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POSTER ABSTRACTS

603.LYMPHOID ONCOGENESIS: BASIC

High-Hyperdiploid Acute Lymphoblastic Leukemia in Children with LZTR1 Germline Variants

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Introduction

Firstly described in 1967, hyperdiploidy (HD) is the most frequent genetic abnormality in B-cell- precursor acute lymphoblastic leukemia (BCP-ALL) in children, comprising about 25% of all cases. A not yet exactly defined proportion have predisposing pathogenic germline variants in DNA repair pathway genes, chromatin remodeling factors, transcription factors regulating B-cell development (particularly *ETV6*) or receptor tyrosine kinases pathway genes like *RAS/RAF*. Among the latter, mutations have mostly been described in *PTPN11* and *SOS1*, but not yet in other components of this central regulatory hub of cellular communication. Germline loss-of-function (LOF) *LZTR1* mutations are typically linked to hereditary nerve sheath tumors. However, it remains largely unknown, if other tumor entities are associated with *LZTR1* LOF germline mutations, potentially broadening the spectrum of malignancies associated with RASopathies.

Aim

Our aim is to understand the frequency and the impact of *LZTR1* germline variants in HD BCP-ALL of childhood.

Material and Methods

We analyzed WES data of 283 children with BCP-ALL for the presence of pathogenic variants in the *LZTR1* cancer predisposition gene. For a part of the detected variants, we performed further functional analyses to investigate the effect of the alteration on protein function. We applied a *Drosophila* model that is particularly suited for functional evaluation of Ras pathway activity.

Results

We identified *LZTR1* germline variants in 10/283 (3.5%) patients (Figure 1). Interestingly, in 6 out of 283 (2.1%) children the *LZTR1* variants were classified as pathogenic/likely pathogenic (P/LP). The majority of patients (5/6) harboring a P/LP germline *LZTR1* variant presented with a HD BCP-ALL. Only two of our patients showed concomitant phenotypic features indicative of an underlying syndromic condition. Patient P1 presented with a HD BCP-ALL at the age of 9 years and mild psychomotor delay. Sequencing revealed a likely pathogenic variant (p.Arg283Trp) that was not yet reported in association with RASopathy syndromes. The second child P8, also diagnosed with a HD BCP-ALL, carried a well-known autosomal dominant mutation described in Noonan syndrome (NS) variant (p.Gly248Arg). The child was characterized by facial dysmorphism, as well as mild developmental delay, although a diagnosis of NS was not established prior to development of the BCP-ALL. The other three patients had no clinical peculiarities other than HD BCP-ALL.

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We functionally characterized patient derived LZTR1 variants in dLztr1-depleted ISC. Like wild-type hLZTR1 ^{wt}, hLZTR1 ^{p.Arg283Trp} and hLZTR1 p.Lys761Arg restored control-like ISC lineage production, suggesting that hLZTR1 p.Arg283Trp and hLZTR1 p.Lys761Arg still regulate Ras ubiguitination. In contrast, hLZTR1 ^{p.Tyr535Ter} results in even 1.8-fold higher ISC lineage production than dLztr1-RNAi. Beyond ISC production as a readout, we employed a second experimental paradigm directly addressing Ras signalling activity with a translocating modified ERK sensor. In line with Ras activity control of LZTR1, hLZTR1^{wt} significantly reduced ERK activity, while the putatively LOF variant hLZTR1 ^{p.Tyr535Ter} variant significantly increased Ras pathway activation by 1.4-fold over controls. We also noticed that hLZTR1 ^{p.Tyr535Ter} induced extensive membrane blebbing and nuclear fragmentation of GFP positive cells likely indicating programmed cell death. Quantification of apoptotic cells revealed an 11.1-fold increase compared to controls, which was not observed for hLZTR1 ^{p.Arg283Trp} and hLZTR1 ^{p.Lys761Arg}.

Most notably, forced expression of hLZTR1 ^{p.Arg283Trp} andhLZTR1 ^{p.Tyr535Ter} increased mitotic recombination by 4-fold and 3.4fold, respectively, which was not observed for the hLZTR1 ^{p. Lys761Arg} variant.

Conclusion

In our cohort, approximately 2% of all children with BCP-ALL harboured a P/LP LZTR1 germline variation, not necessarily linked with clinical appearance of Noonan-syndrome-like features, but to the development of a high hyperdiploid karyotype. By applying a Drosophila model, we demonstrated that patient-derived LZTR1 germline variants affect RAS pathway activation, ERK accumulation, cell proliferation, DNA recombination and apoptosis. Figure 1:

Depiction of the ten LZTR1 variants detected in an unselected pediatric cohort of 283 BCP-ALL patients



Disclosures No relevant conflicts of interest to declare.

Figure 1

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