Case study

A 23-year-old female patient was diagnosed with spindle cell sarcoma aged 21.

She had a strong family history of cancer, including multiple paternal relatives with colorectal, endometrial and urinary tract cancers. One of her paternal aunts had a brain tumour aged 19. Her father was known to carry a pathogenic variant in *MSH2*.

In addition, one of her paternal cousins had a known diagnosis of Ataxia Telangiectasia and a diagnosis of breast cancer in her 30s.

Her oncology team arranged testing on DNA from her tumour. Analysis was extended beyond standard-of-care testing at the request of the treating team.

A number of variants were identified at high variant allele frequencies:

Variant	Variant allele frequency
ATM: c.875C>T, p.(Pro292Leu)	85.3%
MSH2 c.150_191delinsCC p.(Leu51ProfsTer20)	80.8%
RB1 c.958C>T, p.(Arg320Ter)	70.8%
TP53 c.455del p.(Pro152ArgfsTer18)	76.8%

Follow-up germline testing was offered for the *MSH2* variant, given that:

- MSH2 is one of the "most actionable" genes, variants (>30-40% VAF and (likely) pathogenic) in which should be considered for germline follow-up regardless of tumour in which they have been identified
- Known family history of Lynch Syndrome such that germline origin of the variant highly likely
- **Germline origin of the *MSH2* variant was confirmed.**

The known family history of Ataxia Telangiectasia also increases suspicion that the identified *ATM* variant is of germline origin. However, confirmatory germline testing was **not** offered for the *ATM* variant identified in her sample, considering:

- The variant in question is **not** one of the variants (truncating variant/exception variant) for which cascade testing for cancer predisposition is recommended [1]
- Testing for recessive traits is not offered if the population carrier frequency is less than 1 in 70 [2]

Given that this patient is aged <30 years, follow-up targeted testing for the *TP53* c.455del variant could be considered. In this patient's case, diagnostic R216 testing (TP53, POT1) was offered in view of her personal history of sarcoma and her paternal aunt's diagnosis of a malignant brain tumour in her teens [2]. A specific request was made to the laboratory team to comment on the presence/absence of the variant picked up on tumour testing. **No variants were detected, suggesting the *TP53* variant was somatic in origin.**

In this case, follow-up testing for the *RB1* variant was **not** recommended. Although sarcomas have been reported in patients with constitutional RB1 variants, they are typically

osteosarcoma, leiomyosarcoma or rhabdomyosarcoma, and typically preceded by a history of retinoblastoma. Although *RB1* is "highly actionable" gene, this was considered an off-tumour finding. Somatic co-mutation of *RB1* and *TP53* is a common finding in sarcoma. The absence of the *TP53* variant in the germline DNA of the patient, as well as the similar VAF of these two variants provides further evidence favouring somatic origin of the *RB1* variant.

Key points

This case highlights a number of key points.

- Germline genetic testing should be offered where clinically appropriate, based on clinical judgement and considering clinical factors, patient age and family history, and genotype, as well as variant allele frequency.
- Inadvertent identification of known familial germline variants is likely when analysis of tumour-derived DNA includes testing of the relevant gene.
- Finding a number of variants at approximately the same VAF is not an unusual finding in cancer, and typically indicates a clonal event. However, in this instance, distinguishing between variants of somatic and variants of germline origin is impossible in the absence of a paired normal sample.
- When considering testing, clinical teams should follow gene-specific UK recommendations for variant interpretation and reporting, where they exist.
- In cases where it is not immediately obvious that these considerations have been met, we encourage discussion at locoregional or national MDT to determine if testing is justified.

1. UKCGG, *UKCGG/CStAG statement on reporting practice for variants in ATM v.1.0*. 2024: https://www.ukcgg.org/information-education/exceptional-variantsgene-specific-variant-reporting/.
2. NHSE, *National Genomic Test Directory Testing Criteria for Rare and Inherited Disease version 7.1*. 2025: https://www.england.nhs.uk/publication/national-genomic-test-directories/.