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

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GoOD Meeting

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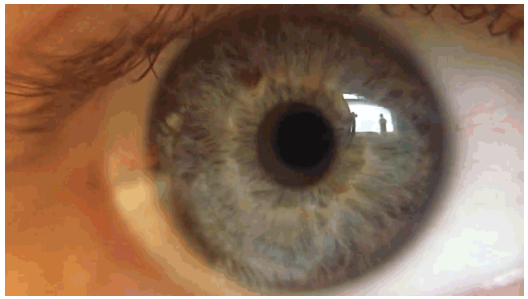
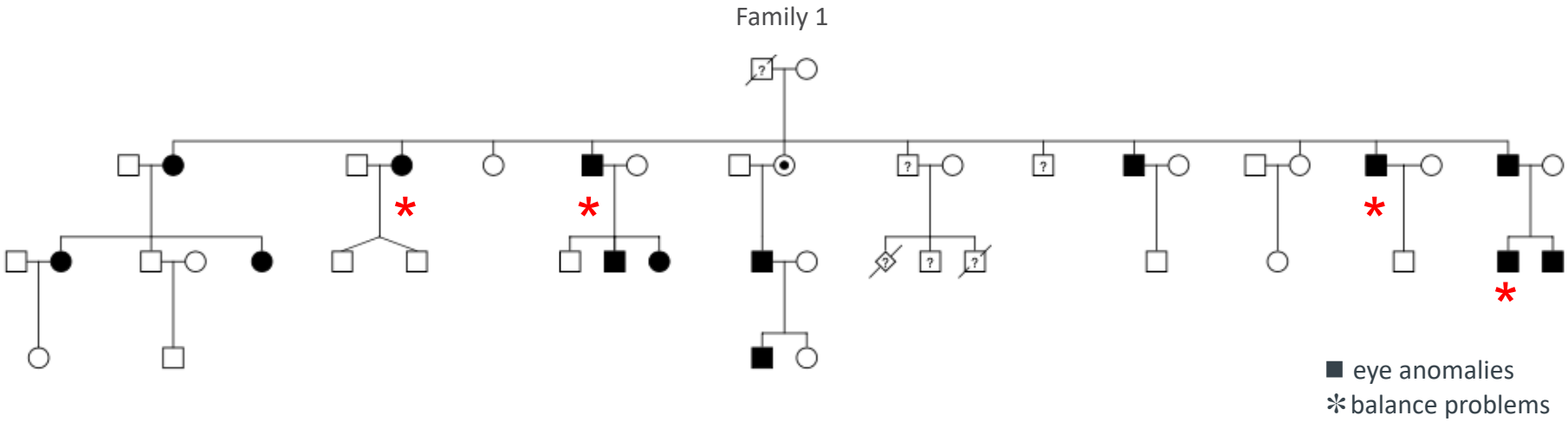
FAMILY 1



- 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)



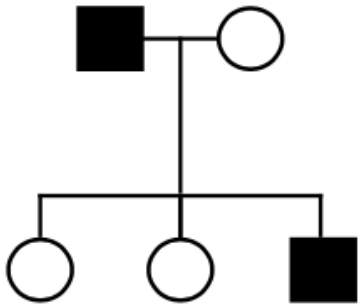
FAMILY 2

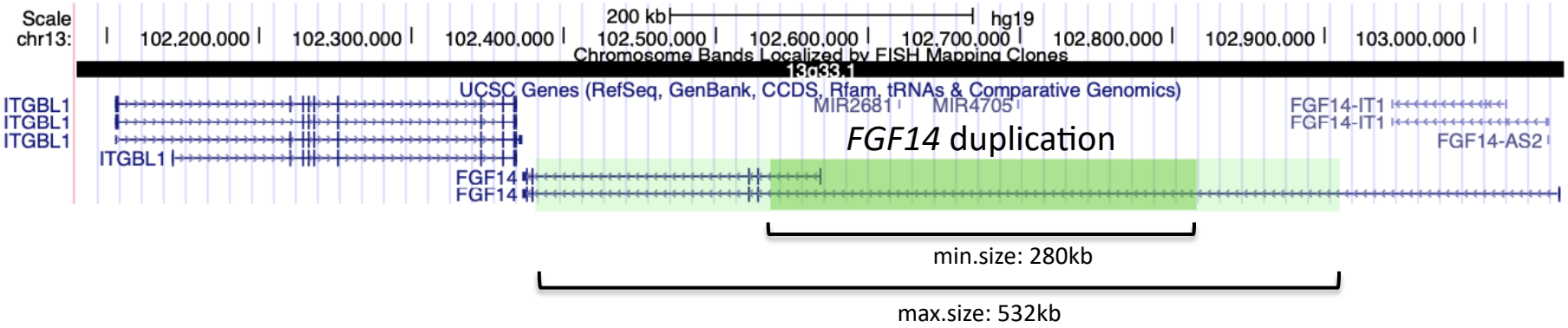
- Phenotype:
  -eye movement anomalies (gaze evoked and upbeat nystagmus, poor smooth pursuit)
  -early onset tremor
  -poor balance and fine motor difficulties
  -mood disorder

