A FIBROBLAST GROWTH FACTOR 14 (FGF14) DELETION UNDERLIES A VESTIBULOCEREBELLAR DISORDER PRESENTING AS EARLY ONSET NYSTAGMUS – AN OLD PEDIGREE REVISITED

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**FAMILY 1**

- **Nystagmus**: involuntary and periodic oscillations of the eye

- **Harris et al., 1993:**
  - Large pedigree with a dominant vestibulo-cerebellar disorder:
    - gaze evoked and upbeat nystagmus
    - absent/poor smooth pursuit
    - poor vestibulo-ocular reflex
    - normal vision
    - normal electroretinograms (ERG), attenuated visually-evoked potentials

- **Ragge et al., 2003:**
  - Linkage study: locus on chromosome 13q31-q33 (NYS4)
FAMILY 2

- Phenotype:
  - eye movement anomalies (gaze evoked and upbeat nystagmus, poor smooth pursuit)
  - early onset tremor
  - poor balance and fine motor difficulties
  - mood disorder

- Affected:
  - proband and father (mild)

- aCGH:
  - intragenic duplication of FGF14 (chr13q33.1)

FGF14 duplication

min.size: 280kb
max.size: 532kb

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(unpublished)
FGF14

- Intracellular fibroblast growth factor involved in multiple neuronal processes: channel gating, neuronal excitability, synaptic transmission and plasticity

- Heterozygous FGF14 variants:
  - Spinocerebellar Ataxia type 27 (SCA27)
  - Episodic Ataxia
  - Paroxysmal non-kinesigenic dyskinesia
  → phenotypes consistent with mouse models

- <20 variants have been reported in families with these phenotypes
Segregation analysis: long range PCR
- Present in 10 affected + 1 mildly affected
- Absent in 8 unaffected

Literature: heterozygous $FGF14$ deletions previously reported in cases with SCA27
$\rightarrow$ Pathogenic variant
CONCLUSIONS

- Family 1
  $FGF14$ heterozygous deletion $\rightarrow$ underlying cause of NYS4

- Family 2
  $FGF14$ heterozygous duplication $\rightarrow$ first duplication reported in SCA27

- $FGF14$ spectrum: from isolated nystagmus to SCA27
  - early onset
  - slow progression
  - inter- and intra-familial variability

- Importance of $FGF14$ screening in cases with childhood nystagmus
  - both sequence and structural variants
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