Investigation of variants that may contribute to the incomplete penetrance of Autism Spectrum Disorder in a family with a microdeletion overlapping the *LINGO2* gene

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Introduction

- Autism Spectrum Disorders (ASD) are marked by deficits in social-communication skills and atypical behaviours and development. A 2018 study by the Canadian government stated that approximately 1 in 66 children between the ages of 5 and 17 had been diagnosed with ASD[1].
- ASD is known to have heterogeneous genetic origins, resulting in significant difficulties in uncovering genetic etiologies for many affected individuals.
- Understanding the genetic factors contributing to ASD can provide necessary information for clinicians to develop better treatment and care management plans for affected families and aid with earlier diagnosis.
- This study will examine a 27-year-old male proband with a maternally inherited copy number variation (CNV) on chromosome 9p21.1 who presents with ASD, Intellectual Disability (ID), and Epilepsy.

Objective: Investigate the genetic etiology of our proband's presentation of ASD and the incomplete penetrance seen in this family.

Methods

ASPIRE Enrollment

- The Proband and the Proband's family voluntarily consented to participate in the Autism Spectrum Interdisciplinary Research (ASPIRE) Program

CMA

- Chromosomal Microarray was performed on blood samples provided by the Proband and family using the Affymetrix CytoScan HD platform (genome build *GRCh37/hg19*).
- Fluorescence in Situ Hybridization confirmation was performed on the family with the BAC probe (RP11-1l3) to validate the presence of the copy number variant.

WES

- Whole Exome Sequencing was performed through Blueprint Genetics

Results

- Chromosomal microarray detected a maternally inherited 173kb copy number loss at 9p21.1 (chr9: 28593228-28766228) that was classified as a Variant of Uncertain Significance (VUS).
- The proband's neurotypical mother and sister both also were confirmed to have the same CNV at 9p21.1
- Whole Exome Sequencing did not identify any variants that could be associated with the Proband's phenotype. WES could not confirm the presence of the identified CNV as only non-coding exons are affected.

Table 1. Phenotype comparisons of our proband and individuals with similarly overlapping copy number deletions on chromosome 9p21.1. Breakpoints locations are reported according to human genome build (GRCh37/hg19). N/A = information unavailable.

Source	Proband	ClinVar Database VCV000689134.1	ClinVar Database VCV000688673.1	Brett et al. 2014	Malhotra et al. 2011 410-10127
Inheritence	Maternal	N/A	N/A	Not Maternal	De novo
Breakpoints	28593228-28766228	28593228-28766228	28593228-28766228	28609725-28743782	28649669-28706716
Size	173 Kb	173 Kb	173 Kb	134 Kb	57 Kb
Sex	Male	N/A	N/A	Male	Male
Autism Spectrum Disorder	yes	N/A	yes	No	N/A
Intellectual disability	yes	N/A	N/A	No	N/A
Developmental Delay	yes - Global	yes	N/A	yes	N/A
Seizure Disorder	epilepsy	N/A	N/A	N/R	N/A
Other	Hyperacusis, Self-injurious behaviour, Pain insensitivity, Tactile defensiveness, Communication and language deficits, Aggressive behaviours	Short Stature	Attention deficit hyperactivity disorder	Absent Speech Gaze avoidance Benign SNVs at Chr16:89346082 Chr12:2800220 Chr6:135611614 ChrX:135314112	Bipolar Disorder

Discussion

- The CNV detected in the proband overlaps with the *LINGO2* gene, which encodes for a transmembrane protein in neuronal tissue[2]. While the function of *LINGO2* remains largely unknown, it has been suggested that this gene is involved in the regulation of neurite outgrowth and involved in synaptic assembly[3,4,5,6]. Pathways regulating synaptic assembly are known to converge with ASD risk genes[7].
- Mutations in the *LINGO2* gene have been associated with neurodegenerative diseases such as Parkinson's disease (PD) and Essential Tremor (ET)[8] and have been described in individuals with ASD[3,9,10,11]. Individuals with similar copy losses to our proband have been reported in the literature to either present with ASD or have characteristics consistent with ASD[11,12](fig.1, table.1). Additional studies by Gazzellone et al. and Matsunami et al. report two individuals each, who have deletions in the *LINGO2* gene that also present with ASD and agree that the microdeletion may be a risk factor for ASD[9,10].
- Recent studies have highlighted the importance of non-coding regions, specifically microRNA (miRNA) on gene regulation concerning ASD[3]. Williams et al. identified rare single nucleotide variants (SNVs) in 4 different miRNA sequences in an ASD cohort[3]. The study determined these variants had the potential to alter gene expression by modifying the binding affinity of the miRNA to its target mRNA[3].
- We hypothesize that the incomplete penetrance seen in this family may result from additional mutation burdens that were not identifiable through previously performed sequencing.

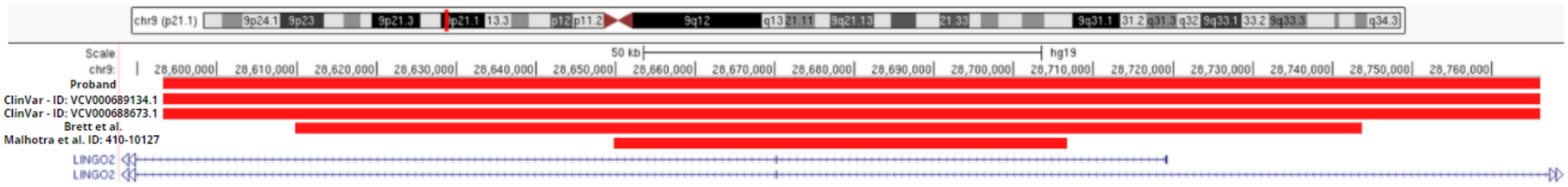

Figure 1. 9p21.1 microdeletions mapped using the UCSC Genome Browser (GRCh37/hg19). *LINGO2* variants are represented by the horizontal blue bars.

Future Directions

- Whole Genome Sequencing
- Evaluation of Sex-biased factors
- Physical Examination
- Functional Study of *LINGO2*

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