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MYELOID NEOPLASIA

Recurrent *CLTC*::*SYK* fusions and *CSF1R* mutations in juvenile xanthogranuloma of soft tissue

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Background. Juvenile xanthogranuloma (JXG) is a histiocytic neoplasm that usually presents in the skin. Rarely, extracutaneous localizations occur; the genetic drivers of this clinical variant of JXG remain incompletely characterized.

Methods. Tumor samples of extracutaneous JXG were obtained through the Dutch Nationwide Pathology Databank and analyzed with an innovative sequencing technique capable of detecting both small genomic variants and gene rearrangements – called targeted locus capture-based next-generation sequencing (TLC-NGS). TLC-NGS leverages DNA crosslinking and fragmentation and is therefore particularly suitable for analyzing decades old FFPE samples in which DNA is inherently crosslinked and fragmented. Pseudonymized clinical data and images were provided by the treating physicians of included patients.

Results. We identified 16 children and 5 adults with extracutaneous JXG, diagnosed between 1987 and 2022 at 10 different hospitals across The Netherlands. Targetable kinase alterations were detected in tumors of 16/16 children and 1/5 adults. Alterations included *CLTC*::*SYK* fusions in 6 children and *CSF1R* mutations in 7 others; all below 2 years of age with soft tissue tumors. One had a *CSF1R* mutation and *MRC1*::*PDGFRB* fusion. Most were treated surgically, although spontaneous regression occurred in 1/6 with *CLTC*::*SYK* and 2/7 with *CSF1R* mutations, underscoring that treatment is not always necessary. Tumors with *CLTC*::*SYK* fusions generally lacked Touton giant cells but exhibited many other histologic features of JXG and concordant methylation profiles. Using multispectral immunofluorescence, phosphorylated–SYK expression was localized to $CD163^{+}$ histiocytes; tumors with *CLTC*::*SYK* fusions also demonstrated mTOR activation, cyclin D1 expression, and variable phosphorylated-ERK expression. $BRAF^{V600E}$ was detected in 1 child and 1 adult with CNS-JXG; both responded to BRAF inhibition. Finally, a *TPM3*::*NTRK1* fusion or *MAP2K1* deletion was detected in 2 children with systemic JXG who experienced spontaneous disease regression.

Conclusion. This study advances the molecular understanding of histiocytic neoplasms and may guide diagnostics and clinical management of patients.

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