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INTRACRANIAL BLEEDING IN A FEMALE HEMOPHILIA PATIENT: MOLECULAR ANALYSIS OF FACTOR 8 GENE AND DETERMINATION OF A NOVEL MUTATION

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An 11 month old female patient was admitted to the emergency department with right occipital fracture and epidural hematoma. The father had severe hemophilia A and the parents were cousins. Laboratory tests revealed normal complete blood count and prolonged aPTT. Mixing test was normalized after mixing with normal plasma. After plasma samples were collected for further diagnostic tests, Fresh Frozen Plasma (FFP) and dexamethasone was administered. The Factor VIII level was: 0.1%,35% and 0.5%, of the patient, mother and

father respectively. The patient's VWF level was: 128 IU/ml, VWF:Ricof: 110 IU/ml, collagen ADP: 110 (71-118) sec and collagen epinephrine: 98 (85-165) sec. Intron 22 inversion was investigated with IS-PCR method and was found to be normal. Whole Genome Analysis including all exonic regions of F8 gene (NM_000132.3) was made and homozygous c.608T>C (L203P) mutation was found.This mutation was not previously reported. As this variant was not reported in any exome databases (ExAC, EVS) and as was shown to be the cause of the disease in at least three silico protein modelling programmes, the mutation was considered as a novel mutation causing hemophilia A (Probably damaging with 0,987 PolyPhen2 score, Disease causing with 0.999 MutationTaster score and damaging with 0 SIFT score). The mutation was also confirmed by Sanger sequencing (Figure 1). Plasma-derived FVIII 2x500 IU/day was administered for 14 days followed by 300 IU/week prophylaxis. Inhibitor screening at 5^{th} and 10^{th} exposure days were negative.

Hemophilia A is rarely seen in female patients due to skewed inactivation of the X chromosome leading to inactivation of the wild type X chromosome, anomalies like Turner syndrome or translocations as well as homozygous/ compound heterozygous mutations for Hemophilia A (1,2,3,4,5) The karyotype analysis of our patient was 46,XX. The patient and the father were hemizygous and mother was heterozygous for c.608T>C (L203P) mutation (Figure-2). The clinical situation of our patient as she admitted with epidural hematoma requiring surgical intervention and the reality that the family did not apply for prenatal diagnosis before birth, pointed out the importance of prenatal diagnosis in regions where consanginous marriage is common.

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Figure 1: Sanger sequencing confirmation. (a) The mother (b) The father and (c) The case shows heterozygous, hemizygous and homozygous c.608T>C (L203P) mutation in *F8* gene

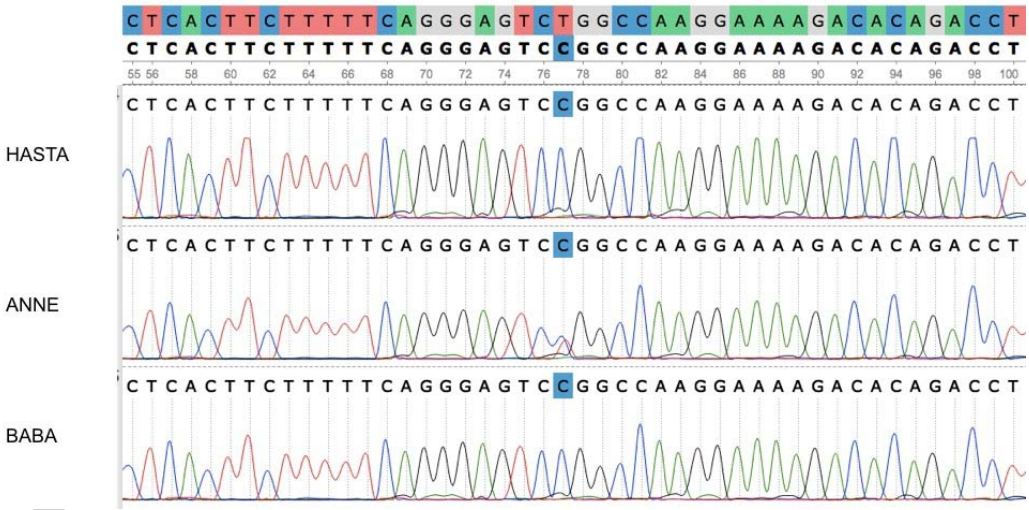

Figure 2: Family Tree. The patient was homozygous, the father were hemizygous and mother was heterozygous for c.608T>C (L203P) mutation