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Clinical Phenotype of a Rare Pathogenic Variant in STXBP1 Gene

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ABSTRACT

The STXBP1 gene encoding syntaxin-binding protein 1 (STXBP1 or Sec1/Munc18-1), is implicated as a significant genetic contributor to neurodevelopmental disorders (NDD) and epilepsy, known as STXBP1-related disorders. Despite the recognition of this association, the genotype and phenotype spectrum of these disorders is highly diverse, with considerable variability even among recurrent STXBP1 variants, consequently, posing a substantial challenge in effectively managing disease. Here, we present clinical details of a patient harboring a rare heterozygous pathogenic variant (STXBP1: c.1095_1096delCT, p. Cys366ProfsTer13) in STXBP1 gene, for which clinical descriptions are lacking. This underscores the complexities involved in understanding and managing STXBP1-related disorders, necessitating further research and personalized treatment approaches.

Keywords: STXBP1, c.1095_1096delCT, genotype-phenotype.

INTRODUCTION

The STXBP1 gene encoding syntaxin-binding protein 1 (STXBP1 or Sec1/Munc18-1), is implicated as a significant genetic contributor to neurodevelopmental disorders (NDD) and epilepsy, known as STXBP1-related disorders. STXBP1 gene working together with another protein syntaxin-1 regulates neurotransmitter release on surface of tiny synaptic vesicles. While previous studies have outlined a diverse phenotypic features (early onset epileptic encephalopathy (EOEE), Ohtahara syndrome (OS), West Syndrome (WS), other developmental and epileptic encephalopathies (DEE), NDD, and atypical Rett Syndrome) due to array of STXBP1 variants (missense, nonsense, splice-site, frameshift, deletion, and others), yet, genotype-phenotype correlations remain less established, underscoring the challenges in precisely correlating genotype with their corresponding phenotype in affected individuals [1,2,3,4,5]. This underscores the complexities involved in understanding and managing STXBP1-related disorders, necessitating further research and personalized treatment approaches. We present phenotypic expression of a patient with a rare heterozygous pathogenic STXBP1 variant chr9:130435525_130435526delCT, c.1095_1096delCT, p.Cys366ProfsTer13 in the STXBP1 gene for which clinical

information in the database and literature is lacking.

CASE REPRESENTATION

A 15-year-old male presented with gross developmental delay and generalized tonic-clonic seizures began at the age of one month, born full term with no relevant prenatal or family history. Physical examination revealed head circumference of 57 cm + 2 SD, frontal bossing, depressed nasal bridge, open mouth, hypotonia, aggression and unusual behavior. Basic blood tests, Cerebrospinal fluid examination, Magnetic Resonance Imaging and electroencephalogram was normal and phenobarbital and phenytoin was initiated. Despite on treatment, infrequent episodes persisted and metabolic disorder was considered which was normal. Psychological assessment indicated moderate retardation. Risperidone addressed behavioural concerns. Seizure frequency increased at 14 years of age; parents opted for levetiracetam addition without repeat EEG.

For genetic diagnosis whole Exome Sequencing employed IDT's xGen™ DNA Library Prep EZ technology on NovaSeq/NextSeq platforms with parental consent. Alignment of FASTQ reads (raw data) to hg19, filteration, ranking, annotation and prioritization of variants was done via proprietary algorithm (SMART-OneTM (Sequence and Meta-analysis Research Toolkit/ GeneUIS®) developed by ComputeGenomics [6].

RESULT

Genetic analysis detected a pathogenic alteration in exon 13 of the STXBP1 gene (chr9:130435525_130435526delCT, c.1095_1096delCT, p.Cys366ProfsTer13), predicted to truncate protein and impair its function. As of now, this newly discovered variant has not been documented with any minimum allele frequency in the gnomAD & ClinVar database. This variant is proximal to known pathogenic variants, p.Arg367Ter and p.Gln370Ter, associated with DEE [7]. The patient's diagnosis of STXBP1-Related DEE indicates the identified genetic variation in STXBP1 gene is likely responsible for symptoms, supported by both genetic and clinical evidence. Segregation analysis was precluded by financial constraints; however, informed consent was obtained for further medical intervention based on genetic findings. The candidate mutant amino acid site's conservation Assessment of Species and Modeling Protein Homology was assessed using UniProt Browser and ClustalX2.1. Full-length STXBP1 wild-type (WT) was obtained from NCBI (accession no.: NP_001027392.1). SWISS-MODEL generated models based on 20 evolutionary-related structures identified through BLAST and HHBlits searches as previously done for other proteins [8]. The Swiss-model retrieved model based on template A0A480WEI6.1 was chosen.