- Affected:
  proband and father (mild)

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

Family 2





D. Osborne, J. Self
(unpublished)

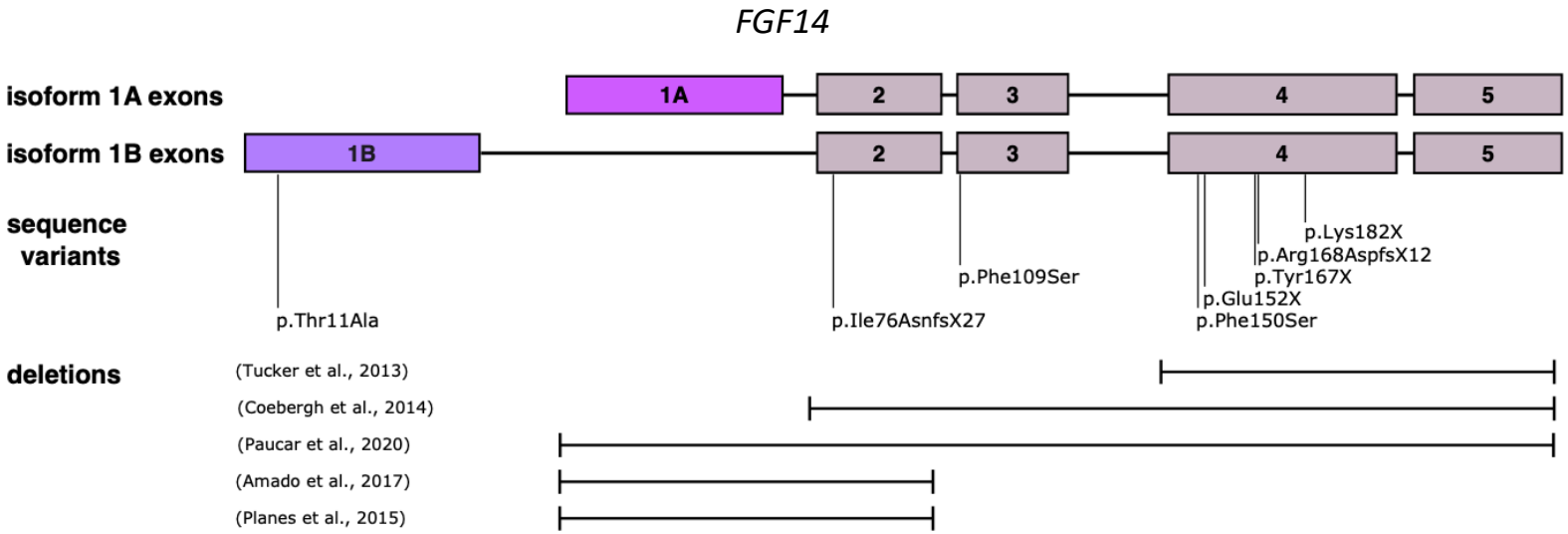
FGF14

- 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

