WFH COMPREHENSIVE CARE SUMMIT

New Developments in Bleeding Disorders and MSK

athn transcends

ATHN Transcends: A Natural History Study of Bleeding Symptoms and Treatment Outcomes in Patients with Glanzmann Thrombasthenia – The Pakistan Site Experience

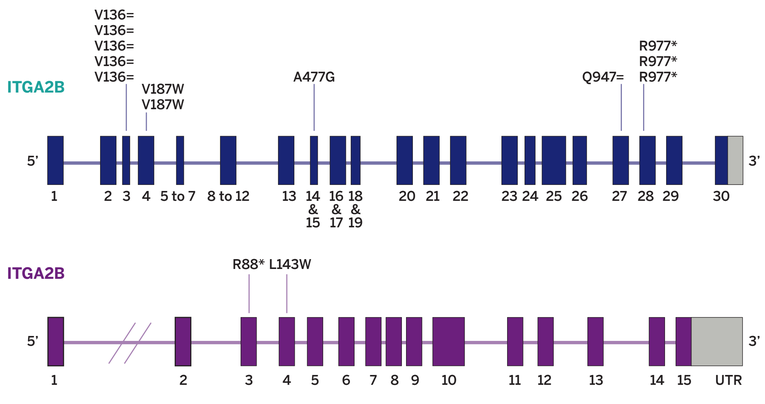
Authors: **Tahira Zafar[1], Divyaswathi Citla-Sridhar[2], Jigar Amin[3], Tammuella Chrisentery-Singleton[4,5], Shelby Domino[4], Hina Fatima[1], Catherine Rea[3], Michael Recht[6,7], Jonathan Schwartz[4], Lubna Zafar[1], Meera Chitlur[8]**

[1]Haemophilia Patients Welfare Society, Haemophilia Treatment Center, Rawalpindi, Pakistan; [2]Arkansas Children's Hospital, Little Rock, AR, USA; [3]Hemab Therapeutics, Cambridge, MA, USA; [4]American Thrombosis and Hemostasis Network, Hickory, NC, USA; [5]Ochsner Clinic Foundation, New Orleans, LA, USA; [6]Yale University School of Medicine, New Haven, CT, USA; [7]National Bleeding Disorders Foundation, New York, NY, USA; [8]Central Michigan University, Children's Hospital of Michigan, Detriot, MI, USA

Introduction

Glanzmann thrombasthenia (GT) is a rare inherited platelet disorder marked by lifelong, often severe mucocutaneous bleeding. It is an autosomal recessive bleeding disorder resulting from ITGA2B or ITGB3 gene mutations. The global prevalence ranges from 1 in 200,000 to 1,000,000, but it is more common in countries like Pakistan with high consanguinity rates. Treatments are largely reactive, relying on platelet transfusions and recombinant factor VIIa, which pose risks such as alloimmunization, allergic reactions, and pathogen transmission. Currently, no primary bleeding prophylaxis exists and data is limited on matching the phenotype to genotype, indicating a need for a worldwide study for standardized phenotyping of GT.[1]

Figure 1. ITGA2B and ITGB3 Mutations from Population



* Represents a **stop codon** (termination)
= Represents **no change** in amino acid sequence despite a mutation
Participant 3 had no exon reported

Aim

To describe the genotype of a subset of participants enrolled in ATHN Transcends (NCT04398628), a multi-institutional, longitudinal, natural history, observational cohort study designed to assess the safety and effectiveness of therapies for people with inherited bleeding and clotting disorders. Here we focus specifically on the Glanzmann Thrombasthenia Module under the ATHN Transcends study.

Methods

- Participants from participating treatment centers consented to the ATHN Transcends: Glanzmann Thrombasthenia Module (NCT04398628).
- Genetic testing was optional and required an additional blood sample within the consent.
- The module has an enrollment goal of 50 participants in the US and 10 participants at an international site (Pakistan). Fifteen participants enrolled at the HTC of Haemophilia Patient's Welfare Society (HPWS), a treatment center in Rawalpindi, Pakistan.
- For laboratory testing, Versiti Diagnostic Laboratory completed the Glanzmann Thrombasthenia Panel using Next Generation Sequencing with supplementary PCR and bi-directional Sanger sequencing.

