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Analysis of Fibroblast Growth Factor 14 (FGF14) structural variants reveals the genetic basis of the early onset nystagmus locus NYS4 and variable ataxia

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Nystagmus (involuntary, rhythmical eye movements) can arise due to sensory eye defects, in association with neurological disorders or as an isolated condition. We identified a family with early onset nystagmus and additional neurological features carrying a partial duplication of FGF14, a gene associated with spinocerebellar ataxia type 27 (SCA27) and episodic ataxia. Detailed eye movement analysis revealed oculomotor anomalies strikingly similar to those reported in a previously described four-generation family with early onset nystagmus and linkage to a region on chromosome 13q31.3-q33.1 (NYS4). Since FGF14 lies within NYS4, we revisited the original pedigree using whole genome sequencing, identifying a 161 kb heterozygous deletion disrupting FGF14 and ITGBL1 in the affected individuals, suggesting an FGF14-related condition. Therefore, our study reveals the genetic variant underlying NYS4, expands the spectrum of pathogenic FGF14 variants, and highlights the importance of screening FGF14 in apparently isolated early onset nystagmus.

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INTRODUCTION

Congenital and early onset nystagmus (involuntary, repetitive oscillation of the eyes) typically manifests within the first months of life. It can be apparently isolated, associated with visual deficits, or seen in the context of numerous neurological disorders. Given the genetic and clinical heterogeneity of these conditions, detailed visual and neurological phenotyping, with analysis of supranuclear eye movements, can direct clinicians towards the underlying genetic causes [1, 2]. However, typical patterns of clinical features suggesting an underlying cause, such as those observed in Infantile Nystagmus Syndrome (INS) or cerebellar-type nystagmus, are not always present [3]. Whole-scale genetic testing is now assisting in diagnosing complex disorders such as nystagmus and, as described here, redefining phenotypes associated with individual gene-related conditions.

Here, we describe a father and son with nystagmus, early onset tremor, and motor difficulties, including mild ataxia. Array-CGH revealed that both individuals carry a partial duplication of FGF14 (Fibroblast Growth Factor 14, OMIM: 601515). Heterozygous FGF14 variants are associated with spinocerebellar ataxia type 27 (SCA27) [4] and episodic ataxia (EA) [5], although some individuals display milder phenotypes, including tremor without ataxia [5] or nystagmus with occasional episodes of vertigo and incoordination [6]. Detailed eye movement analysis revealed oculomotor anomalies strikingly similar to those described in a large dominant pedigree with linkage to a locus on chromosome 13q31.3-q33.1 (NYS4, OMIM: 193003) [7, 8], containing FGF14. Herein, we revisited the original NYS4 pedigree and identified a heterozygous deletion disrupting FGF14 and ITGBL1 in the affected individuals, suggesting an FGF14-related condition. Therefore, our study determines the genetic variant underlying NYS4 and highlights the importance of FGF14 structural variants in milder forms of SCA27, including apparently isolated childhood nystagmus.

CASES AND METHODS

Families 1 and 2 were recruited to a national ‘Genetics of Eye and Brain Anomalies study’ (REC 04/Q0104/129). Informed consent was obtained according to the tenets of the Declaration of Helsinki. Family 1: Copy Number Variant (CNV) screening was performed using a 60-mer oligo-array (8x60K International Standard Cytogenomic Array [ISCA] Consortium configuration [Oxford Gene Technology, Oxford, UK]). Paternal DNA was sequenced with an Illumina HiSeq and SureSelect Ataxia Panel v1 including FGF14 (Agilent Technologies, Santa Clara, CA, USA). Family 2: Whole genome sequencing (WGS) was performed using paired-end, 2 × 150, and 30x coverage with an Illumina NovaSeq 6000 (Theragen Bio, Republic of Korea). The presence of sequence variants in diagnostic ataxia or nystagmus genes was assessed (PanelApp panels *Hereditary ataxia and cerebellar anomalies -
Structural variants were identified using bbmap (https://sourceforge.net/projects/bbmap/). Breakpoints were identified from bbmap-aligned files using the GRIDSS package [9] and validated by PCR and Sanger sequencing.

