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509.BONE MARROW FAILURE AND CANCER PREDISPOSITION SYNDROMES: CONGENITAL

Clonal Hematopoiesis in Cartilage-Hair Hypoplasia

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Background: Cartilage-hair hypoplasia (CHH) is an autosomal recessive disorder characterized by short stature, hypotrichosis, combined immunodeficiency, and macrocytic anemia. CHH is caused by germline mutations in the *RMRP* gene encoding the RNA component of the mitochondrial RNA processing endoribonuclease. CHH is heavily enriched in the Finnish (1 in 23000 births) and the Amish (1 in 1340 births) populations. Transient macrocytic anemia is common in children with CHH, whereas severe hypoplastic macrocytic anemia is only present in 10% of pediatric CHH patients and can be treated with allogeneic hematopoietic stem cell transplantation (HSCT). The mechanism behind hypoplastic anemia in CHH is unknown: while erythroid differentiation from hematopoietic stem cells is impaired *in vitro* in CHH, immune dysregulation may also play a role in this phenotype.

Clonal hematopoiesis is a common phenomenon of aging. Patients with inherited and immune-mediated bone marrow failure (BMF) show distinct spectra of clonal hematopoiesis mutations, reflecting context-specific selection of hematopoietic stem cell clones. However, the spectrum of clonal hematopoiesis is yet to be characterized in CHH.

Methods: To assess the landscape of somatic alterations in hematopoietic cells in CHH, we performed whole exome sequencing (WES) on twelve bone marrow samples of four pediatric (age 4 to 13 years) and eight adult (age 20 to 52 years) unrelated subjects with CHH. Three children with CHH had severe hypoplastic anemia at the time of DNA sampling and three patients underwent HSCT during follow-up. Seven adults with CHH had normal blood counts and no severe immune phenotypes despite other clinical manifestations of CHH. Matched skin fibroblast samples were available for five CHH adults in the cohort for whom we performed tumor-normal variant calling. For the remaining cases, variant calling was based on tumor-only samples and stringent filtering to exclude germline variants. Additionally, we queried the FINRISK dataset, a Finnish cohort comprising WES and SNP microarray data from 10 129 participants, for the presence of CHH associated *RMRP* variants and evaluated their association with clonal hematopoiesis of indeterminate potential (CHIP) and mosaic chromosomal alterations (mCAs).

Results: The median WES coverage of the bone marrow samples was 445x (347-505). Eleven out of 12 patients were homozygous for the *RMRP* founder variant n.71A>G and one patient was compound heterozygous for two pathogenic *RMRP* variants. We observed no somatic reversion of the germline *RMRP* variants. Two pediatric patients had variants in the CHIP genes: CHH1 (age 13 years) with *TP53* hotspot variant R175C (variant allele frequency, VAF 0.006) and CHH2 (age 4 years) with *BCORL1* P1681Qfs*20 (VAF 0.025). One fifty-year-old patient had a *DNMT3A* splicing variant c.1555-1G>C (VAF 0.022), likely consistent with CHIP observed in older general population. To identify clonal hematopoiesis outside the classical CHIP genes, we performed conservative filtering of the remaining somatic variant calls, resulting in a list of 36 high-confidence coding variants (VAF >0.02). These variants were present in 10 out of 12 patients; no recurrent genetic alterations were observed. Finally, the analysis of the FINRISK dataset revealed eleven participants with *RMRP* disease-associated variants; each participant had one heterozygous *RMRP* variant. No enrichment of CHIP variants or mCAs were observed in carriers of *RMRP* variants.

Conclusion: We observed *TP53* and *BCORL1* mutations in the bone marrow samples of pediatric patients with CHH. In comparison to other CHIP-associated conditions, *BCORL1* variants are disproportionately represented in immune-mediated aplastic anemia, potentially suggestive of similar immune-mediated origin of hypoplastic anemia in CHH. *TP53* mutations are abundant in inherited BMF syndromes; however and in contrast to classical inherited BMF syndromes, CHH is not associated with increased risk of myeloid malignancies. No enrichment of classical or non-classical clonal hematopoiesis mutations were observed in adults with clinical CHH diagnosis or in *RMRP* variant carriers in the population-level FINRISK cohort. This is consistent with transient selection pressure on hematopoietic stem cells in childhood CHH. To our knowledge, our study is the first attempt to characterize the spectrum of clonal hematopoiesis in CHH.

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