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CLINICALLY-RELEVANT GERMLINE VARIANTS ARE COMMON IN CHILDREN WITH NON-MEDULLARY THYROID CANCER

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Objectives: The underlying genetic cause of non-medullary thyroid cancer (NMTC) in children is often unknown, hampering both predictive testing of family members and preventive clinical management. We investigated the potential heritability in the largest childhood NMTC cohort that has been genotyped to date.
Method: Using whole genome sequencing (WGS), we analyzed DNA from 97 patients with pediatric NMTC for the presence of germline variants in 779 genes, including 66 genes associated with autosomal dominant tumor predisposition syndromes and 40 previously-reported NMTC candidate susceptibility genes.
Results: In total, 15 of 97 patients (15%) carried a germline (likely) pathogenic (P/LP) variant in a well-known tumor predisposition gene (APC [n=1], BRCA2 [n=2], CHEK2 [n=4], DICER1 [n=4], HOXB13 [n=1], LZTR1 [n=1] MITF [n=1] and SLC24A6 [n=1]). Although clinical phenotype, family history, histology and somatic variants are all important factors in the recognition of an underlying genetic syndrome, around 50% of the clinically-relevant P/LP variants identified in this study were nevertheless absent from our initial differential diagnosis. In addition, nine variants of high interest were found in NMTC candidate susceptibility genes.
Conclusions: Genetic screening of a large, unbiased pediatric NMTC cohort detected a relatively high prevalence (15%) of P/LP germline variants in well-known tumor predisposing genes. The majority of the tumor predisposition syndromes detected by us are associated with a risk for second cancers for which additional surveillance is recommended, and additionally show autosomal dominant patterns of inheritance that enable pre-symptomatic genetic testing of at risk family members. The unexpected involvement of double-strand DNA break repair genes in nearly half of all cases with P/LP variants indicates a possible role for this pathway in the development of pediatric NMTC cases. Overall, the high prevalence of clinically-actionable germline variants leads us to strongly recommend family counseling and, preferably gene panel, testing for all childhood NMTC patients.