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Genetic testing for infantile nystagmus syndrome with or without associated findings

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Abstract

PURPOSE—To review the published literature assessing the clinical utility of genetic testing in individuals with infantile nystagmus syndrome (INS), defined as binocular conjugate nystagmus and onset prior to 6 months of age, with or without associated findings.

METHODS—A literature search was last conducted in October 2022. The results were limited to articles published in English. The search yielded 517 abstracts, of which 72 papers were reviewed in full text. Of these papers, 4 met the criteria for inclusion and were graded by a study methodologist.

RESULTS—The 4 studies that met inclusion criteria used next-generation sequencing with gene panels ranging from 31 to 336 genes. The overall molecular diagnostic rate ranged from 35% to 60% in the included studies, although the yield was higher when genetic testing was guided by clinical phenotyping (approximately 80%) and in the subsets of patients with a family history (up to 88%). As many as 30% of patients tested had a reclassification of the diagnosis based on the genetic testing results.

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CONCLUSIONS—Genetic testing has the potential to provide a definitive diagnosis and identify treatable conditions in patients presenting with INS, especially when considered in conjunction with clinical phenotyping and family history.

Infantile nystagmus syndrome (INS) is characterized by the involuntary oscillation of one or both eyes presenting prior to 6 months of age.[1] Although many inherited retinal disorders present with nystagmus, INS is a broad category of diagnoses that includes familial and idiopathic cases, such as idiopathic INS (previously termed *congenital motor nystagmus*) as well as sensory nystagmus due to conditions such as oculocutaneous albinism.[1,2] In patients with INS, a complete ophthalmological examination is essential, and in some cases will identify the cause of the nystagmus. Subsequent diagnostic workup may include ocular imaging such as fundus photography, autofluorescence, and optical coherence tomography (OCT); neuroimaging, such as brain magnetic resonance imaging (MRI); and functional testing, such as electroretinography (ERG) and visual evoked potential testing. Although the quality of ocular imaging tests may be limited in some children with nystagmus due to the ocular oscillations, low vision limiting the ability to fixate, and limited cooperation, these tests are often an important part of the clinical assessment.[3,4] ERG may be considered when there is suspicion for a retinal dystrophy; however, in young children this may require sedation or general anesthesia. Not only does general anesthesia carry systemic concerns,[5] it can modify the visual electrophysiology results and the data should be interpreted accordingly.[6-9] Furthermore, access to electrophysiology may be limited. MRI may be indicated if clinical findings (optic atrophy, papilledema, optic nerve hypoplasia, or other neurological abnormalities) raise a specific concern for underlying central nervous system pathology, but MRI, like ERG, may require sedation or general anesthesia. Additionally, the yield of MRI is low for INS in general. A retrospective study of all patients diagnosed with nystagmus with onset prior to 6 months of age reported that the yield of MRI alone as the first test ranged from 0%-16%, and emphasized that ERG, OCT, and molecular testing should be performed early in patients with INS in the absence of other neurologic signs.[3]

The expansion of genetic testing provides more opportunities to evaluate children with INS. Although the diagnostic yield of genetic testing for conditions such as inherited retinal diseases that can be associated with nystagmus has been established,[10] there is less data available for the broader population of patients presenting with INS with and without systemic findings. Genetic testing can be useful for several reasons, including the ability to determine a specific etiology of the nystagmus, which may inform the visual prognosis and help direct additional systemic or neurological workup related to the diagnosis. For example, some disorders that cause nystagmus, such as Alstrom syndrome, may have systemic implications such as cardiac or endocrine abnormalities, and a precise diagnosis is necessary to guide further systemic investigations. Additionally, establishing a genetic diagnosis is important for genetic counseling and recurrence risk. Clarifying the genetic diagnosis is also increasingly important for eligibility for newly emerging gene-based therapies.[11]

Advances in genetic testing have the potential to change the diagnostic algorithm of patients with INS and thus the everyday clinical approach for this disease. Herein, we review the literature to determine the current clinical utility of genetic testing in children with INS with and without associated findings.

Methods

A literature search was conducted in October 2022 in the PubMed database, with no date restrictions, but limited to articles published in English. The search strategy used the following terms: (“nystagmus, congenital”[tiab] OR “nystagmus”[ti] OR “nystagmus in infancy”[tiab] OR “infantile nystagmus”[tiab] OR “nystagmus, congenital”[MeSH terms] OR “nystagmus in infancy and childhood”[tiab] OR “nystagmus”[tiab] AND (“pediatric”[tiab] OR “child”[tiab] OR “childhood”[tiab])) OR (“genetic testing”[mh] OR “gene”[tiab] OR “genes”[tiab] OR “genetic”[tiab] OR “genetics”[tiab] OR “genetic testing”[tiab] OR “gene”[tiab] OR “genetic”[tiab]) AND (“test”[tiab] OR “testing”[tiab] OR “evaluation”[tiab] OR “whole exome sequencing”[tiab] OR “microarray”[tiab] OR “molecular genetic testing”[tiab] OR “DNA mutational analysis”[MeSH terms] OR “genetic markers”[tiab] OR “*FRMD7* associated”[tiab] OR “FRMD7”[tiab]).

