Individuals with Pathogenic Variants in DDX41: Management Guidelines for Healthcare Professionals

General information\(^{4,5,6}\)

- Germline pathogenic variants (GPV- including class 4 likely pathogenic and class 5 pathogenic variants) in the DDX41 gene are associated with Myeloproliferative/lymphoproliferative neoplasms, familial (multiple types), susceptibility to (OMIM #616871) (also referred to as DDX41-related haematologic malignancy predisposition syndrome) and follow an autosomal dominant inheritance pattern.
- DDX41 heterozygotes are at increased risk of haematological malignancy, mainly myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML).
- Overall ~3-8% of patients diagnosed with myeloid malignancy have DDX41-related disease (3% in MDS, 5% in AML and 8% in older AML)\(^1\).
- DDX41 germline variants are the most common genetic predisposition to adult MDS/AML and are usually associated with late-onset disease (57 to 70 years), male gender skewing (3:1), hypocellular bone marrow and normal karyotype.
- A personal history of cytopenia has been reported in around 50% of DDX41 heterozygotes.
- A family history of haematological malignancy is reported in 30% of DDX41 heterozygotes.
- DDX41 germline AML has a high probability of achieving complete remission (>90%) following intensive chemotherapy but has a high relapse rate; there is no strong evidence on the role of Venetoclax-Azacitidine in this entity nor on the place of transplant.
- Somatic mutation of the other allele is common in DDX41 germline AML.

Associated risks

MDS/AML

- As DDX41 is a newly discovered entity the penetrance estimates are likely to be affected by ascertainment bias and may be lower than published estimates.
- Lifetime risk up to ≈50% with nearly all risk conferred after age 40 (mean age =68 years)\(^6\).

Management recommendations

Surveillance

No clinical practice guidelines exist. 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 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 DDX41 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 hematopoietic stem cell transplant using related donors with pathogenic germline DDX41 variants should be avoided due to risk of donor cell-derived leukaemia\(^2,7,8\).
- Urgent referral to Clinical Genetics of potential donor at-risk relatives for genetic counselling and consideration of germline testing.

Lifestyle advice

- 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).
- Predictive testing is normally considered in adulthood (specific age cut-off does not exist).
- Refer to clinical genetics for discussions on reproductive options, where applicable.

Key references

1. [https://www.ukcgg.org/information-education/ukcgg-consensus-meetings/](https://www.ukcgg.org/information-education/ukcgg-consensus-meetings/)

Patient resources

- Under development by UKCGG in collaboration with Leukaemia Care and MDS UK Patient Support Group