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Impact of rare synonymous variants on cancer predisposition

Background: Although synonymous variants do not alter protein sequences, they can influence gene regulatory functions like splicing, transcription factor binding, codon optimality, and mRNA stability. Their role in cancer predisposition and rare genetic disease development remains unclear. **Aim**: To evaluate the potential impact of rare synonymous variants in neuroblastoma (NB), a pediatric cancer originating from aberrant neural crest cell development. **Methods**: Whole-exome sequencing was performed on 724 NB patients to identify rare synonymous variants with an allele frequency below 0.01 in non-Finnish European population database. Variants in 675 cancer predisposition genes (CPGs) from five gene lists were analyzed. The identified variants were classified according to their function based on the Cancer Gene Census list of cancer-associated genes. SpliceAI assessed splicing impact using cut-offs (0.8, 0.5, 0.2). Variants were annotated by their distance from the nearest exon-intron boundary and occurrance in the first or last exon. The genes in which variants occurred were subject to gene enrichment analysis for ''Disease'' and ''Reactome'' categories. The impact of sSNV on trascriptional factor binding was evaluated building a consensus of open chromatin regions identified through DNaseI, Footprint and CHiP seq data. ATAC-seq data from 23 NB cell lines identified regulatory elements for mesenchymal (MES) and adrenergic (ADRN) NB identities. **Results**: We identified 3923 rare synonymous variants (0.84% of the variants annotated) in 543 CPGs, with a median of 5 mutations per gene. Synonymous variants were enriched in the 'tumor suppressor gene' category (TSG) (26.9%) compared to 'oncogenes' (6.7%). Of the identified genes, 191 (4.86%) had at least a mutation in their last exon, 60 (1.52%) in their first exon, and 28 (0.71%) in both exons. Gene enrichment analysis WebGestalt tool revealed that the 191 genes enriched specifically for NB disease category and DNA repair pathway. Interestingly, this enrichment was observed only with mutations in the last exon, suggesting their role in altering gene expression regulation, mRNA stability, or transcript termination. Most mutations were in tumor suppressor genes across all SpliceAI cutoffs. At the 0.5 cutoff, twenty-two genes, including SMARCA4, ATM, PALB2, FANCA and RTEL1, were identified across multiple gene lists. Synonymous variants in regulatory regions of adrenergic and mesenchymal NB had higher median CADD scores, suggesting their biological significance in altering the gene espression regulation. **Conclusions**: Our findings suggest that synonymous variants can influence splicing, gene regulation and consequently predisposition to NB. Variants in regulatory regions exhibit higher pathogenicity scores, suggesting involvement in gene regulatory mechanisms such as alterations of transcription factor binding sites. Additional studies are ongoing to investigate the role of other types of functional synonymous variants (splicing regulation, transcription factor binding, miRNA binding, codon optimality, and mRNA secondary structure). Further studies are also in progress to assess the potential impact of synonymous variants, on the previously described mechanism, in other pediatric tumors.

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