6 2Months/M	Thrombus in left pulmonary artery, CHD		Stansel Jr et al. 1972 **[25]**
26.	3Y/F	A large thrombus in right atrium, CHD		Kimura M et al. 2016 **[26]**

27.	2Y/M	Non ketoic hyperglycemic coma, Ileofemoral artery thrombosis		Belmonte MM et al. 1970 **[27]**
28.	34Y/F	Cerebral venous thrombosis, Severe spondalitis		Finelli PF et al. 1995 **[28]**
29.	13Y/M	Hypothyroidism, Antiphospholipid antibody syndrome, Type I diabetes mellitus, Cerebral thrombosis		Arabshahi B et al. 2007 **[29]**

FVL-Factor V Leiden; Y-Years, M-Male; F-Female; CHD-Congenital Heart Defect; ALL- Acute Lymphoblastic Leukemia; AML-Acute Myeloid Leukemia; COVID19- Corona virus Disease 2019; DVT- Deep Vein Thrombosis

Supplementary Table 2: Summary of allelic, genotypic and phenotypic frequency of FVL in Indian population

S.No	N (No of individuals)	GG	GA	AA	Phenotypic frequency	Allelic frequency	References
1	150	148	2	0	0.013	0.006	Herrmann FH et al. 1997**[30]**
2.	32	31	1	0	0.03	0.015	Herrmann FH et al. 1997**[30]**
3.	120	118	2	0	0.016	0.008	Anadure R et al. 2017 **[31]**
4.	100	100	0	0	0.000	0.000	Vora S et al. 2007 **[32]**
5.	130	130	0	0	0.000	0.000	Kangne HK et al. 2015 **[33]**
6.	316	306	10	0	0.03	0.001	Garewal G et al. 2003 **[34]**
7.	49	47	2	0	0.04	0.020	Kumar SI et al. 2005 **[35]**
8.	80	80	0	0	0.000	0.000	Mukhopadhyay R et al. 2009 **[36]**
9.	500	488	12	0	0.02	0.012	Parveen F et al. 2013 **[37]**
10.	588	573	15	0	0.02	0.012	Kaur L et al. 2013 **[38]**
11.	569	551	18	0	0.03	0.016	Aggarwal S et al. 2011 **[39]**
12.	200	185	15	0	0.075	0.03	Tripathi G et al. 2010 **[40]**

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