Both CNVs were evaluated according to the ACMG guidelines [10] using the ClinGen CNV Interpretation Calculator (https://cnvcalc.clinicalgenome.org/cnvcalc/).

RESULTS

Family 1

An 8-year-old boy (II.3, Fig. 1A) was referred to the eye clinic with apparently isolated nystagmus since age 4 years. History and clinical examination revealed that he had mild developmental delay and had started walking after age 2 years. His visual acuity was within normal range (logMAR < 0.18 either eye). He had vertical upbeat nystagmus in primary position, horizontal gaze-evoked nystagmus in side gazes and horizontal rebound nystagmus. Eye movement recordings showed that horizontal and upward smooth pursuits were absent, but downward smooth pursuits were present with reduced gain. His electroretinogram (ERG), visual evoked potentials (VEPs), and cranial magnetic resonance imaging (MRI) were normal. Subsequent neurological examination identified bilateral intention tremor, mild dysmetria, dysdiadochokinesis, and difficulties with heel-to-toe walking. He also had behavioural issues, including mood disorder and aggressiveness (Table 1, Supplemental Material).

His father (I.1) had poor balance, fine motor difficulties, and mood disorder. He had a history of tremor since childhood, initially attributed to asthma medication. He displayed mild left beating nystagmus in primary position, and eye movement recordings showed subtly asymmetric horizontal smooth pursuits. This was only evident on eye tracking with normal smooth pursuit response when moving the eyes to the left, but mildly reduced response when moving the eyes to the right. Neurological examination showed similar findings to the proband, including mild ataxia and mild intention tremor. His cranial MRI was normal (Table 1).

Array-CGH identified a partial FGF14 duplication in both I.1 and II.3 between ~280 kb (chr13:102,535,482-102,815,349, hg19) and ~532 kb (chr13:102,379,344-102,911,282, hg19), which was absent from ClinVar (August 2022) and DECIPHER (April 15th, 2022 release). The two main isoforms of FGF14, 1A (NM_004115) and 1B (NM_175929), differ with respect to their first exon, with the minimum coordinates of the duplication encompassing at least exon 1 of isoform 1A (Fig. 2A). Read depth analysis of next-generation sequencing data from the father and seven normal controls suggests that exons 2–3 are also included in the duplication. If the duplication is in tandem, this would potentially lead to a frameshift in isoform 1B. Given that FGF14 is a haploinsufficient gene, the CNV would therefore be classified as pathogenic [10]. Sequencing data confirmed the absence of pathogenic FGF14 single nucleotide variants (SNVs) in the father.

Family 2

The NY54 pedigree [7, 8] now consists of 17 affected individuals with eye movement anomalies (Fig. 1B). These include nystagmus (gaze-evoked, upbeat and rebound), poor or absent smooth pursuit, and hyperactive vestibulo-ocular reflex. II.16 and III.29 also manifested ataxia, while II.6, II.8, and III.35 had balance problems. II.10 and III.34 reported dizzy spells and mild coordination problems, respectively, without nystagmus. Strabismus and seizures were variably present. Clinical features are summarised in Table 1.

WGS of III.63 and III.64 did not detect pathogenic SNVs in known nystagmus or ataxia genes. However, a 161 kb heterozygous deletion within the NY54 interval was identified in both individuals (chr13:102,250,764-102,412,039, hg19), encompassing 2 exons of FGF14 and 4–5 exons of ITGBL1 (depending on isoform) (Fig. 2A, B). This CNV was also absent from ClinVar (August 2022) and DECIPHER (April 15th, 2022 release). Segregation analysis by PCR showed the deletion was present in 12/12 affected and 0/9 unaffected individuals (Table 1). The deletion was classified as pathogenic according to the ACMG guidelines [10].

DISCUSSION

We identified FGF14 structural variants in two families with early onset nystagmus and variable neurological and behavioural features: a partial duplication of FGF14 in a two-generation family and a heterozygous 161 kb deletion disrupting FGF14 and ITGBL1 in a previously described four-generation pedigree. These data finally elucidate the genetic variant underlying NY54, a locus previously linked to the vestibulocerebellar condition described in the latter family.