The search identified 517 potentially relevant abstracts, which were reviewed by the first author (KMC). Of these, 72 were selected for full-text review. Those that met the following inclusion criteria were included in the final assessment: (1) the research was original; (2) the primary objective of the study was to test for genetic etiologies of INS using gene panels for more than 1-2 genes; (3) the study focused on human subjects (not animal models); and (4) the study focused on more than one family and more than three patients (ie, not an extended pedigree of one family or case report).

After full-text review, 4 articles met the inclusion criteria. The methodologist (RT) then assigned a level of evidence based on the rating scale developed by the Oxford Centre for Evidence-Based Medicine.[12] A level I rating was assigned to well-designed and well-conducted randomized controlled trials and systematic reviews. A level II rating was assigned to well-designed cohort studies and nonrandomized controlled cohort/follow-up trials. A level III rating was assigned to case-series or to lower-quality case-control or cohort studies.

Results

The 4 included studies were all graded as level III evidence. The patient characteristics, type of testing, diagnostic yield, variants identified, and diagnosis reclassification are summarized in Table 1.

Choi and colleagues[13] studied 37 unrelated patients (mean age with standard deviation, 36.3 ± 16.9 years; range, 6-72) with onset of nystagmus within the first 6 months of life. Patients were classified into “ocular” (20), “neurologic” (2), “motor” (10), and “unknown” (5) groups. Of all patients, 27 were sporadic, and 10 had a first- or second-degree family history of nystagmus. All patients underwent analysis with next-generation sequencing (NGS) 98 gene panel designed using a web-based application by Agilent Technologies that included genes for inherited conditions causing nystagmus, albinism, and retinal dystrophies. The overall molecular diagnostic rate was 35% (13/37). Overall, genetic testing confirmed a prior clinical diagnosis in 9 of 13 patients and identified a molecular diagnosis in 2 of 5 previously “unknown” patients. A family history and a pendular waveform of nystagmus

were both associated with genetically confirmed idiopathic infantile nystagmus syndrome. The yield in the 10 patients with a known family history of nystagmus was 80% (8/10). Family history had the highest predictive power of a positive molecular diagnosis, with a sensitivity of 61.5% and specificity of 91.7%, and was present in 8 of 13 patients (62%) with molecular diagnosis compared to 2 of 24 patients (8%) without a molecular diagnosis. The sensitivity of clinical findings for a molecular diagnosis ranged from 23.1% for strabismus to 69.2% for foveal hypoplasia. However, when combining family history with clinical signs, such as anterior segment dysgenesis, pendular nystagmus, and foveal hypoplasia, the sensitivity improved to 76.9%, 76.9%, and 84.6%, respectively. The specificity of findings ranged from 47.4% for foveal hypoplasia to 93.3% for both anterior segment dysgenesis and pendular nystagmus; however, the specificity did not improve with combining clinical signs (range, 47.4%-79.2%). The initial clinical diagnosis was revised in 4 patients (30%): 2 in the ocular group and 2 in the unknown group. The 4 revisions included 1 patient whose diagnosis changed from foveal hypoplasia to idiopathic infantile nystagmus, 1 patient from unknown to congenital stationary night blindness, 1 patient from Leber congenital amaurosis to achromatopsia, and 1 patient from unknown to Leber congenital amaurosis. Although ERG was not included prior to genetic testing, 1 patient had an ERG after molecular diagnosis that was consistent with the diagnosis of Leber congenital amaurosis. *PAX6* variants, commonly associated with aniridia, and *FRMD7* variants, which have been linked to idiopathic infantile nystagmus syndrome in a normal visual system, were the most common of the 6 gene variants identified. These results highlight that a revision in the clinical diagnosis may occur after genetic testing as clinical signs can be nondefinitive, particularly due to overlapping phenotypic appearances in various conditions. Therefore, a targeted NGS panel can be a useful ancillary diagnostic tool to confirm a clinical diagnosis especially in patients with a positive family history or foveal hypoplasia.

