DELETIONS NEIGHBORING *TWIST1* IN PATIENTS WITH CRANIOSYNOSTOSIS AND/OR NEURODEVELOPMENTAL DELAY: FURTHER EVIDENCES OF THE *HDAC9* CONTRIBUTION.

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Introduction:

- Structural variants encompassing only *HDAC9*, and not comprising *TWIST1*, were reported in the medical literature in individuals presenting developmental delay, with associated craniosynostosis in some cases, suggesting the involvement of *TWIST1* regulatory elements that reside within *HDAC9*[1,2].
- Although currently there is no well-established phenotypic association for *HDAC9*, it has high expression in brain and is predicted to be highly intolerant to loss of function (pLi=1)[3].
- Here, we describe three individuals with 7p21 deletions, encompassing *HDAC9*, without direct involvement of *TWIST1* sequence.
- They presented in common neurodevelopmental delay/intellectual disability and dysmorphisms; at least one of them presented craniosynostosis.

Objective:

- To describe individuals with 7p21 deletions partially or completely encompassing *HDAC9* sequence without involving *TWIST1* sequence;
- To compare their phenotype with individuals previously described in the literature with 7p21 contiguous gene deletions;
- To perform genotype-phenotype correlation.

Table 1. Patients comparison with deletion at 7p21 encompassing *HDAC9* and *TWIS1* loss of function SNV.

	Deletion at 7p21 encompassing *HDAC9* This study (N=3)				***TWIST* loss of function SNV**
Phenotype	Patient 1 (6.6 Mb)	Patient 2 (8.0 Mb)	Patient 3 (110 kb)	PMID: 28220539 (900kb)	Saethre-Chotzen syndrome
Neurodevelopmental delay/intellectual disability	*	*	*	*	NR
Dysmorphisms	*	*	*	*	*
Craniosynostosis	NO	*	NE	*	*
Supratentorial ventricular dilatation	NO	NO	*	NR	NR
Seizure	NO	NO	*	NR	NR

Legend: *: present; NO: not observed; NE: not evaluated; NR: not reported.

Discussion:

- All individuals described here presented developmental delay/intellectual disability, being *HDAC9* the main candidate gene in the common region of overlap due to loss of function predictors and the importance of histone deacetylase family genes in neurodevelopmental disorders.
- Additionally, disruption of *TWIST1's* regulatory elements nested in *HDAC9* in the main hypothesis for the presence of craniosynostosis in part of these patients. Additional genes in the 7p21 contiguous genes deletions may contribute to other clinical characteristics.

Acknowledgement:
To the patients and relatives of this study.

Methods:

- The CNVs were detected by SNP-array technique (GSAv3 Chip - Illumina, San Diego, USA) and Whole Exome Sequencing (WES), using Target Enrichment Twist Biosciences 4 version, sequenced on the Illumina NovaSeq X Plus.
- CNVs calls in SNP-array data were performed using PennCNV2 methods, and in WES data using ExomeDepth.
- The results were analyzed using Abracadabra® software developed by Mendelics Análise Genômica.
- The variants were classified using current ClinGen/ACMG recommendations.

Results:

- We found three deletions with 8,0 Mb, 6,6 Mb and 110 kb, all encompassing a common region at 7p21 affecting *HDAC9* (Figure 1).
- Two were classified as likely pathogenic, and one as a variant of unknown clinical significance.
- The patients presented neurodevelopmental delay/intellectual disability (3/3); dysmorphisms (3/3); craniosynostosis (1/3), supratentorial ventricular dilatation (1/3), seizure (1/3). (Table1).

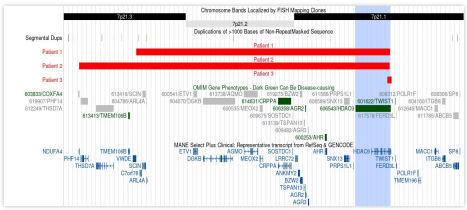

Figure 1. In red are deletions of patients of this study. The blue highlight is showing the *HDAC9* gene (OMIM in green and MANE transcript in blue) (Adapted from UCSC Genome Browser on Human - GRCh38/hg38).

Conclusion:

- Our results provide additional evidence of *HDAC9* as the main candidate gene for intellectual disability in patients with Saethre-Chotzen syndrome due to 7p21 deletions.
- Besides, it reinforces the possible contribution of *HDAC9* in craniosynostosis observed in some patients with 7p21 deletions not encompassing *TWIST1*.

References:

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