FGF14 encodes an intracellular fibroblast growth factor involved in multiple neuronal processes, including channel gating and neuronal excitability [11]. Individuals with pathogenic FGF14 variants manifest EA or develop SCA27, a progressive cerebellar
Table 1. Clinical features of the two families described in this study and previously reported individuals carrying FGF14 deletions.

| Study          | Indiv | FGF14 status | Affected status | Age at last examination (y) | Oculomotor anomalies | Neurological features | Neuroimaging | Development and psychiatric features |
|----------------|-------|---------------|-----------------|-----------------------------|----------------------|-----------------------|--------------|--------------------------------------|
| Current study - Family 1 | I.1   | DUP A         | 31              | LN                          | Asymmetric horizontal SmP | Yes                   | Poor         | Fine motor difficulties              | Normal                  |
|                | II.3  | DUP A         | 8               | UN horizontal GPN and RN    | No horizontal and upward SmP; no vertical saccades, horizontal OKR asymmetry | Yes                   | Yes (mild)  | Frequent falls                        | Fine/gross difficulties, dysmetria, DDK | Normal |
| Current study - Family 2 | I.1   | N/A NE        | Deceased        | NE                          |                       |                       |             |                                       | Motor and speech delay, mood disorder, aggressiveness |
|                | I.2   | WT U          | 65              | None                        |                       |                       | Seizures     |                                       |                         |
|                | I.4   | N/A A         | 47              | UN, GPN SP                  |                       |                       |             |                                       |                         |
|                | I.6   | DEL A         | 46              | UN, GPN SP                  |                       |                       |             |                                       |                         |
|                | I.7   | N/A U         | 43              | None                        |                       |                       |             |                                       |                         |
|                | I.8   | DEL A         | 40              | UN, GPN                     |                       |                       |             |                                       |                         |
|                | I.10  | N/A UA        | 37              | None                        |                       |                       | Dizzy spells|                                       |                         |
|                | I.11  | WT NE         | 36              | NE                          |                       |                       |             |                                       |                         |
|                | I.13  | N/A NE        | 35              | NE                          |                       |                       |             |                                       |                         |
|                | I.14  | N/A A         | 33              | UN, GPN, RN SP              |                       |                       |             |                                       |                         |
|                | I.15  | N/A U         | 31              | None                        |                       |                       |             |                                       |                         |
|                | I.16  | DEL A         | 54              | UN, GPN SP                  |                       |                       | Dizzy spells| Dysarthria (mild)                      |                         |
|                | I.18  | DEL A         | 28              | UN, GPN                     |                       |                       |             |                                       |                         |
|                | I.21  | N/A A         | 26              | GPN                         |                       |                       | Seizures     |                                       |                         |
|                | I.22  | N/A U         | 24              | None                        |                       |                       |             |                                       |                         |
|                | I.24  | DEL A         | 23              | UN, GPN                     |                       |                       |             |                                       |                         |
|                | I.25  | N/A U         | 12              | None                        |                       |                       | Poor**       |                                       |                         |
|                | I.26  | N/A U         | 12              | None                        |                       |                       | Poor**       |                                       |                         |
|                | I.27  | WT U          | 15              | None                        |                       |                       |             |                                       |                         |
|                | I.28  | DEL A         | 14              | UN, DN, GPN, RN             |                       |                       | Normal       |                                       |                         |
|                | I.29  | DEL A         | 32              | UN, DN GPN SP               |                       |                       | Dizzy spells| Normal                                | Bordeline personality disorder, depression |
|                | III.30| N/A A         | 21              | GPN, unsteady upgaze        |                       |                       |             |                                       |                         |
|                | III.31| N/A NE        | 10              | NE                          |                       |                       |             |                                       |                         |
|                | III.32| WT U          | 5               |                            |                       |                       |             |                                       |                         |
|                | III.33| WT U          | 25              | None                        | Dyspraxia              |                       | Normal       |                                       |                         |
|                | III.34| WT U          | 25              | None                        |                       |                       |             |                                       |                         |
|                | III.35| DEL A         | 4               | UN, GPN                     |                       |                       | Poor         |                                       |                         |
|                | III.36| DEL A         | 1.5             | GPN                         |                       |                       |             |                                       |                         |
|                | III.37| WT U          | 1*              | NE                          |                       |                       |             |                                       |                         |
|                | III.38| WT U          | 3               | None                        |                       |                       |             |                                       |                         |
|                | III.39| DEL A         | 3               | GPN SP                      |                       |                       |             |                                       |                         |
| Study                | Indiv | FGF14 status | Affected status | Age at last examination (y) | Oculomotor anomalies | Neurological features | Neuroimaging | Development and psychiatric features |
|----------------------|-------|---------------|-----------------|----------------------------|----------------------|----------------------|--------------|-------------------------------------|
| Tucker et al. 2013   | IV.40 | N/A           | U               | 5                          | None                 |                      |              |                                     |
|                      | IV.65 | WT            | U*              | NE                         | NE                   |                      |              |                                     |
|                      | IV.66 | WT            | U*              | NE                         | NE                   |                      |              |                                     |
|                      | IV.81 | N/A           | A*              | NE                         | None                 |                      |              |                                     |
| Coebergh et al. 2014 |       |               |                 |                            |                      |                      |              |                                     |
|                      | Mother | DEL          | A               | NR                         | Yes                  | Yes (mild)           | Normal       | Low IQ, speech delay                 |
|                      | Proband | DEL          | A               | NR                         | Yes                  | Yes (mild)           | Normal       |                                     |
| Planes et al. 2015   |       |               |                 |                            |                      |                      |              |                                     |
|                      | Proband | DEL          | A               | 20                         | NR                   | Delayed and slow saccades | Yes          | Moderate ID, speech delay            |
|                     | Amado et al. 2017 | Adopted twins | DEL          | 4                          | Yes                  | Yes                  | No           |                                     |
|                     | II.1 | N/A           | A               | 83                         | Yes                  | Yes                  | Yes          |                                     |
|                     | II.2 | DEL           | A               | 65                         | All directions        | Weak horizontal and absent vertical OKN | Yes          | Low IQ, memory and executive function impairment |
|                     | II.5 | DEL           | A               | 63                         | Yes                  | Weak horizontal and vertical OKN | Yes          | Low cognitive profile, SE, hypertension, depression |
|                     | III.1 | DEL          | A               | 48                         | Yes                  | Yes                  | Yes          | Low IQ, memory and executive function impairment |
|                     | III.2 | DEL          | A               | 39                         | GPN                  | Weak vertical and horizontal OKN | Yes          | Low IQ, language delay dystonia, SE, ADHD |
|                     | IV.1 | DEL           | A               | 18                         | Vertical and GPN      | Weak vertical OKN   | Yes          | Low cognitive profile, dyscalculia, SE, ADHD, anger outbursts |
| Zech et al. 2021     | Proband | DEL          | A               | 10                         | NR                   | NR                   | Yes          | Childhood-onset segmental dystonia, myopathy |

