CASE REPORT: TWO SIBLINGS WITH UNC80 DEFICIENCY

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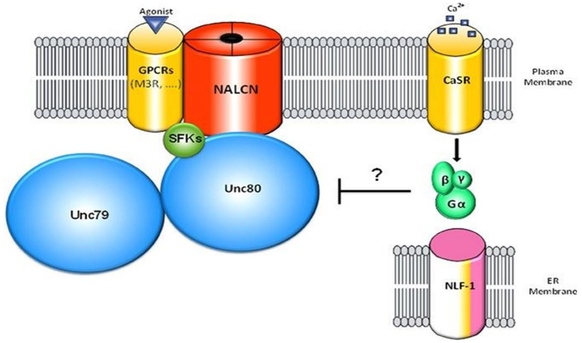
Introduction

- Infantile hypotonia with psychomotor retardation and characteristic facies -2 (IHPRF2) due to UNC80 Deficiency (MIM 616801)
  - Neonatal hypotonia
  - Neurodevelopmental delay with severe intellectual disability
  - Post natal growth delay
  - Subtle dysmorphic features
  - Sleeping difficulties
- UNC80 forms part of the “NALCN channelosome”
- Autosomal recessive inheritance

Case report

- Two siblings from non-consanguineous parents with poor growth, feeding difficulties, hypotonia and neurodevelopmental delay presented to the Genetic clinic
- Subtle dysmorphic features
- Bilateral undescended testicles in male infant
- Diagnostic odyssey:
  - Chromosome studies and chromosomal microarray normal
  - CDG isoelectric focusing; serum transferrin profile indicated slight hypoglycosylation
  - Congenital Disorders of Glycosylation Panel – one pathogenic variant in *SLC35C1* (heterozygous thus carrier and not affected)
  - Metabolic work-up - normal
  - MRI of brain - normal
- Whole exome sequencing identified a likely pathogenic homozygous variant in the *UNC80* gene
  - *UCN80* (NM_001271986.1): c5757delC;pIle1920fs
- Less than 50 individuals described to date

“NALCN channelosome”



- Large sodium leak channel complex consisting of multiple proteins:
  - NALCN (13q32.3-33.1), FAM155A (13q33)
  - UNC80 (2q34)
  - UNC79 (14q32.12)
  - G protein-coupled receptors (GPCRs)
- NALCN important for neuronal excitability, motor function, pain sensitivity and circadian rhythm.
- Pathogenic and likely pathogenic variant in *NALCN* and *UNC80* causes a variety of diseases:
  - ***NALCN***
    - Infantile hypotonia with psychomotor retardation and characteristic facies -1 (IHPRF -1) when homozygous/compound heterozygous
    - Congenital contractures of limbs and face, hypotonia and developmental delay (CLIFAHDD) when heterozygous
  - ***UNC80***
    - Infantile hypotonia with psychomotor retardation and characteristic facies -2 (IHPRF -2)
  - ***UNC79***
    - Neurodevelopmental disorder recently described

Conclusion

- Management is supportive
  - Developmental services and educational support
  - Treatment of sleep disturbance, seizures and irritability
  - Feeding difficulties may necessitate gastrostomy
  - Orthopaedic management of contractures and scoliosis
- Genetic counseling now possible
- WES initially would have made the diagnostic odyssey shorter

References

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Acknowledgements and contact

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- The research forms part of an initiative called Nngwe (Sesotho: the One) to improve the diagnosis and patient care of Rare Disease Patients

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1Nngwe One life matters
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