The Potential Genetic Contributions of Novel Variants in *BCL11A, GATAD2B*, and *PIK3R2* to Cerebral Palsy

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OBJECTIVES

Cerebral Palsy (CP) is a group of neurodevelopmental disorders characterized by injury to the developing brain. CP is caused by environmental and genetic factors; however, the genetic contributions are poorly understood. To better understand genetic factors, we conducted whole genome sequencing on DNA from CP patients and their parents and identified potential clinically relevant variants.

- **Of these variants, I confirmed the *de novo* predictive loss-of-function and missense variants using Sanger Sequencing.**
- **I highlight three novel *de novo* variants in genes previously linked to neurodevelopmental disorders.**

MATERIALS AND METHODS

Set of 72 de novo, missense and predictive loss of function variants

Pick primers for each variant

Test primers through PCR

Conduct PCR on DNA samples (Fig. 1) and clean PCR products

Submit to Sanger Sequencing and analyze results

Search for identified variants in genomic databases (OMIM, ClinVar, etc.) and existing literature

In depth literature search on a few select genes previously linked to neuro-developmental conditions

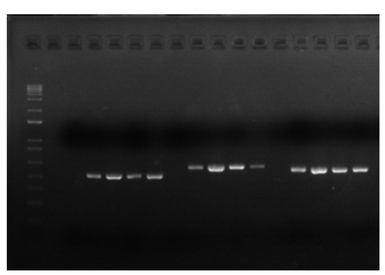
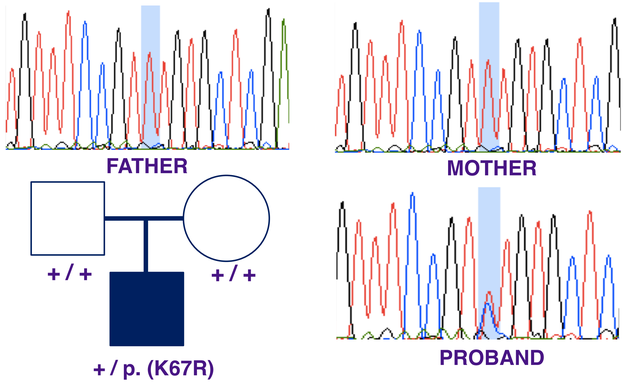


Fig. 1: Gel of PCR results of variants on *PPP2R5A*, *GATAD2B*, and *WDR3*

BCL11A (B-cell lymphoma 11A)

NM_022893, c.A200G:p.(K67R)



BCL11A encodes a transcription regulating protein that suppresses fetal hemoglobin after birth and promotes axonal growth and branching.

Variants: Other variants have been identified in exon 2 of *BCL11A* related to intellectual disability (ID)

- 3 missense and 4 loss of function variants (Fig. 2)

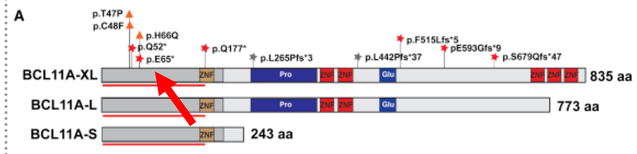
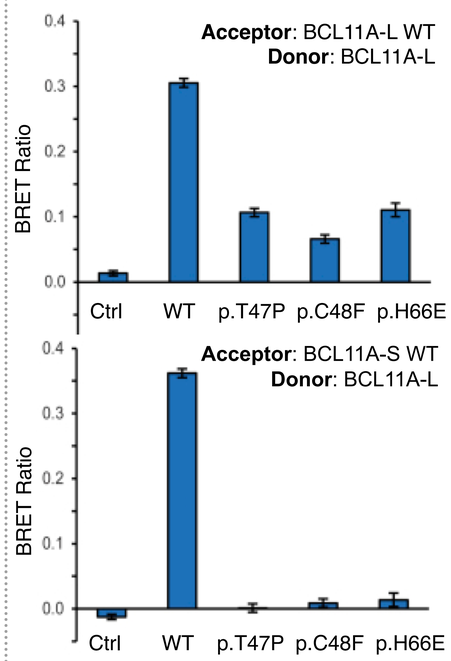


Fig. 2: Genomic map of recorded *BCL11A* variants



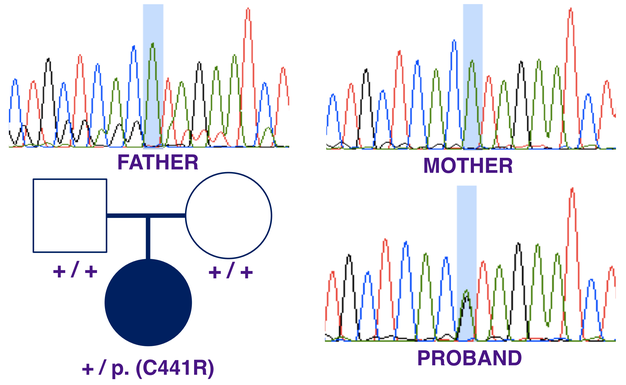
Mice Models: *BCL11A* variants were shown to decrease brain volume and social recognition.

