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LETTER TO THE EDITOR

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Three novel *F8* mutations in sporadic haemophilia A cases

Rashid Hussain^{1*}, Noman Bin Abid², Sajjad Hussain³, Zeeshan Shaukat³, Mudassir Altaf³, Sara Altaf³ and Gulzar Niazi³

Hemophilia A (HA) is an X-linked hereditary disorder characterized by bleeding of variable severity through mild, moderate to severe owing to large range of mutations in the Factor VIII (*F8*) gene (Bowen 2002). All kind of *F8* mutations, except repeats, have been reported for HA, in total up to 2370 (Human Genome Mutation Database 2005). A preliminary study was conducted in our lab for identification of mutations in *F8* gene in Pakistani HA patients. Correlation of *F8* mutations with clinical manifestation of HA patients was the main objective of the study. Blood samples were collected from 62 HA patients from all over the Pakistan and clinical history of all HA patients was recorded (only patients frequently visiting medical centers for the replacement of Factor VIII were selected for the study). Genomic DNA was extracted from whole blood by standard organic procedure. Specific primers (Figure 1) were designed using “Primer3” (http://biotools.umassmed.edu/bioapps/primer3_www.cgi) to amplify the coding region of *F8* gene; amplified products were sequenced by ABI 310 and ABI 3100 sequencer (Applied Biosystems, Carlsbad, CA, USA). The sequencing results were visualized using “Chromas 2.33” software (Applied Biosystems) and mutations were detected using “BLAST” software available on the NCBI website (<http://blast.ncbi.nlm.nih.gov/Blast.cgi>). Three novel mutations (1 deletion; 2 point mutations) were detected in four sporadic HA patients, all from different ethnic backgrounds (Table 1). The deletion of T in exon 7 within the A1 domain represents a frame-shift change disrupting the protein structure and function, which result in severe manifestation of the disease. A missense point mutation in the A3 domain occurs in codon 1907 at nucleotide number 5720, replacing Serine with Isoleucine, and

confers a moderate type of severity. It should be noted that Serine is a polar and acidic amino acid while Isoleucine is a nonpolar and basic amino acid. A nonsense point-mutation was found in two unrelated patients in the C3 domain (exon 26) and was correlated with moderate clinical findings. Beside these mutations, 27 common SNPs were also detected in *F8* gene for the studied patients (Table 2). The allelic data and accession numbers of these SNPs were collected from Ensembl Genome Browser (Ensembl 2000). The results of the study will form the basis not only for an enlarged study but also for diagnosis and genetic counseling of classical hemophilia in Pakistan.

Competing interests

The authors declare that they have no competing interests.

Author's contributions

RH managed the project and wrote the paper. NBA, SH, ZS, MA, SA performed experiments. GN designed the project. All authors read and approved the final manuscript.

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Table 2 Common SNPs in F8 gene (exonic region) (Continued)

12	All 62 Samples	12	Y: T/C	T/T	<u>CTT</u>	622	Ancestral: T	rs1800290
13	All 62 samples	15	R: G/A	G/G	<u>CAG</u>	1764	Ancestral: A	rs5986891
14	All 62 samples	16	R: G/A	G/G	<u>ATG</u>	1842	European = G/G	rs28943674
15	All 62 samples	16	Y: C/T	C/C	<u>CCC</u>	1844	European = C/C	rs28933675
16	All 62 samples	16	M: A/C	A/A	<u>ACT</u>	1845	?	rs28933676
17	All 62 samples	16	Y: C/T	C/C	<u>GCC</u>	1853	European = C/C	rs28933677
18	All 62 samples	17	D: G/A/T	G/G	GAT	1865	Not Available	CI076951
19	All 62 samples	17	R: A/G	A/A	<u>CAC</u>	1867	Ancestral: G	rs28933679
20	All 62 samples	17	S: C/G	C/C	<u>CCC</u>	1873	European = G/G	rs28933680
21	All 62 samples	17	R: G/A	G/G	<u>GAG</u>	1904	European = C/C	rs28933681
22	All 62 samples	17	S: G/C	G/G	<u>TGC</u>	1922	European = G/G	rs4384155
23	All 62 samples	17	S: C/G	C/C	<u>TGC</u>	1922	European = C/C	rs4520342
24	All 62 samples	18	R: A/G	A/A	AAT	1940	?	CM083806
25	All 62 samples	18	D: G/A/T	G/G	<u>CGA</u>	1960	?	rs28937294
26	All 62 samples	18	R: G/A	G/G	GGC	1967	?	rs111033615
27	All 62 samples	24	Y: C/T	C/C	TAC	2214	Ancestral: C	rs1800296