Individuals with Pathogenic Variants in ETV6: Management Guidelines for Healthcare Professionals

General information

- Germline pathogenic variants (GPVs- including class 4 likely pathogenic and class 5 pathogenic variants) in the ETV6 gene are associated with Thrombocytopenia 5 (OMIM #16216) (also referred to as ETV6 Thrombocytopenia and Predisposition to leukaemia) and follow an autosomal dominant inheritance pattern.
- ETV6 heterozygotes are at increased risk of B-cell acute lymphoblastic leukaemia (B-ALL) and other haematological malignancies (myelodysplastic syndrome, acute myeloid leukaemia and myeloproliferative neoplasms).
- The median age of onset of a haematological malignancy is 11 years (range from two to 82 years)\(^1,5\).
- ETV6 heterozygotes have lifelong, mild to moderate thrombocytopenia (90% of cases) with absent to moderate bleeding tendency.

Associated cancer risks

| Haematological malignancies | • Lifetime risk =30% (median age of onset =11 years). About two thirds will develop B-ALL\(^5,5\). |
| Solid tumours               | • The exact risk is yet to be defined\(^4\). |

Management recommendations

Surveillance

- All patients with ETV6-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 easy bleeding/bruising or any constitutional signs and symptoms of ALL (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 ETV6 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 ETV6 variants should be avoided due to risk of donor cell-derived leukaemia\(^2\).
- 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