Heterozygous *GOSR2* Mutation Associated Epilepsy and Muscular Dystrophy

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Introduction:

Homozygous mutations in Golgi SNAP receptor complex member (*GOSR2*), a SNARE protein involved in Golgi Vesicle transport, have been linked with North Sea Progressive Myoclonus Epilepsy (NSPME). Heterozygous mutations are rare and present with varying manifestations including progressive myoclonic epilepsy (PME) and severe muscular dystrophy.

Case Presentation:

A one year old male with no significant past medical history, presented with hypotonia, motor delay, and one episode of brief generalized shaking before 6 months of age. After an unremarkable evaluation, a Brain MRI showed plagiocephaly. Creatine kinase was increased (9,116 U/L), EMG was myopathic. Biopsy at 17 months revealed a dystrophic process with normal dystrophin, indicating severe dystrophic myopathy and ruling out common dystroglycanopathies, including Becker's and Duchenne's (Fig.1). Neuromuscular gene panel was negative.

Head nods and drop attacks developed at 25 months, increasing during drowsiness and early sleep. Video-electroencephalogram (V-EEG) demonstrated frequent 2-3Hz generalized spike wave discharges with a high amplitude, disorganized, slow background activity(Fig.2). Multiple seizure types were captured by V-EEG: absence, myoclonic with bilateral upper extremity jerks, and atonic with drop attacks. A subsequent EEG, while treated with ethosuximide and sodium valproate, revealed occasional bilateral shifting occipital spikes and occipital intermittent rhythmic delta activity (OIRDA) (Fig.3).

An epilepsy gene panel was performed revealing compound heterozygous pathogenic variants *in GOSR2*, c.430G>T and c.336+1G>A. SNP microarray identified a 589kb duplication of chromosome 1q21.1, associated with neurodevelopmental disorders, dysmorphism, and hypotonia. This variant is notable for incomplete penetrance and variable expressivity. Thus, it does not account for his myoclonic and absence epilepsy.

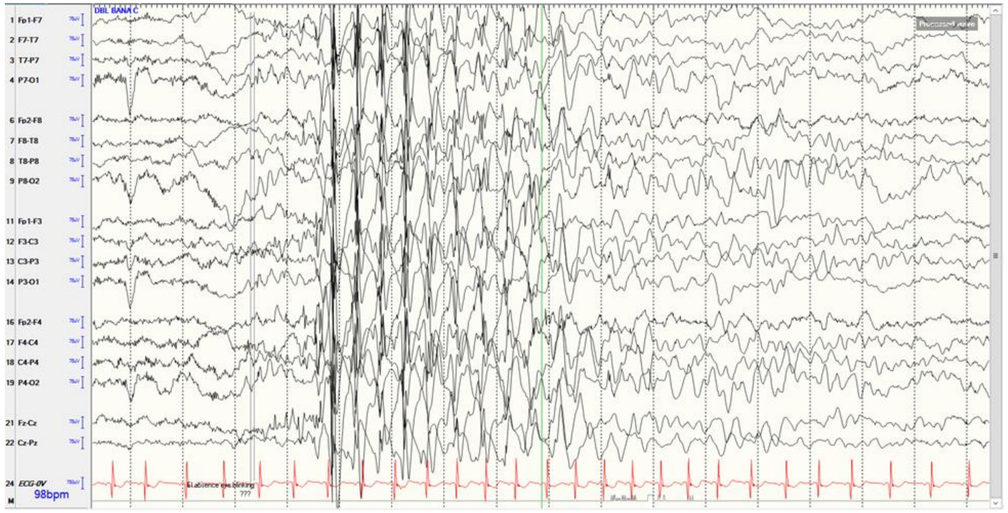

Fig 2. 15uV sensitivity; 15s window: Pre-Treatment: 2-3 Hz generalized spike-wave discharges and high amplitude slow background