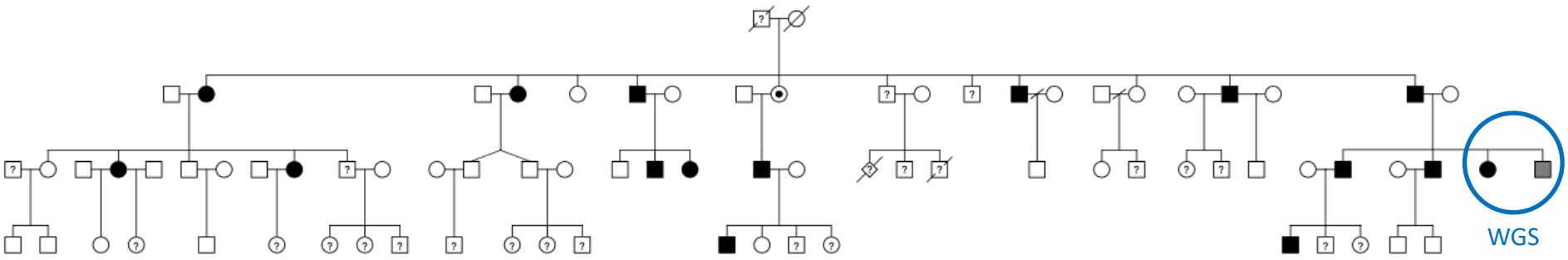
  → phenotypes consistent with mouse models

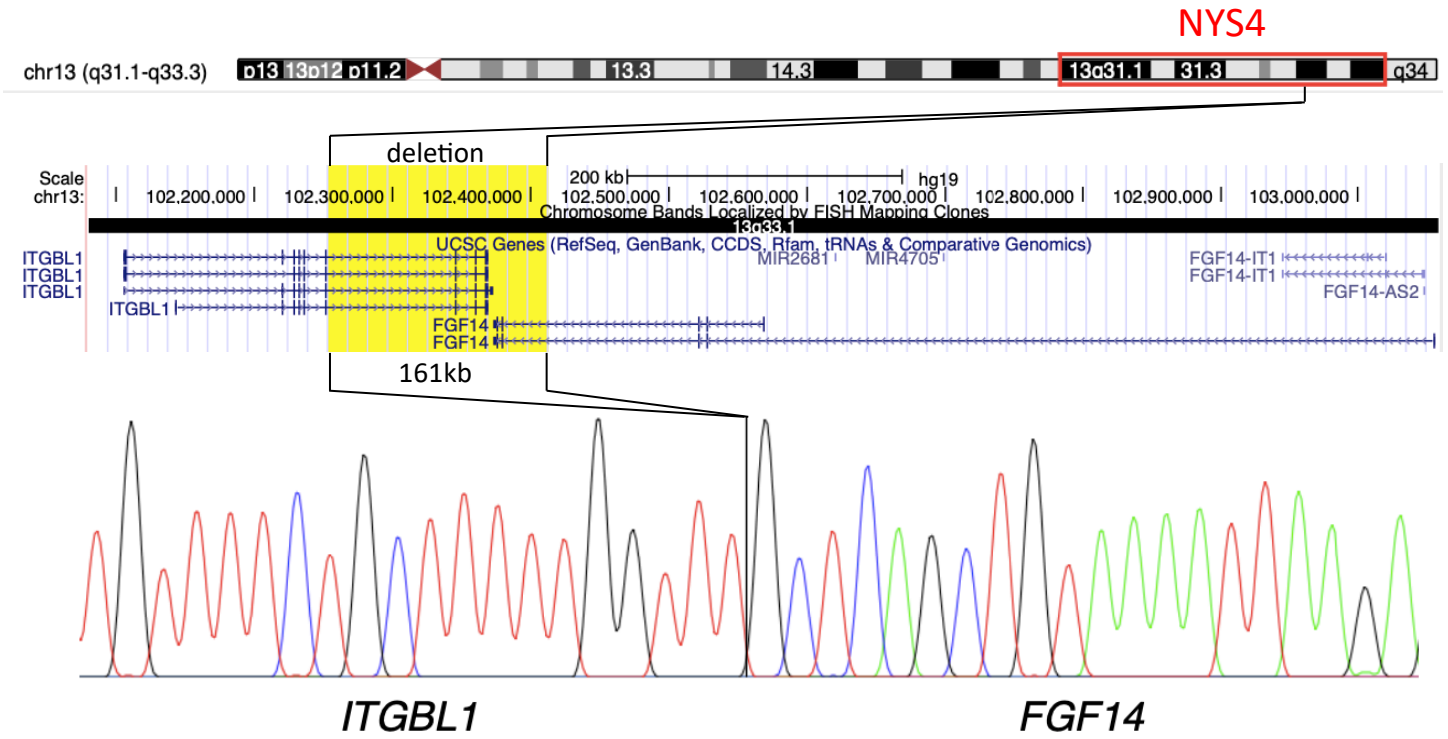
- <20 variants have been reported in families with these phenotypes



