Genetic Variant Analysis in Children and Adults with Hemophilia: Experience From a Large Hemophilia Center in the US

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INTRODUCTION

- Although the benefits of identifying the pathogenic variant in patients with hemophilia are well-known, the cost of genetic testing and lack of insurance coverage is prohibitive for many patients and their families.
- In October 2013, the Gulf States Hemophilia and Thrombophilia Center (GSHTC) began offering to eligible hemophilia patients the opportunity to participate in the My Life, Our Future (MLOF) genotyping project, a partnership of the American Thrombosis & Hemostasis Network (ATHN), National Hemophilia Foundation, Bloodworks Northwest (BWNW), and Biogen.

OBJECTIVE

Participation in the My Life, Our Future (MLOF) genotyping project, combined with genetic counseling, would provide patients with:

- An enhanced understanding of their condition
- Genotype-phenotype correlations
- Carrier testing and family planning options
- The elimination of financial barriers to genetic testing
- Prediction of inhibitor development in mild HA

METHODS

Blood samples were sent to BloodWorks Northwest Genomic Testing Laboratory for either *F8* or *F9* molecular analysis. Patient clinical and demographic information was collected through chart review.

Table 1. Hemophilia A and B genotyping data

F8 Variant Type	Mild (%[1])	Moderate (%[1])	Severe (%[1])	Inhibitor (%[1])
Intron 22 Inversion	0	0	34 (37.4)	8 (29.6)
Intron 1 Inversion	0	0	1 (1.1)	0
Missense	35 (89.7)	14 (87.5)	16 (17.6)	2 (7.4)
Nonsense	0	0	9 (9.9)	3 (13.6)
Frameshift	0	0	20 (22.0)	5 (22.7)
Large Structural Change (>50 bp)	0	0	5 (5.5)	4 (18.2)
Small Structural Change (<50 bp)	0	0	1 (1.1)	0
Splice site[1]	1 (2.6)	0	5 (5.5)	1 (4.5)
Synonymous	1 (2.6)	2 (12.5)	0	1 (4.5)
Unidentified	2 (5.1)	0	0	0
Total	39	16	91	27

F9 Variant Type	Mild (%[1])	Moderate (%[1])	Severe (%[1])	Inhibitor (%[1])
Missense	9 (90.0)	7 (100)	7 (53.8)	0
Nonsense	0	0	5 (38.5)	1 (100)
Frameshift	0	0	1 (7.7)	0
Synonymous	1 (10.0)	0	0	0
Total	10	7	13	1

[1] Percent is out of the total in each column.

Table 2. Novel variants

Hemophilia Type	HGVS cDNA Name	Variant Type	HGVS Protein Name
Severe A	c.5220-?_7056+?del	Large structural change (>50 bp)	
Severe A	c.1010-?_1537+?del	Large structural change (>50 bp)	
Severe A	c.1904-?_2113+?del	Large structural change (>50 bp)	
Severe A	c.1017_1024del	Frameshift	p.Met339Ilefs*18
Severe A	c.3745_3748del	Frameshift	p.Leu1249Alafs*6
Severe A	c.5829_5839dup	Frameshift	p.Thr1947Argfs*29
Severe A	c.3465dupA	Frameshift	p.Ser1156Ilefs*10
Severe A	c.5815G>C	Missense	p.Ala1939Pro
Severe A	c.1095T>G	Nonsense	p.Tyr365*
Moderate A	c.2005T>C	Missense	p.Ser669Pro
Mild A	c.2108A>C	Missense	p.Asn703Thr
Mild A	c.853G>A	Missense	p.Val285Met
Severe B	c.377dupA	Frameshift	p.Asn127Glufs*3
Mild B	c.223C>G	Missense	p.Arg75Gly

Table 3. Inhibitor development in Hemophilia A and B by pathogenic variant

Hemophilia Type and Severity	HGVS cDNA Name	Variant Type	HGVS Protein Name	High Titer Inhibitor	Low Titer Inhibitor
Severe A	c.6429+?_6430-?inv	Inversion		6	2
Severe A	c.5220-?_7056+?del	Large structural change (>50 bp)		1	0
Severe A	c.1010-?_1537+?del	Large structural change (>50 bp)		0	1
Severe A	c.1904-?_2113+?del	Large structural change (>50 bp)		0	1
Severe A	c.788-?_1443+?del	Large structural change (>50 bp)		1	0
Severe A	c.209_212del	Frameshift	p.Phe70*	0	1
Severe A	c.934_935delTT	Frameshift	p.Phe312Profs*25	0	1
Severe A	c.2962_2963delAG	Frameshift	p.Ser988Trpfs*2	1	0
Severe A	c.5829_5839dup	Frameshift	p.Thr1947Argfs*29	1	0
Severe A	c.3091_3094del	Frameshift	p.Lys1031Leufs*9	1	1
Severe A	c.1063C>T	Nonsense	p.Arg355*	1	0
Severe A	c.5878C>T	Nonsense	p.Arg1960*	1	0
Severe A	c.6682C>T	Nonsense	p.Arg2228*	0	1
Moderate A	c.6977G>A	Missense	p.Arg2326Gln	0	2
Moderate A	c.1569G>T	Synonymous	p.(=)	2	0
Mild A	c.1538-18G>A	Splice Site Change		0	1
Severe B	c.223C>T	Nonsense	p.Arg75*	1	0
Total				16	11

RESULTS

- To date, 178 participant results are available:
  - –146 hemophilia A and 32 hemophilia B (Table 1)
- Ninety-six total variants were identified
  - – 14 were novel (Table 2)
  - –Twenty-one variants were present in 57.3% of patients
- Twenty-seven participants had a history of an inhibitor (Table 3)
  - – 21 (77.8%) of these have severe hemophilia A
- Of note, 91 (51.1%) patients had Medicaid, Medicare or were uninsured

CONCLUSIONS

While not all active GSHTC patients (N=405) were eligible or could be offered the MLOF genotyping project, at least 178 (43.9%) of GSHTC patients participated. During genetic counseling, results were discussed with patients and families at routine visits to the GSHTC. The identification of familial pathogenic variants has facilitated carrier testing, provided genotype-phenotype correlations, modified treatment of at-risk patients for inhibitors and has made reproductive options available for several families.