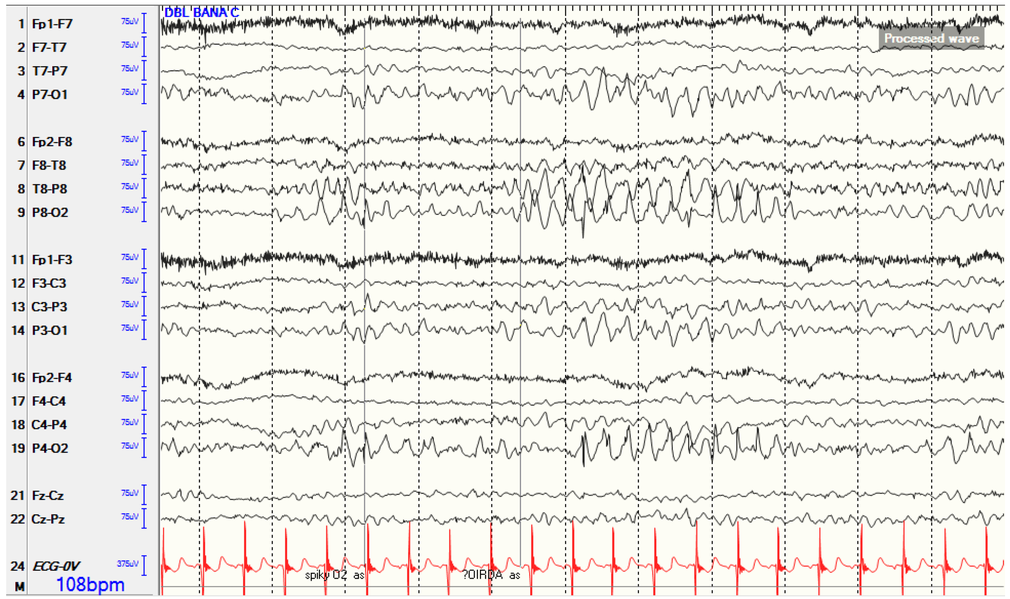

Fig 3. 15 uV sensitivity; 15s window: Post-treatment slow background with embedded spikes and occipital sharps with Occipital Intermittent Rhythmic Delta (OIRDA)

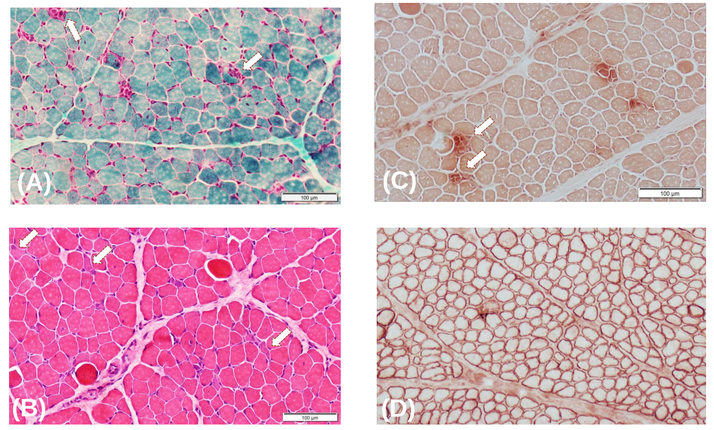

Fig 1. Muscle Biopsy: (A) Trichrome staining shows necrotic muscle fibers undergoing phagocytosis, (B) Regenerating fibers with basophilic sarcoplasm on hematoxylin and eosin staining, (C) Acid phosphatase highlighting macrophages in necrotic fibers, (D) Normal dystrophin immunostaining.

Conclusion:

Compound heterozygous pathogenic variants in *GOSR2* present with both muscular dystrophy and progressive myoclonic epilepsy. As compound heterozygosity is rare with this syndrome and not well-documented in the literature, it is important to note that our case revealed muscular dystrophy and absence and myoclonic seizures, further expanding the phenotypic spectrum of this disorder. *GOSR2* should be included in gene panels for both neuromuscular and epilepsy syndromes.

References:

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