General information

- Germline pathogenic variants (GPV- including class 4 likely pathogenic and class 5 pathogenic variants) in the RUNX1 gene are associated with Familial Platelet Disorder and associated Myeloid Malignancy (OMIM #601399) (also referred to RUNX1-FPDMM) and follow an autosomal dominant inheritance pattern.
- Individuals with RUNX1-FPDMM have lifelong symptoms of easy bleeding/bruising (=90%) due to low platelet counts and/or dysfunctional platelets. They can also have skin manifestations (=50%). Only a minority of RUNX1 heterozygotes remain symptom-free3.
- RUNX1 heterozygotes are at increased risk of acute myeloid leukaemia (AML) and myelodysplastic syndrome (MDS) (25-50%)5.
- 50% of RUNX1 heterozygotes will have a known family history of haematological malignancy.
- Haematological malignancy in the setting RUNX1-FPDMM is not thought to be curable with chemotherapy alone; HSCT is almost always required in eligible patients.

Associated cancer risks

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Risk Information</th>
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<tbody>
<tr>
<td>MDS/AML</td>
<td>Lifetime risk = 25-50% (mean age = 33 years ranging from early infancy to later adulthood)5,6.</td>
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<tr>
<td>Lymphoid malignancy</td>
<td>Risk not known. =25% of families have at least one member with lymphoid malignancy5.</td>
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</tbody>
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Management recommendations

**Surveillance**

- All patients with RUNX1-related thrombocytopenia should be referred to a haematologist with specialist interest in Haemostasis and offered registration with a UK Haemophilia Centre.
- Planned and unplanned invasive procedures including dental procedures, pregnancy and delivery should be discussed with the patient’s Haemophilia Centre.

No clinical practice guidelines exist relating to surveillance for myeloid malignancies. There is lack of evidence regarding the utility of surveillance (type and frequency)3.
- All patients should be offered advice about symptom awareness.
- Patients need to seek medical advice promptly, if they develop worsening bleeding/bruising or any constitutional signs and symptoms of MDS/AML (e.g., fatigue, infections, bleeding, and skin changes).
- You can find more information regarding additional surveillance options in the FAQs here: https://www.ukcgg.org/information-education/ukcgg-leaflets-and-guidelines/

- Referral to haematology of all RUNX1 heterozygotes who develop a blood phenotype (pre-malignant/malignant) for monitoring and follow up (if not already under the care of haematologist).

**Transplant considerations**

- Where possible allogeneic haematopoietic stem cell transplant using related donors with pathogenic germline RUNX1 variants should be avoided due to risk of donor cell-derived leukaemia2,7.
- Urgent referral to Clinical Genetics of potential donor at-risk relatives for genetic counselling and consideration of germline testing.

**Lifestyle advice**

- Use of medications that may increase risk of bleeding or affect platelet function (e.g., anticoagulants, NSAIDs and anti-platelet agents) should be discussed with the patient’s Haemophilia Centre.
- Encourage patients to discuss work or leisure activities that place them at risk of trauma or bleeding with their Haemophilia Centre.
- Provide information on the benefits of smoking cessation, maintaining a healthy weight and minimising exposure to chemicals and radiation to lower the chance of developing haematological cancer.

**Family matters**

- Refer to clinical genetics for further genetic counselling and for discussion of predictive genetic testing in at-risk family members (if not seen in genetics previously). Genetic counselling may be provided in some Haemophilia Centres.
- The age at which predictive testing is offered to asymptomatic at-risk children should be individualised taking into account the genotype and family history, in shared decision making with the family.
- Refer to clinical genetics for discussions on reproductive options, where applicable.

Key references


Patient resources

- Under development by UKCGG in collaboration with Leukaemia Care and MDS UK Patient Support Group
- https://www.runx1-fpd.org/intro-patient