Individuals with Pathogenic Variants in *RUNX1*: Management Guidelines for Healthcare Professionals

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-free[4].
- *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

MDS/AML	Lifetime risk ≈25-50% (mean age ≈33 years ranging from early infancy to later adulthood)[5,6].
Lymphoid malignancy	Risk not known. ≈25% of families have at least one member with lymphoid malignancy[5].

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 haematology).
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 leukaemia[2,7]. - 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

1. https://www.ukcgg.org/information-education/ukcgg-consensus-meetings/
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3. Speight B, et al., 2023. Germline predisposition to haematological malignancies: Best practice consensus guidelines. Br J Haematol. 2023 Feb 6. doi: 10.1111/bjh.18675. Epub ahead of print. PMID: 36744544.
4. Deuitch *et al*, 2021. *RUNX1* Familial Platelet Disorder with Associated Myeloid Malignancies. GeneReviews® https://www.ncbi.nlm.nih.gov/books/NBK568319/
5. Brown AL, et al., 2020. RUNX1-mutated families show phenotype heterogeneity and a somatic mutation profile unique to germline predisposed AML. Blood Adv. Mar 24;4(6):1131-1144. doi: 10.1182/bloodadvances.2019000901. PMID: 32208489; PMCID: PMC7094007.
6. DiFilippo EC, et al., 2020. Spectrum of abnormalities and clonal transformation in germline RUNX1 familial platelet disorder and a genomic comparative analysis with somatic RUNX1 mutations in MDS/MPN overlap neoplasms. Leukemia. doi: 10.1038/s41375-020-0752-x.. PMID: 32060405.
7. Simon L, et al., 2020. High frequency of germline RUNX1 mutations in patients with RUNX1-mutated AML. Blood. May 21;135(21):1882-1886. doi: 10.1182/blood.2019003357. Erratum in: Blood. 2022 Apr 7;139(14):2259. PMID: 32315381.

Patient resources

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

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