FAMILY 1

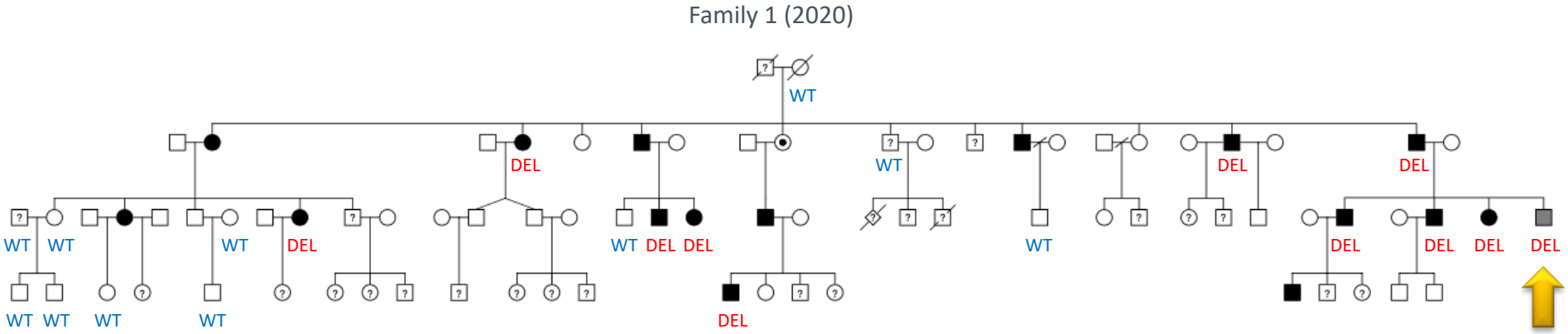
Family 1 (2020)





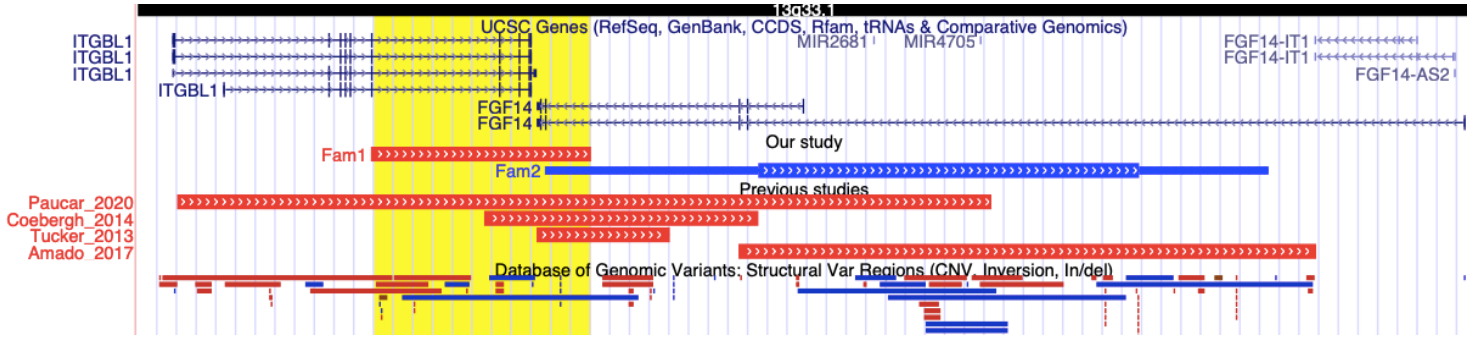
Sam Clokie
(unpublished)

FAMILY 1



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
→ Pathogenic variant



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CONCLUSIONS

- Family 1
  FGF14 heterozygous deletion → underlying cause of NYS4
- Family 2
  FGF14 heterozygous duplication → 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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