Sarcoma and germ-line *DICER1* mutations

Authors' reply

We thank de Kock and Foulkes for their letter and compelling summary table of *DICER1* mutations linked to sarcomas. For population-based studies such as ours,[1] statistically robust methods are required to identify genes enriched in pathogenic variation.[2,3] The principles of controls, replication sets, multiple test correction, and independent sources of experimental evidence, should be regarded as essential evidence for causality. Such an approach was the basis for reporting enrichment of pathogenic variants in *ATM*, *ATR*, *BRCA2*, and *ERCC2* in our study.[1]

We have studied *DICER1* in the cohort, but did not see an excess of putatively pathogenic rare variation compared with the limited set of controls available for this comparison (11 [1%] rare missense variants in our 1162 cases and five [2%] in 235 controls; odds ratio 0·44 [95% CI 0·14–1·47], p=0·231). Additionally, no frameshift, nonsense, or essential splice site variants were seen in *DICER1*, although these types of mutations were a consistent feature of genes such as *TP53*, *ERCC2*, and *BRCA2* in our cohort. We note that the data from de Kock and Foulkes contained multiple mutations of this type in *DICER1*. Finally, we reviewed the pedigrees of all cases in whom we observed missense variants in *DICER1*, and did not observe phenotypes typically associated with mutations in this gene (eg, pleuropulmonary blastoma, renal, ovarian, or thyroid tumours).[4]

This might be because of the age of our population or a lack of power to identify sarcoma subtype-specific excess risk or both. As de Kock and Foulkes point out, the population we studied was focused on adult-onset sarcomas (90% of sarcomas arise in adults), whereas the data on *DICER1*-associated sarcomas are from patients with a median age of 12 years (range 6 weeks–53 years).[1] It is also possible that different types of mutation, including non-coding changes or structural variants, might affect *DICER1*—these types of variation could become apparent using whole genome sequencing, for example. Adequately powered studies that span the full range of ages and sarcoma subtypes, and which encompass the full range of genetic variation, will be essential for any complete view of the genetic basis of sarcomas.

We declare no competing interests.

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4 Foulkes WD, Priest JR, Duchaine TF. DICER1: mutations, microRNAs and mechanisms. *Nat Rev Cancer* 2014; **14:** 662–72.