A Affected, ADHD Attention Deficit Hyperactivity Disorder, Cen Central, Cor Cortical, Crb Cerebellum, Csp Cervical spine, CT Computerised Tomography scan, DDK Dysdiadochokinesis, DEL FGF14 deletion, DN Downbeat Nystagmus, DUP FGF14 duplication, GPN Gaze evoked Nystagmus, ID Intellectual Disability, IQ Intelligence Quotient, LN Leftbeat Nystagmus, MPMC Minipolymyoclonus, MRI Magnetic Resonance Imaging, N/A Not Available, NE Not Examined, NR Not Reported, OKN Optokinetic Nystagmus, OKR Optokinetic Reflex, RN Rebound Nystagmus, SE Special Education, SmP Smooth Pursuit, SP Saccadic Pursuit, U Unaffected, UA Unassigned (examined but inconclusive symptoms/signs), UN Upbeat Nystagmus, Ver Vermis, WM White Matter, WT Wild-Type (no FGF14 variant), y years. *Affected status reported by the family (not examined); **The twins had severe hearing loss, needing hearing aids, present since the neonatal period when they had severe complications requiring intensive care treatment. Their mild balance problems have been linked to these early difficulties.
ataxia frequently presenting with nystagmus, tremor, dysarthria, limb ataxia, and variably associated with psychiatric symptoms and cognitive impairment. Eighteen pathogenic variants have been reported to date, including six heterozygous deletions \([12–17]\), three of which overlap that of family 2 (Fig. 2C). While translocations and deletions are likely to cause functional haploinsufficiency, the effect of duplications is harder to predict. The variant in family 1 is the first report of a partial \(FGF14\) duplication and affects between one and three exons. Depending on the localisation and orientation of the duplicated fragment, this
variant could alter the production, folding, localisation and/or function of the protein.

