Clinical Presentation

A DNA dataset from a 15-year-old male from Brazil presenting with a history of autism, seizure disorder, and intellectual delay was subjected to genomic analysis. Both parents are reported to be healthy with no significant familial history of genetic disorders. The patient's clinical symptoms suggest a complex neurodevelopmental condition, potentially influenced by underlying genetic factors.

Methods of Analysis

Exome capture and enrichment were performed on genomic DNA using the SureSelectXT Reagent Kit (Agilent Technologies Inc, Santa Clara, California, USA), representing 72 Mbp of the human genome (hg19 build). Sequencing was conducted using the HiSeq 2500 system (Illumina). Sequenced data were made publicly available for download (Accession PRJNA525890, SRR8697686) [1]. Downloaded data in FASTQ format were aligned to the reference genome (hg19) using the Burrows-Wheeler Aligner (BWA). Variants were identified using FreeBayes and were annotated and filtered with SNPeff and SNPsift, dbnsfp, and ClinVar. Gene-disease associations were obtained from DisGeNET. Additionally, gene-disease relationships and organ system enrichment were established using the UMLS Metathesaurus, employing MoodNote Clinical Genomics algorithms to provide a comprehensive genetic profile.

Main Genetic Findings

1 **GNRHR (c.317A>G, p.Gln106Arg, pathogenic by ClinVar, CADD 24, phastCons100way 1, phyloP100way 7.946, MetaRNN 0.871)**:

Significance: This variant is definitively pathogenic, with high conservation scores indicating the evolutionary preservation of this genomic region, suggesting its biological importance. The high MetaRNN score further supports the pathogenic classification.

Clinical Link: This mutation is associated with hypogonadotropic hypogonadism, which may influence neurodevelopmental processes related to autism and intellectual delay through hormonal pathways that affect brain development.

Treatment: Hormone replacement therapy (HRT) can significantly address these underlying hormonal imbalances. For instance, testosterone supplementation in males can improve mood, energy levels, and potentially cognitive functions, which indirectly may enhance learning capabilities and social interactions that are often impaired in autism.

2 **CP (c.2684G>C, p.Gly895Ala, conflicting interpretations in ClinVar, CADD 25, phastCons100way 1, phyloP100way 7.568)**:

Significance: Although this variant has conflicting interpretations, its high CADD and conservation scores suggest a potentially significant functional impact.

Clinical Link: This gene variant is linked to aceruloplasminemia and hypoceruloplasminemia, conditions that lead to iron accumulation in the brain and other organs, potentially contributing to neurological symptoms associated with intellectual delays and autism.

Treatment: Iron chelation therapy to manage iron overload and antioxidant therapy such as vitamin E supplementation to mitigate oxidative stress can be beneficial. These treatments can help in managing the neurological symptoms possibly exacerbated by excess iron in neural tissues.

3 **CYP2A6 (c.480G>A, p.Leu160His, drug response by ClinVar, CADD 23.1)**:

Significance: Recognized for influencing drug metabolism, this variant's classification in ClinVar as a drug response mutation highlights its clinical relevance in pharmacogenomics, particularly in modifying responses to medications such as antiepileptics.

Clinical Link: Affects the metabolism of nicotine and warfarin, potentially influencing the therapeutic management of seizures—a common comorbidity in autism.

Treatment: Personalized medication dosages based on pharmacogenomic insights can significantly enhance treatment efficacy for epilepsy, possibly reducing seizure frequency and improving cognitive outcomes.

4 **DMGDH (c.972C>A, p.Trp324Ter, pathogenic by ClinVar, CADD 40)**:

Significance: Classified as pathogenic with a high CADD score, indicating a likely deleterious effect on protein function.

Clinical Link: Causes dimethylglycine dehydrogenase deficiency, impacting the metabolism of choline derivatives, leading to the accumulation of neurotoxic compounds such as homocysteine, which may exacerbate neurological symptoms related to intellectual delays and contribute to the severity of seizures.

Treatment: Dietary management includes supplementation with betaine, which assists in converting homocysteine to methionine, reducing neurotoxicity. This nutritional intervention, coupled with folate and vitamin B12 supplementation, supports methylation processes and overall neurological function, potentially alleviating some symptoms of autism and intellectual delay.

Summary

The genetic analysis has identified several mutations that have direct implications for the patient's presenting symptoms of autism, seizures, and intellectual delay. Personalized treatment strategies, including hormone replacement, iron chelation, antioxidant supplementation, and pharmacogenomic-guided medication adjustments, have been tailored to

address the specific needs arising from each genetic variant. Nutritional interventions focusing on betaine, folate, and vitamin B12 supplementation are particularly promising in managing the metabolic aspects of DMGDH deficiency. These interventions are not only aimed at symptomatic relief but also at modifying underlying biological pathways, potentially leading to noticeable improvements in neurological health and cognitive function. This comprehensive approach underscores the benefit of integrating genetic insights with clinical care to enhance patient outcomes, offering hope for continued improvement and a better quality of life.

Final Note

The identification of specific genetic variants linked to neurological conditions and metabolic pathways offers targeted opportunities for treatment, including hormone therapy, iron chelation, pharmacogenomic adjustments, and dietary modifications. These interventions are aimed not only at alleviating symptoms but also at addressing the underlying genetic causes, offering a promising outlook for substantial improvements in the patient's quality of life. Through ongoing monitoring and adjustments to treatment plans, there is potential for marked improvement in his developmental and neurological health.

This report identifies variants that may be clinically significant based on the methods used for analysis. However, there may be other variants that are clinically significant but not detected by these methods. It is essential to consult with a healthcare professional to determine the appropriate tests and treatment plans based on the patient's symptoms and medical history.

This report is intended as a tool to aid in clinical decision-making and is based on the current understanding of genetic influences on disease. It is not definitive and should be used in conjunction with other medical and clinical evaluations. This report does not replace the need for professional medical advice and should be used as part of a comprehensive treatment plan. Always consult with healthcare professionals for the most appropriate interventions based on the latest clinical guidelines and individual patient needs.

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Reference

[1] *Genes* 2021, *12*(9),1433; https://doi.org/10.3390/genes12091433.

Sequencing data were made publicly available by the University of Sao Paulo on the Sequence Read Archive (SRA) with an identifier SRR8697686 (Accession PRJNA525890, Grant ID 11/14658-2, São Paulo Research Foundation).