Germline testing of sarcoma revealed frequent mutations in genes involved in DNA repair, RNA metabolism, and epigenetic regulation

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BACKGROUND

Sarcomas are rare mesenchymal tumors whose etiology remains largely unclear. The germline genetic susceptibility to sarcoma is poorly characterized.

METHODS

We conducted targeted sequencing of a 139-gene panel (OncoPanscan, Genetronhealth) of the genomic DNA from 779 patients with sarcoma and quantified the prevalence of pathogenic or likely pathogenic germline variants.

RESULTS

The median age of this cohort was 48 (0-88) years, and 72% were soft tissue sarcoma (STS), 13% were osteosarcoma, 15% were unknown. Nineteen (2.4%) patients had a variant that mapped to a known sarcoma-associated cancer predisposition syndrome gene (CHEK2, Dicer1, Nf1, Recql4, SMARCA4, TP53, WRN). 39 (5.0%) patients harbored deleterious mutations in DNA damage repair (DDR) genes including Brca2 (n = 1), Bard1 (n = 1), Palb2 (n = 1), Rad50 (n = 1), Rad51D (n = 1) of the homologous recombination repair (HRR) pathway, Msh6 (n = 2), Pms2 (n = 2), Pms1 (n = 1) of the mismatch repair (MMR) pathway, and Recql (n = 3), Recql4 (n = 1), WRN (n = 2) of the DNA helicase family.

SMARCA4 and SMARCE1 encode key components of the BAF chromatin-remodeling complex and mutations of these two genes are known to drive rhabdoid tumor predisposition syndrome 2 and inherited spinal meningioma, respectively. Interestingly, we observed three sarcoma patients harboring truncating variants in SMARCA4 (n = 1) or SMARCE1 (n = 2). Dicer1 encodes a component of the microRNA biogenesis machinery and its deficiency was recently linked to sarcoma. Deletion of Dicer1 in osteosarcoma patients reduced expression of Sbds, which encodes a ribosomal maturation factor and is mutated in 90% of Schwachman-Bodian-Diamond syndrome cases. In addition to two patients with Dicer1 truncating variants, we observed 11 sarcoma patients harboring the same pathogenic Sbds c.258+2T>C mutation.

CONCLUSION

Our study provides novel insights regarding the contribution of germline mutations to the pathogenesis of sarcomas. These findings have the potential to identify sarcoma patients who may benefit from precision therapy and genetic counseling.