SCA27 is characterised by early onset and slow progression (ataxia onset: 23.7±16.7 years), with only 13.8% of patients developing severe gait impairment [18]. In family 2, nystagmus was the most frequent and consistent feature, while balance problems were more variably present. Of note, four of five affected members exhibiting unsteadiness or ataxia were age ≥30 years at their last examination, whereas those not exhibiting ataxia/balance problems were mostly younger when examined [8]. Therefore, young age of assessment together with the variable presentation of ataxic features may account for the absence of gait impairment among family 2 carriers of the FGF14 deletion.

Phenotypic intra- and inter-familial variability is a hallmark of FGF14 variants [5,18]. Family 2 expands this variability to include isolated nystagmus and milder clinical features. While III.63 had early onset nystagmus diagnosed by the age of three, her brother III.64 was initially reported as unaffected. Re-examination of III.64 on the basis of our genetic findings revealed a similar, but far more subtle, pattern of eye movement anomalies including horizontal gaze-evoked nystagmus, saccadic pursuit, and dysmetric saccades. Similarly, the affected status of II.10 was originally unassigned as she exhibited dizzy spells without nystagmus. While DNA was unavailable, the inheritance pattern of the deletion indicates that she is an obligate carrier, suggesting her phenotype represents an extremely mild form of SCA27. Therefore, family 2 supports an emerging model whereby mild phenotypes, including apparently isolated nystagmus, can result from variants in genes associated with ataxia [19].

Furthermore, this study highlights how detailed characterisation of oculomotor anomalies within a broader movement disorder can provide insights into the genetic basis of conditions such as SCA27. Early onset nystagmus with minimal or absent tremor and ataxia could be mistaken for other forms of nystagmus seen in infancy. In our families, the oculomotor pattern is mainly characterised by vertical nystagmus and horizontal gaze-evoked nystagmus with decelerating slow phases, which would be indicative of neurological nystagmus [20]. This supports some of the previous descriptions for FGF14-related conditions where details of eye movements are mentioned [12,14]. However, since such detailed eye movement evaluation is rarely possible in routine clinical practice, particularly in children, we recommend the inclusion of FGF14 on gene panels for childhood nystagmus.

In conclusion, our study identifies the genetic basis of NYS4, expands the spectrum of FGF14 variants, refines the phenotypes of the associated oculomotor anomalies, and demonstrates the value of screening FGF14 in children with apparently isolated early onset nystagmus.

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DATA AVAILABILITY

The two variants described in this study have been submitted to the ClinVar repository (SCV002570104, SCV002570105).

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AUTHOR CONTRIBUTIONS
JES and NKR designed the study. FC, DO, JES and NKR wrote the manuscript. FC, SC and EJC performed data generation, analysis and interpretation. NKR, DO, MJD, JES and CMH performed clinical examinations of the families. DAB carried out research coordination. All authors read and approved the manuscript.

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COMPETING INTERESTS
The authors declare no competing interests.

ETHICS APPROVAL
The families included in this study were recruited to a national ‘Genetics of Eye and Brain Anomalies study’ (approved by the UK Regional Ethics Committee Cambridge-East, REC 04/Q0104/129). Informed consent was obtained according to the tenets of the Declaration of Helsinki.

INFORMED CONSENT
Informed consent was obtained according to the tenets of the Declaration of Helsinki.

ADDITIONAL INFORMATION
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