GENOOX

TRANSFORMING COMPLEX DATA
INTO CLINICAL ANSWERS

DISCOVERY OF NEW GENES USING GENOOX'S AUTOMATED ALGORITHMS

RAMBAM Health Care Campus

The identification of a novel mutation in a rare hereditary disease deciphered by the Genoox platform.

The Genetic Institute at the Rambam Health Care Campus provides comprehensive genetic services for regional community clinics and hospitals. The institute provides genetic counseling for common and hereditary diseases, family planning, and diagnostic services for both patients and their relatives. A correct genetic diagnosis is critical for both preventing and managing the often-devastating disease. Here we report on the identification of a novel gene function in a rare hereditary disease, never previously reported within clinical literature and was deciphered by the Genoox platform.

Case

Four different individuals from two different families presented at birth with facial dysmorphism, encephalopathy, arthrogryposis, hypotonia progressing to hypertonicity with startle-like clonus, and respiratory failure. After exhaustive clinical review, a confirmatory diagnosis of the dysmorphisms had not been determined. Patient DNA samples were analyzed using Whole Exome Sequencing (WES) following referral to genetic consult of one of the individuals.

Comprehensive DNA data analysis was performed using the Genoox platform. The Genoox variant interpretation engine employs an automatic variant prioritization algorithm designed to determine which mutations may be relevant for a given patient. The algorithm considers multiple factors, including classification of the variant according to ACMG guidelines, and their association to the patient's phenotypes. This process significantly reduces the possible number of causal variants, allowing focus on the most clinically relevant results. In addition, the platform offers "out-of-the-box" templates for family analysis and sample comparison using different inheritance models.

Result

Whole Exome Sequencing of the one of the proband's DNA was sequenced using HiSeq2000 (Illumina) and analyzed by the Genoox platform. A single variant was identified by the system following combined variant calling classification and phenotypic integration in the SLC6A9 gene. This five-nucleotide deletion in the SLC6A9 gene had not previously been detected or reported within the clinical literature before [c.928_932delAAGTC (p.Lys310Phefs*31) (GenBank: NM_201649.3)]. Based on this identification, additional pregnancy within the same family was terminated followed abnormal ultrasound inspection in 12-13 weeks. DNA analysis revealed a normal male karyotype and homozygosity for the same c.928_932delAAGTC variant. An overview of the hospital's medical records for undiagnosed individuals led to the identification of a second family with similar clinical features. Sanger sequencing of SLC6A9 gene in this second family revealed a novel homozygous nonsense variant in exon 12, c.1717C>T (p.Gln573*), which also had not been previously reported within the clinical literature.

Further research using SLC6A9 mutant mice and zebrafish animal model systems reported phenotypes consistent with those seen in the affected patients,. The data suggest that truncating SLC6A9 mutations lead to a distinct human neurological syndrome hallmarked by mildly elevated CSF glycine and normal serum glycine.

Key Takeaways

Genoox employs an advanced classification tool based on ACMG guidelines to automatically identify and prioritize pathogenic variants applying machine learning algorithms, generating a complete variant overview and providing impact scoring based on the specific phenotype, disease or treatment.

The ability to examine multiple samples while simultaneously comparing the results against an historical "in-house" variant database can yield results which would have otherwise been missed. Every rare genetic disorder resolved benefits families across the world who may also be may also be looking to resolve a causal mutation that is responsible for similar phenotypes across the world. It can also lead to personal tailored therapy since the causative mutation is identified and potential treatments (in research and in practice) can be applied and investigated.

The Genoox platform is an effective tool in providing a confirmatory, actionable diagnosis for rare genetic disorders.

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Loss of Glycine Transporter 1 Causes a Subtype of Glycine Encephalopathy with Arthrogryposis and Mildly Elevated Cerebrospinal Fluid Glycine

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