A case of unexpected moderate haemophilia A in a female neonate within a family with mild haemophilia A in affected males: what happened?

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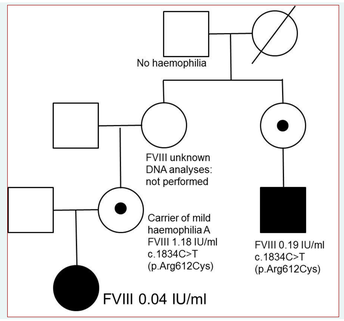
Prenatal counselling

A pregnant carrier of the F8 mutation c.1834C>T (p.Arg612Cys) with a Factor VIIIc of 1.18 IU/ml was counselled that her unborn daughter had 50% chance of inheriting this mutation, which is associated with mild haemophilia A in affected males (Waseem et al., Thromb Haemost 1999;81:900-5), and resulted in Factor VIIIc of 0.19 IU/ml in her affected cousin. No additional precautions, apart from regular prenatal and obstetrical care, were advised for the patient and the policy was to test her daughter's factor VIIIc value postnatally.



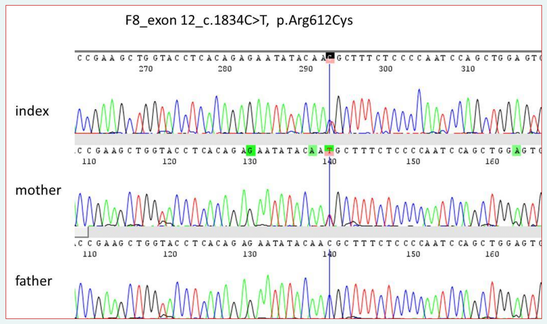
Postnatal clinical presentation

At 4 months, the daughter surprisingly was diagnosed with moderate haemophilia A (Factor VIIIc : 0.04 IU/ml, vWF ag: 0.78 IU/ml). Additional investigations were performed to unravel the cause of this unexpected low Factor VIIIc value.

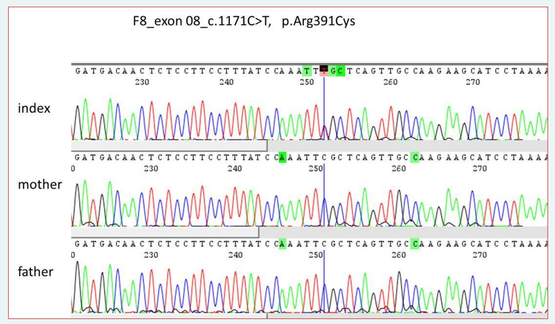
Additional investigation

Skewed X inactivation seemed unlikely, because even when only affected X chromosomes are activated in each cell, the patients clinical features would resemble the familial mild form of haemophilia A of the affected males. This would also be the case when she had monosomy X (Turner syndrome) or a sub microscopic deletion on the contralateral X chromosome. Tests to rule out these possibilities were all normal indeed.

Additional *F8* gene investigation, however, identified the familial c.1834C>T mutation, and a second mutation c.1171C>T (p.Arg391Cys), which is associated with mild to severe haemophilia A (Green PM et al., Br J Haematol. 2008 Oct;143(1):115-28). These two mutations explain the daughter having moderate haemophilia A.



Familial F8 mutation associated with mild haemophilia A on the maternal X chromosome



Second *de novo* F8 mutation associated with mild to severe haemophilia A on the paternal X chromosome

Recurrence risk

The second mutation was not identified in her parents DNA in blood. A low recurrence risk for future pregnancies was counselled (<1%). Nevertheless, if a (small) percentage of her father's germ cells do carry the second mutation (due to paternal germline mosaicism), then this couple faces an increased risk of having a more severe form of haemophilia A in their female offspring (if the mother passes the familial mutations as well), compared to their affected male offspring, because their future sons only have 50% chance of inheriting their mother's mild haemophilia A mutation. Their second child, a boy, was diagnosed with mild haemophilia A (FVIII 0.11 IU/ml).

Conclusion

DNA analysis in female carriers of haemophilia with unexpected low FVIII levels should include whole F8 gene sequencing and not be limited to the familial pathogenic mutation.

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