

# Bleeding tendencies in female carriers of haemophilia A

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Female carriers of haemophilia A commonly present with non-haemophilic FVIII levels but occasionally also report a considerable tendency to bleeding. Because carriers usually have one unaffected allele, the FVIII concentration often is about 50% of normal. But symptomatic carriers of haemophilia A can present with bleeding symptoms like a male patient with mild haemophilia A. Female carriers of haemophilia might not only have an increased bleeding tendency but the symptoms may be frequent and severe. Therefore, the assessment of the bleeding risk is very important for improving care.

In our study we investigated a possible relationship between mutation type and bleeding tendency in carriers of haemophilia A.

## Methods

The patients included were carriers of haemophilia A who attended the Haemophilia Center of the University Hospital Frankfurt/Main, Germany. The carrier status was confirmed by analysis of the FVIII gene mutation (Prof. J. Oldenburg, Bonn/Würzburg, Dr. C. Geisen, Frankfurt/Main). To exclude the additional presence of a von Willebrand-syndrome the von Willebrand-antigen was measured in all carriers by ELISA method.

Forty six carriers were questioned about their bleeding tendencies. The following symptoms were recorded:

- easy bruising,
- nose bleeding,

- gum bleeding,
- long or severe menstrual bleeding,
- postpartal bleeding,
- bleedings after surgical procedures.

Measurement of FVIII was carried out by one-stage clotting assay (ACL 300, reference range: 64–167%) with FVIII-deficient plasma from Instrumentation Laboratory (IL).

## Results, conclusion

The median age of the 46 included carriers was 36.5 years (15–80 years). The median FVIII concentration of all carriers was 55% (4–114%) (► Tab. 1). 32 of the 46 carriers (70%) reported on the occurrence of easy bruising (31 carriers) or nose bleeding (7 carriers) and gum bleeding (2 carriers). Prolonged menstrual bleeding (=5 days) was experienced by 23 carriers (50%) and prolonged bleeding after surgical intervention by 22 of 36, after tooth extraction by 17 of 22 carriers (77%). Prolonged bleeding after giving birth was reported by 10 of 23 carriers (43%). 7/46 (15%) carriers reported that they did not remember any bleeding tendency, four of the seven did not have surgical interventions and five did not give birth. Joint bleeding or bleeding during pregnancy was not observed in any carrier (► Tab. 2). FVIII mutations could be detected in all carriers:

- Nine carriers had an intron 22-inversion,
- two carriers a deletion (one deletion was small),
- two had a nonsense mutation,
- the majority of the carriers showed a missense mutation (33 carriers).

All carriers had a family history of haemophilia and in 44 of 46 carriers the severity of haemophilia of the relative is known:

- 12 carriers had male family members affected by severe haemophilia A (FVIII level <1%),
- 7 carriers had moderate haemophilia (FVIII 1–5%) in their family,

**Tab. 1** Patient characteristics and FVIII gene mutations

number of carriers	46
median (range) age at questionnaire	36.5 years (15–80)
median (range) FVIII activity	55% (4–114)
intron-22 inversion	9 (20%)
missense mutation	33 (71%)
nonsense mutation	2 (4%)
deletion	2 (4%)

**Tab. 2** Bleeding symptoms of the carriers of haemophilia A

symptoms	n	%
easy bruising	32	70
nose bleeding (ever reported)	7	16
gum bleeding (present)	2	5
menorrhagia	23	50
prolonged postpartal bleeding (23 carriers)	10	43
bleeding after surgery (36 carriers)	22	61
prolonged bleeding after tooth extraction (22 carriers)	17	77
no bleeding tendency	7	15

- 14 mild haemophilia (FVIII 5–10%),
- 11 had subhaemophilic (FVIII >10%) relatives.
- The haemophilia status of the family of two carriers is not known.

Our results show a huge variability of bleeding symptoms in carriers of haemophilia A. Even carriers with a FVIII activity as high as 50–60% are already at risk of bleeding in everyday life and of prolonged bleeding from surgery or after giving birth.

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### Blutungsneigung bei Konduktorinnen für Hämophilie A

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