Results

- Age at diagnosis ranged from birth to 15 years (median of 1 year). The cohort included 7 males (47%) and 8 females (53%).
- Mutations in ITGA2B were seen in 13/15 (87%) and ITGB3 in 2/15 (13%).
- Two ITGA2B mutations, c.408G>A and c.2348+5G>T, which have not been previously reported, were identified in 2 unrelated patients diagnosed following bleeding symptoms at <1 yr of age.

Conclusion

There is a high prevalence of Glanzmann thrombasthenia in Pakistan. In the subset population studied, most had well-documented pathogenic variants. However, we identified 7 participants with undocumented mutations (4 different variants were identified), highlighting the genetic diversity in the country. There is a need for continued research to identify more genetic variations.

References

1. Alan T. Nurden, Mathieu Fiore, Paquita Nurden, Xavier Pillois; Glanzmann thrombasthenia: a review of ITGA2B and ITGB3 defects with emphasis on variants, phenotypic variability, and mouse models. Blood 2011; 118 (23): 5996–6005. doi: https://doi.org/10.1182/blood-2011-07-365635

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Table 1. Genetic Testing Results

PARTICIPANT #	AGE (YEARS)	AGE OF DX	SEX AT BIRTH	BASELINE PLT	GENE NAME	EXON	NUCLEOTIDE CHANGE	PROTEIN CHANGE	ZYGOSITY	VARIANT TYPE	CLINICAL SIGNIFICANCE	REFERENCE SEQUENCE
001	6	1 year	Female	368 x10(3)/mcL	ITGB3	Exon4	c.428T>G	p.Leu143Trp	Homozygous	Missense	Pathogenic	NM_000212.3
002	12	3 months	Female	364 x10(3)/mcL	ITGB3	Exon3	c.262C>T	p.Arg88*	Homozygous	Nonsense	Pathogenic	NM_000212.3
003	28	4 months	Male	332 x10(3)/mcL	ITGA2B	N/A	c.2348+5G>T	N/A	Homozygous	Insertion	Variant of Uncertain Signficance	NM_000419.5
004	26	8 months	Male	173 x10(3)/mcL	ITGA2B	Exon3	c.408G>A	p.Val136=	Homozygous	Silent Mutation	Likely Pathogenic	NM_000419.5
005	12	3 years	Male	239 x10(3)/mcL	ITGA2B	Exon3	c.408G>A	p.Val136=	Homozygous	Silent Mutation	Likely Pathogenic	NM_000419.5
006	25	12 years	Female	Not reported	ITGA2B	Exon14	c.1424_1427dup	p.Ala477Glyfs*111	Homozygous	Frameshift	Pathogenic	NM_000419.5
007	4	8 months	Male	139 x10(3)/mcL	ITGA2B	Exon28	c.2929C>T	p.Arg977*	Homozygous	Nonsense	Pathogenic	NM_000419.5
008	17	10 months	Male	267 x10(3)/mcL	ITGA2B	Exon27	c.2841G>A	p.Gln947=	Homozygous	Silent Mutation	Variant of Uncertain Signficance	NM_000419.5
009	26	5 years	Female	172 x10(3)/mcL	ITGA2B	Exon4	c.559del	p.Val187Trpfs*37	Homozygous	Frameshift	Pathogenic	NM_000419.5
010	30	<1 year	Female	485 x10(3)/mcL	ITGA2B	Exon4	c.559del	p.Val187Trpfs*37	Homozygous	Frameshift	Pathogenic	NM_000419.5
011	12	1 year	Female	Not reported	ITGA2B	Exon28	c.2929C>T	p.Arg977*	Homozygous	Nonsense	Pathogenic	NM_000419.5
012	19	9 months	Female	230 x10(3)/mcL	ITGA2B	Exon28	c.2929C>T	p.Arg977*	Homozygous	Nonsense	Pathogenic	NM_000419.5
013	32	3 years	Female	206 x10(3)/mcL	ITGA2B	Exon3	c.408G>A	p.Val136=	Homozygous	Silent Mutation	Likely Pathogenic	NM_000419.5
014	16	15 years	Male	Not reported	ITGA2B	Exon3	c.408G>A	p.Val136=	Homozygous	Silent Mutation	Likely Pathogenic	NM_000419.5
015	28	3 years	Male	198 x10(3)/mcL	ITGA2B	Exon3	c.408G>A	p.Val136=	Homozygous	Silent Mutation	Likely Pathogenic	NM_000419.5