In 1974 after the birth of her first child, the patient developed an ileo-femoral vein thrombosis followed by a pulmonary embolism. General coagulation screening at that time revealed hypercoagulability, but unfortunately no records are available. She had experienced no complications until after the use of oral contraceptives and was started on warfarin therapy. In 1977 she fell pregnant with her second child and suffered no complications. In 1984 she had a hysterectomy during which she bled profusely requiring 6 units of blood. After this episode her warfarin was stopped. In 1991 she had major orthopaedic surgery and again bled profusely. This time she was not on anticoagulation therapy. Between 1991 and 2008 she suffered repeated deep venous thromboses of the lower limbs. In 2000 she had a 2nd suspected but unconfirmed, pulmonary embolism and again bled profusely. This time she was started on warfarin therapy. While in hospital in 2007, there was placed back on warfarin therapy.

Index case presentation

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she had a reaction which was attributed to warfarin. Warfarin was stopped and she was started on Clexane but developed epistaxis on therapeutic dosages and was put back on warfarin. She was referred to our clinic in late 2008 for thrombophilia screening after a subclavian vein thrombosis and possible allergy to warfarin. The patient was screened for thrombophilia using the following tests which were all normal except for a slightly elevated homocysteine (Table 1).

Thrombophilic mutations, Factor V Leiden, Prothrombin F2G20210A and MTHFR C677T were then evaluated using the standard PCR techniques and all three mutations were found to be present in the heterozygous state (Figure 1-3).

After this discovery, the patient informed us that a sister, one of three siblings (two sisters and a brother), had a similar but not as serious a thrombotic history as well as having had three miscarriages. The other two siblings were completely asymptomatic. The affected sister had one daughter, who is so far asymptomatic and married with a 6 week old baby girl. The asymptomatic brother suffered from leg ulceration but no other details were available. In light of our patient’s positive link with Factor V Leiden and contraceptive usage as well as the positive family history, we agreed to test the family members, at their own request (Figure 1-3). The brother who had a history of leg ulcerations, declined to be tested. Screening for thrombophilic mutations was carried out on the mother of the patient, the two sisters and the daughter of the sister with thrombotic symptoms. A sole survivor from the paternal side of the family, a sister of the patient’s father, offered to be tested as well. Informed consent forms were completed and the patients were counselled prior to testing. PCR testing of the patient’s mother revealed the

![Figure 1: Results of Factor V Leiden mutation screens on the patient and her family.](image1)

![Figure 2: Results of the MTHFR mutation screens on the patient and her family.](image2)

![Figure 3: Results of the Prothrombin mutation screens on the patient and her family.](image3)

![Figure 4: Family tree of the patient showing affected family members.](image4)
The F2G20210A mutation is found in about 1-3% of Caucasian populations, but is less common in Hispanics, African-Americans and very rare in people of Asian descent.[3,4,5,6]

The MTHFR C677T mutation is surrounded by controversy regarding its implication in the aetiology of thrombosis and its role when in the presence of the other two mutations needs further investigation.[10,11,12,13] One study by Alluri et al demonstrated that a significant group of patients with ischemic stroke associated with hyperhomocysteinemia had an increased incidence of the MTHFR C677T mutation[14] and in addition the mutation has been found to be more common in younger persons with atherosclerotic stroke. In other study aimed at substantiating the hypothesis that the presence of the MTHFR C677T mutation could be a risk for increased venous thrombosis, the previous findings were not confirmed.[15,16] In a recent study it was demonstrated that leg ulceration of the lower extremities has been associated with the presence of the MTHFR mutation in either the hetero- or homozygous form.[17]

Our patient showed positivity in the heterozygous form for all three mutations. Positivity in all three mutations has been reported previously, but to our knowledge there has not been a report of triple heterozygosity with thrombotic tendencies. Most of the reported cases have been homozygous/ heterozygous mixed. During our dealings with this family, we did not experience any aversion or hesitancy against testing, nor intrusion into their privacy. All members agreed to be tested of their own free will and went to considerable trouble, travelling long distances to make sure that they were tested. Counselling was provided by a qualified consultant and it was stressed that a negative mutation result did not necessarily protect them from thrombotic incidents in the future. The family members with thrombotic symptoms having experienced multiple thrombotic incidents were already well informed about thrombosis even though at that stage, they had no diagnosis. Those with the mutation and thrombotic tendencies were asked if their positive mutational status would change their lives replied ‘that their lives had already changed as a result of already experienced thrombotic episodes’. The asymptomatic daughter with the Prothrombin G20210A mutation said that she would not change her lifestyle even though she was a carrier of the mutation but that she was relieved that her daughter had no sign of the mutation. Counselling was provided pre- and post-testing. Ethics approval for this study was obtained from the Ethics Committee of the Faculty of Health Sciences (ETOV 103/2010).

Even with our small family group, the experience was similar to some of those expressed in a 2007 study performed by Heshka et al[18] who found that participants in their study had no regrets about participation and in general thought that the results would only have a small impact on their change of behaviour regarding their own health issues.

REFERENCES

C677T variant on risk of venous thromboembolism: interaction with factor V Leiden and prothrombin (F2G20210A) mutations. *Br J Haematol*; 103:42-44.