Rim and colleagues[14] investigated the utility of 113-gene NGS panel (which included genes related to genetic conditions causing nystagmus without a sensory vision abnormality, albinism, *PAX6* and retinal dystrophies) in 48 patients (mean age, 9.2 ± 10.3 years; range, 0.3-39.8) with infantile nystagmus syndrome. The initial clinical diagnoses included idiopathic (15 patients), ocular albinism (4), *PAX6*-related phenotypes (3), achromatopsia (3) and Leber congenital amaurosis (23). Of the 48 total patients, 32 (67%) underwent ERG testing prior to genetic testing and 8 (17%) had a family history of nystagmus. The molecular diagnostic rate was 58.3% (28/48) and was higher in those with a family history (88%, 7/8) than in the 40 patients without a family history (21/40 [53%]). The findings are summarized below by initial clinical diagnosis group (prior to ERG).

Of the 15 patients in the idiopathic group, 8 (53%) had a confirmed or possible molecular diagnosis (1 *PRGR1P1* and *1 CRB1* with Leber congenital amaurosis, 1 *GPR143* with ocular albinism, 2 *PAX6* with PAX6-related phenotypes, 2 *FRMD* with idiopathic INS, 1 *CACNA1F* with congenital stationary night blindness). Of these 8 patients diagnosed through genetic testing, most had horizontal nystagmus, with either a jerk (5) or pendular (2) waveform. The fundus was grossly normal in 6, while 2 had an abnormal fundus; 1 with pigmentary mottling had the diagnosis changed from idiopathic to Leber congenital amaurosis and 1 with no foveal reflex was changed from idiopathic to *PAX6*-related after genetic testing. Three of the 8 had ERG data; in 2 patients whose initial clinical diagnosis

was revised to Leber congenital amaurosis after genetic testing, the ERG was extinguished, while 1 patient whose diagnosis was revised to congenital stationary night blindness had a normal ERG.

In the groups with an initial clinical diagnosis other than idiopathic, the clinical diagnosis was confirmed or likely based on genetic testing in 3 of 4 (75%) in the ocular albinism group, 2 of 3 (67%) in the *PAX6*-related phenotypes group, 3 of 3 (100%) in the achromatopsia group, and 16 of 23 (70%) in the Leber congenital amaurosis group. A molecular diagnosis remained unresolved in 12 patients. Apart from the idiopathic group, the diagnoses of 3 patients were revised. These patients were initially diagnosed with Leber congenital amaurosis and were changed to achromatopsia in 1 patient, Senior-Loken syndrome in 1 patient, and infantile cerebellar-retinal degeneration in 1 patient. The authors concluded that genetic testing is useful for both diagnosis and revision of an initial diagnosis, because it enables clinicians to tailor further testing and counsel patients and their families.

Thomas and colleagues[15] reported on 15 patients (range, 1-58 years of age) randomly selected from a database of 300 familial cases of patients with onset of nystagmus within the first 6 months of life. The clinical diagnosis was idiopathic nystagmus in 5 patients, albinism in 5 patients, *PAX6*-related phenotype in 3 patients and congenital stationary night blindness in 2 patients. Electroretinography was performed and interpreted as normal in 10 patients, not performed due to limited cooperation in 3 patients, and had a negative waveform in 2 patients. The patients then underwent genetic testing with a 336 NGS panel, which included genes related to inherited conditions causing nystagmus without a sensory vision abnormality, albinism, *PAX6* and retinal dystrophies. The overall molecular diagnostic rate was 60% (9/15) when masked to clinical features, with 2 idiopathic, 2 ocular albinism and 2 *PAX6*-related phenotype patients resulting in an unknown diagnosis. When clinical information such as best corrected visual acuity, refraction, color vision, nystagmus characteristics, iris transillumination defects, and fundus appearance was added and a reanalysis was performed, the yield increased to 80% (12/15). The final genetic diagnoses were *FRMD7* in 3 patients, *TYR/TYRP1* in 6 patients, *CRYBA1* in 1 patient and *CACNA1F* in 2 patients. The results of genetic testing revised the clinical diagnosis in 3 of 12 patients (1 *TYR* variant, 1 *CRYBA1* variant and 1 *TYRP1* variant). Both patients with a clinical diagnosis of congenital stationary night blindness had a genetic diagnosis of *CACNA1F*. Of the 5 patients with a clinical diagnosis of idiopathic infantile nystagmus syndrome, all had a horizontal jerk waveform, normal fundus appearance and normal color vision. An ERG was performed in 3 and was normal. A genetic diagnosis was reached in 4 of 5 patients in the idiopathic INS group (*FRMD7* in 3 patients and *TYRP1* in 1 patient). Three patients remained without a diagnosis (2 *PAX6*-related phenotype and 1 idiopathic). These results highlight the importance of using clinical phenotyping along with genetic testing in evaluating patients with nystagmus.

