

Are sarcomas hereditary?

Oncologists who treat sarcomas are frequently asked by their patients about the cause of their cancer. Until now, with the exception of Li-Fraumeni syndrome,¹ hereditary retinoblastoma,² and neurofibromatosis, which could be excluded by history and physical examination, the answer was usually: “almost all cases of sarcomas are not hereditary”. A genetic study by Mandy Ballinger and colleagues³ reported in *The Lancet Oncology*, now throws this answer into a different light. In one of the most important studies on sarcomas in recent years, the investigators performed targeted exon sequencing on 72 genes, selected because of associations with increased cancer risk, in 1162 patients in four sarcoma cohorts, and using a case-control rare variant burden analysis found that about half of the patients had an excess of pathogenic (and potentially aetiological) germline variants.

170 (15%) patients had two or more primary cancers. Although the risk of cancer in first-degree relatives was increased only slightly, the risk of sarcoma more than doubled compared to risk in the general population (standardised incidence ratio 2.65, 95% CI 1.6–4.4). Similarly, the risks of brain tumours, breast cancer, and melanoma were also increased in first-degree relatives compared with the general population. It would be of interest to see whether this increased risk persisted after correcting for *TP53* abnormalities.

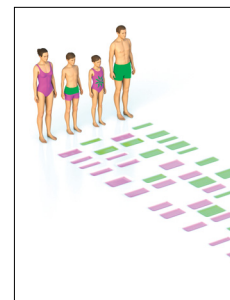
Rare variants from the DNA analysis were stratified into three classes approximating the International Agency for Research on Cancer clinical classification for genetic variation according to the risk of causing disease, from known variants (class 5 [C5]), to expected variants (class 4 [C4]), to predicted variants (class 3 [C3]). There were 956 C3–5 variants found in 638 patients, including 100 C4 variants in 95 patients and 127 C5 variants in 122 patients. Individuals with C4–5 variants developed their first cancer at a younger median age than did patients with C3 variants or no variants. Progressively earlier cancer diagnosis was noted in patients with increasing numbers of C3 variants. The most striking effects were seen among 36 individuals who carried either biallelic variants in one gene or C4 or C5 variants in two or more genes, with the same median age of 34 at first cancer diagnosis as patients with variants of *TP53*.

Several of the genes noted in Ballinger’s report have been previously linked to sarcomas, whereas some are novel. The most notable finding is not the nature of the abnormalities but their prevalence. The genes that seemed to contribute most to the risk of sarcoma included not only *TP53*, but also genes implicated in DNA damage sensing (*ATM*, *ATR*) and homologous recombination (*BRCA2*). Although *BRCA2* is commonly associated with increased risk of breast, ovarian, and (less commonly) pancreatic cancer, it has rarely been linked to sarcomas.⁴

The authors also noted deleterious variants of *ERCC2*, a helicase involved in nucleotide excision repair associated with the rare, autosomal recessive, cancer-prone syndrome, xeroderma pigmentosum (type D), not previously associated with sarcomas. Mutations in *ERCC2* affect DNA binding, DNA-damage sensing, helicase activity, and basal transcription, and cause an increased sensitivity to cisplatin (a drug used routinely for osteosarcoma, but rarely for soft-tissue sarcomas).⁵ Whether germline mutations of *ERCC2* lead to increased response to cisplatin in affected patients with sarcoma, or increased toxicity, remains to be explored. DNA-damage is clearly linked to sarcoma development after radiation, so the involvement of DNA damage response–repair genes in promoting sarcomagenesis is very plausible. Finally, the role of germline mutations in apparently sporadic sarcomas remains to be fully explored. What is the fraction of de-novo mutation in these diseases?

The model for hereditary sarcomas is Li-Fraumeni syndrome, thought to be driven by mutations in *TP53*⁶ and associated with increased risk of several cancers including soft-tissue sarcomas, osteosarcoma, breast cancer, leukemia, adrenal cortical carcinoma, and less frequently melanoma and carcinomas of the lung, pancreas, cervix, and prostate.¹

Although Ballinger and colleagues’ also noted mutations in *TP53*, the observed polygenic mutation and a recessive pattern of inheritance are novel in the study of heritable sarcomas. Furthermore, Ballinger and colleagues’ results might explain why some patients fit the clinical description of Li-Fraumeni syndrome but have no abnormality in *TP53*.⁷ Elucidation of the interaction of the pathways regulated by the multiple



Lancet Oncol 2016

Published Online

August 4, 2016

[http://dx.doi.org/10.1016/](http://dx.doi.org/10.1016/S1470-2045(16)30292-3)

[S1470-2045\(16\)30292-3](http://dx.doi.org/10.1016/S1470-2045(16)30292-3)

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[S1470-2045\(16\)30147-4](http://dx.doi.org/10.1016/S1470-2045(16)30147-4)

genes found in this study is needed to better understand how the polygenic abnormalities contribute to sarcoma development.

Specific causative mutations for sarcoma subtypes were not identified, as Ballinger and colleagues did not break down their analysis by sarcoma subtype. However, although the clinical usefulness of identifying blanket genetic mutations in sarcoma is arguably limited, hereditary tumour syndromes often involve multiple sarcoma types and some cancers that clearly are not sarcomas. Thus, this study might provide insight into hereditary cancer syndromes in which sarcomas often occur.

Further studies of genetic abnormalities in patients with sarcomas are sorely needed. In paediatric cancers, mostly not sarcomas, Zhang and colleagues⁸ found that 95 (8%) of 1120 cases had pathogenic or probably pathogenic genetic abnormalities. In a smaller paediatric series of 59 patients, Chang and colleagues⁹ found 20 germline abnormalities in 16 (27%) patients, with reportable germline abnormalities in almost half (12% of all patients studied). The data on polygenic inheritance presented by Ballinger and colleagues suggest that genetic abnormalities, heretofore not considered reportable, may still have major clinical implications.

Thus, when patients ask if their sarcomas are hereditary, the answer is now: "Yes, at least partly, in most cases". Ballinger and colleagues' study³ opens up a new series of challenges. Their data, especially if confirmed in other series of patients with sarcoma, suggest that offering germline testing for all patients with sarcomas might be warranted, especially in the

context of a comprehensive assessment of family history. Targeted therapy for sarcoma has, with few notable exceptions, been unrewarding. Although precisely how these new genetic findings could lead to improved therapeutic outcomes is not yet clear, improved understanding of the complex interactions caused by multiple genetic abnormalities could help to identify new therapeutic targets.

*Robert S Benjamin, Andrew Futreal

Department of Sarcoma Medical Oncology (RSB) and Department of Genomic Medicine (AF), The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA
rbenjami@mdanderson.org

We declare no competing interests.

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