DISCUSSION

In our patient, a rare pathogenic mutation in the STXBP1 gene was found, resulting in early-onset seizures, developmental delay, mental retardation, unusual behavior, and laughter. This variant was considered an assumed de novo variant, aligning with the previous literature showing majority of the de novo variants in this gene [3]. Literature reveals a wide range of symptoms associated with STXBP1-related developmental and Epilepsy Encephalopathy, including developmental delay (100%), intellectual disability (≥90%), seizures (70-95%), movement disorders (>87%), and neurobehavioral disorders (~65%) [3]. Seizure onset in STXBP1-related disorders varies greatly, displaying diverse seizure and epilepsy syndromes. Remarkably, STXBP1 mutations can lead to late-onset epilepsy or may occur even without epilepsy altogether [1]. STXBP1 encephalopathy, linked to mutations in the STXBP1 gene crucial for neurotransmitter release, is marked by early developmental delays. Studies reported developmental delays across various domains, with a

significant proportion of affected adults exhibiting symptoms within the first year of life, often necessitating mobility aids [9]. Balagura et al (2022) reported that the wide-ranging intellectual disability in STXBP1 encephalopathy significantly impacts neurodevelopmental outcomes, highlighting the crucial role of STXBP1 mutations in neurodevelopmental disorders. Our patient's behavioral patterns parallel those observed previously, indicating consistent behavioral issues in adults with STXBP1 encephalopathy [7]. Despite severe intellectual disability, our patient's head circumference was above +2SD, supported by literature suggesting normal head circumference in STXBP1 gene mutation patients [1]. Furthermore, our case's brain MRI findings align with existing literature, indicating normal results in a significant percentage of cases and normal EEG in our case, differing from majority with varied abnormalities [10]. Though there is no clear correlation between variants and phenotypes but Xian et al. 2022 observed that different STXBP1 variants exhibited a varied phenotype [5].

MODELING PREDICTIONS OF VARIANT IMPACT

For modeling predictions of variant impact a homology model explored how frameshift mutation at Cys366 in STXBP1 affects its structure, disrupting conserved amino acids within Sec-1 like_dom3 region, a conserved domain found in proteins that are structurally similar to Sec-1 (Figure 1A,B). It is involved in interactions with other proteins, such as syntaxin-1. Structural analysis reveals notable disparities between WT and mutant proteins and confirms reliability and accuracy (Figure 1C,D, E,F). The frameshift variant p.Cys366ProfsTer13 causes premature translation termination, leading to critical amino acid absence (Fig 1B). This analysis elucidates STXBP1 splice variants, aiding genotype-phenotype correlations and precision medicine.

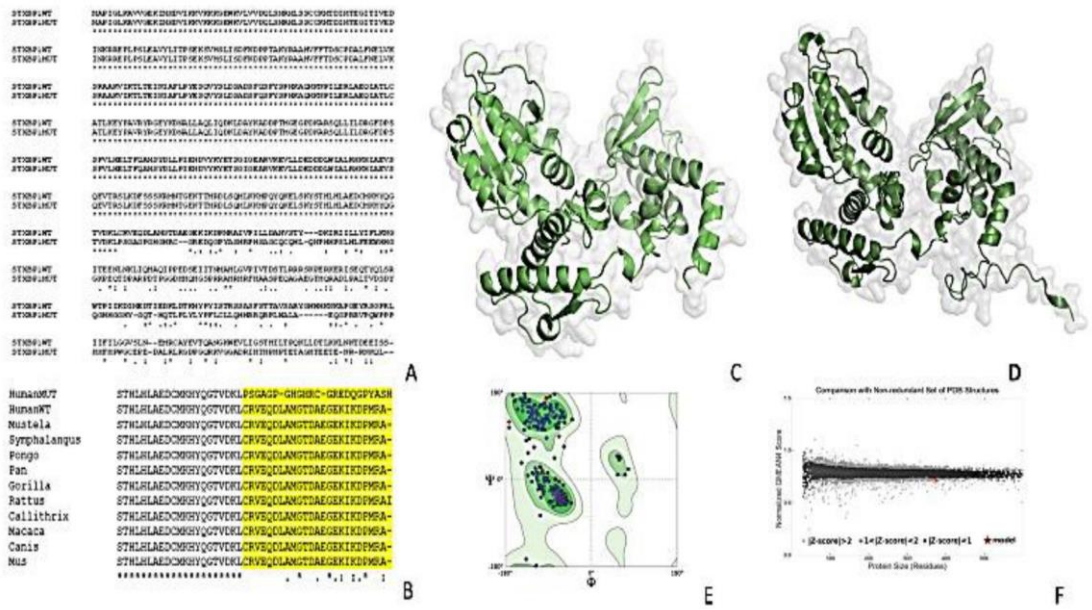

Figure 1. The position, conservation and homology models of the mutant protein.

(A) The mutation was located in the Sec-1 like_dom3, *STXBP1* variant chr9:130435525_130435526delCT, c.1095_1096delCT, p.Cys366ProfsTer13, affecting a length of amino acids located from the end of the *STXBP1* to the half of the Sec-1 like_dom3.

(B) The residues from Leucine to the end are evolutionarily conserved Homo sapiens, Mustela putorius, Symphalangus

syndactylus, Pongo pygmaeus, Pan paniscus, Gorilla, Rattus norvegicus, Callithrix jacchus, Macaca nemestrina, Canis lupus, Mus musculus.
(C) Wild-type (residues 1–594),
(D) Mutant (residues 1–377) homology model. The mutant STXBP1 lacks substantial beta-sheets and helical regions, implying compromised functionality. Fig.
(E & F) MolProbity analysis reveals a high-quality structure with a score of 0.77 and minimal clashes (0.47). With 97.47% residues in favored Ramachandran regions and a QMEANDisCo score of 0.81, the structure is reliable.

CONCLUSION

In conclusion, understanding genotype-phenotype relationships in STXBP1 developmental and epileptic encephalopathies requires further exploration through newly identified case reports and variants to enhance disease treatment efficacy.

Declaration by Authors

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