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Abstract

Post-GWAS Functional Analysis of the 11p11.2 Risk Locus Identifies *HSD17B12* as a Neuroblastoma Susceptibility Gene Involved in Lipid Metabolism †

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1. Introduction

Genome-wide association studies (GWASs) have contributed to the study of neuroblastoma (NB) genetics by identifying common risk variants that activate cancer-related processes associated with NB susceptibility.

2. Aim

This study aims to functionally characterize the 11p11.2 predisposition locus identified in our GWAS on 2101 cases and 4202 controls, evaluating how the regulatory variant and its target gene can influence NB development.

3. Methods

To identify functional variants, we annotated 72 candidate SNPs with functional data from public NB databases and validated the functional SNP's regulatory activity via luciferase assays in NB cells. The candidate SNP was predicted to map inside a GATA3 binding motif and differential GATA3 allele binding was evaluated using ChIP-qPCR. eQTL analysis and CRISPR/Cas9 genome editing allowed us to identify the target gene of the functional SNP. To evaluate its role in NB tumorigenesis, we correlated gene expression with clinical features using RNA-seq data from 498 tumors and performed MTT and invasion assays after gene silencing in NB cells. Targeted lipidomic assays were performed to study the involvement of the target gene in lipid metabolism.

4. Results

rs2863002T > C represents the candidate functional SNP of the risk locus. The rs2863002-C allele correlated with high expression levels of its target gene *HSD17B12*

and showed a lower binding affinity for the transcription factor GATA3 in NB cells, suggesting that it may alter the GATA3 binding motif. High *HSD17B12* expression levels correlated with poor prognosis and survival in NB tumors, and gene silencing in NB cells reduced proliferation and invasiveness, supporting the oncogenic role of *HSD17B12* in NB. Lipidomic results showed that *HSD17B12* silencing in NB cells altered lipid metabolism, affecting lipid molecules related to energy production and cellular membrane chemical-physical properties.

5. Conclusions

This study highlights the importance of the post-GWAS functional characterization of risk loci to identify new susceptibility genes and new biological mechanisms underlying NB predisposition.

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Data Availability Statement: Public ATAC-seq data are available in the NCBI Gene Expression Omnibus (GEO) under accession nos.: GSE80152, GSE138315, GSE80152, GSE136279, and GSE138293. Public DNase-I hypersensitivity (DHS) data are available in the NCBI Gene Expression Omnibus (GEO) under accession nos.: GSM736508 and GSM1008585. Public H3K27Ac ChIPseq data are available in the NCBI Gene Expression Omnibus (GEO) under accession no. GSE128463. Public GATA3 ChIPseq data are available in the NCBI Gene Expression Omnibus (GEO) under accession nos.: GSE94824, GSE65664, and GSE169616. Public RNA-seq data are available in the NCBI Gene Expression Omnibus (GEO) under accession no.: GSE62564. Public eQTL data are available in the public GTEx database v8 at https://gtexportal.org/home.

Conflicts of Interest: The authors declare that they have no conflicts of interest.