Cellular Mechanisms: Other exon 2 missense variants interfere with protein localization and dimerization (Fig. 3).

Fig. 3: *BCL11A* exon 2 missense variants reduce interactions with wild type isoforms of *BCL11A*

GATAD2B (GATA Zinc Finger Domain Containing 2B)

NM_020699, c.T1321C:p.(C441R)



GATAD2B encodes the protein p66: a subunit of the nucleosome remodeling and histone deacetylase (NuRD) complex which regulates transcription and is linked to neural development.

Variants: *GATAD2B*-associated neurodevelopmental disorder (GAND) is caused by missense and loss of function variants

- Identified in over 50 patients (Fig. 4).
- GAND phenotype includes ID, impaired language development, and strabismus.

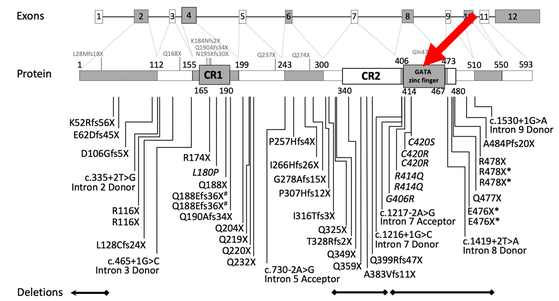


Fig. 4: Genomic Map of *GATAD2B* variants

Cellular Mechanisms: Nearby missense variants have been shown to inhibit interactions of the protein with other proteins in the NuRD complex and disrupt the structure of the region (Fig. 5).

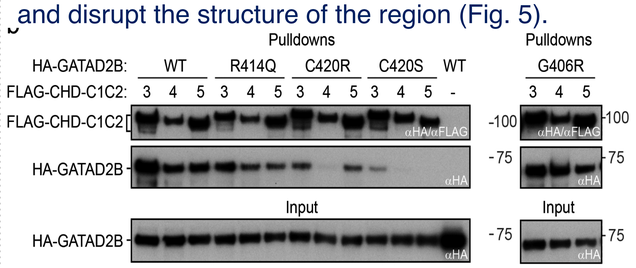
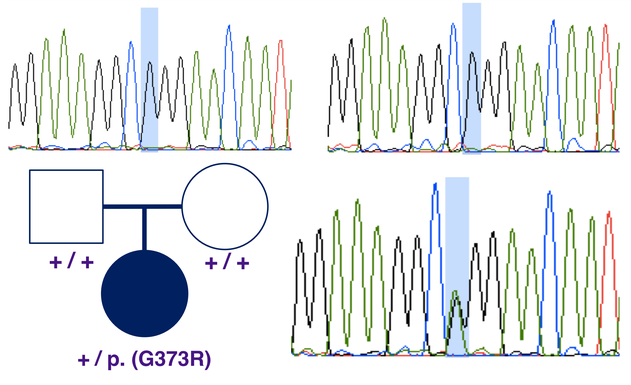


Fig. 5: Missense variants disrupt binding of *GATAD2B* to NURD components

PIK3R2 (Phosphoinositide-3-kinase regulatory subunit 2)

NM_005027, c.G1117A:p.(G373R)



PIK3R2 encodes a regulatory subunit of a kinase which is involved in growth signaling and transcription regulation.

Variants: Over 40 reports have been made of individuals with our identified variant (Figure 7); it is associated with megalencephaly, overgrowth and asymmetry, intellectual disability, developmental delay, and other neurologic issues such as seizures and polymicrogyria.

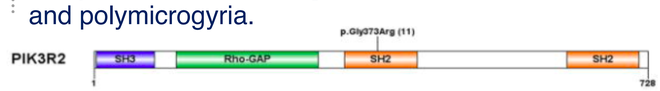


Fig. 8: *PIK3R2* variant found in over 40 individuals

Cellular Mechanisms: Abberations on PIK3R2 alter activity of the mTOR pathway by preventing PI3K from entering its inactive conformation and thus keep the pathway permanently in a high activity state and thus altering brain development.

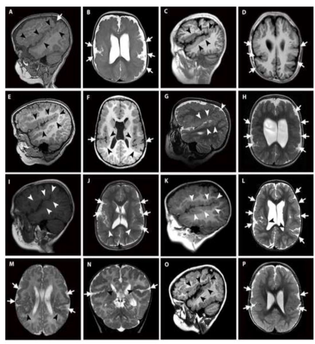


Fig. 8: Megalencephaly linked to PIK3R2 variants.

CONCLUSIONS

Our validation of sequence level variants adds to the growing database of genes and variants connected to CP, including three novel variants on genes that have not previously been linked to CP.

By reviewing existing literature, we can conclude that these variants may be damaging and linked to CP.

Further investigation is needed on other genes linked to neurodevelopmental conditions and how their variants impact gene function.