O'Gorman and colleagues[16] published a study of 81 unrelated patients (0-18 years of age) with infantile nystagmus syndrome for whom neither full clinical examination nor systematic ERG (which was performed in all patients prior to genetic testing) yielded a diagnosis other than albinism, and in whom the nystagmus therefore was presumed

idiopathic or related to albinism. Patients underwent phenotyping and were subsequently divided into four groups: clinically idiopathic with complete phenotyping (group 1, 18 patients), clinically idiopathic with incomplete phenotyping (group 2, 15 patients), clinical phenotyping consistent with albinism (group 3, 20 patients) and clinical features suggestive of albinism with incomplete phenotyping (group 4, 28 patients). Next-generation sequencing with the 31 gene *UKGTN* gene panel for nystagmus and albinism was performed. The overall diagnostic yield was 43.2%, lower in the patients with a clinical diagnosis of idiopathic nystagmus (groups 1 and 2, 12/33 [36.3%]) compared to the patients with suspected albinism (groups 3 and 4, 23/48 [47.9%]). In group 1 consisting of 18 patients with idiopathic nystagmus with complete phenotyping and a normal ERG and OCT, 7 (38.9%) had likely causal variants (*CACNA1A, CACNA1F, FRMD7, HPS5, TYR*). In the 15 patients in group 2 who had idiopathic nystagmus with incomplete phenotyping including normal, equivocal or untested ERG and OCT, 5 (33%) had likely causal variants (*CACNA1A, CACNA1F, FRMD7, OCA2, SACS*). For group 3 with clinical albinism, normal ERG and an OCT demonstrating foveal hypoplasia, 10 of 20 patients (50%) had likely causal variants (*OCA2, TYR, TYRP1*). Finally, in group 4, 13 (46%) of 28 with clinical features suggestive of albinism but with equivocal ERG and/or untested, equivocal or normal OCT results had likely causal variants (*CACNA1A, CACNA1F, HPS5, OCA2, PAX6, TYR*). Six patients had pathogenic variants that identified disease that would have been misdiagnosed based on the clinical appearance alone. For example, 1 patient who was diagnosed as idiopathic was found to have a likely disease-causing variant in the *OCA2* gene. The gene panel used contained only 31 genes, compared to 98 to 336 in the other studies included in this review. Therefore, the diagnostic yield of genetic testing for infantile nystagmus syndrome is likely underestimated by this study. Nonetheless, the authors concluded that genetic testing is relatively high yield in children with infantile nystagmus syndrome and tailored gene panels may result in more efficient workflows.

Discussion

Due to the significant differences in methodology used across the small number of published studies, a direct comparison of the results between studies is limited. The data from the level III evidence reviewed in this assessment suggest that genetic testing for INS has clinical utility as it may increase the diagnostic yield to up to approximately 80% when used in conjunction with clinical findings and family history, which could potentially result in clinically relevant re-classification of disease. All four studies demonstrated a revision of the initial clinical diagnosis even in some cases of isolated INS, with similar findings by Choi and colleagues[13] (30%), Rim and colleagues[14] (21%), and Thomas and colleagues[15] (20%). The lower rate that O'Gorman and colleagues[16] found (7.4%) may be attributed to the fact that ERG was systematically attempted on all patients and those with an ERG diagnosis were excluded from the analysis, so there were fewer conversions of "idiopathic" to retinal dystrophy.

Genetic testing has several limitations. First, testing does not guarantee that a condition will be identified, and a negative test does not necessarily exclude a clinical condition, because not all conditions have known or identified genes. Second, incidental or secondary findings on genetic testing may require interventions such as referral to other subspecialists

and/or further testing to clinically correlate the incidental findings. Additionally, obtaining genetic testing may be expensive due to varied insurance payment and reimbursement structures, and may take a long time. Other concerns include inadequate coverage of the gene of interest, the uncertain clinical relevance of variants of unknown significance, identification of pre-symptomatic non-actionable syndromic diagnoses and the potential for genetic discrimination. Finally, resources for selecting appropriate testing from among a variety of options, interpreting the results of genetic testing, and genetic counseling may not be readily available. INS in particular represents a heterogeneous group of disorders, and panels for nystagmus vary considerably in what genes are included; clinical phenotyping can play a valuable role in guiding appropriate genetic testing. Despite the limitations, our findings suggest that genetic testing in children with INS has the potential to clarify a clinical diagnosis or identify a condition that may require nonophthalmologic intervention or monitoring, particularly when used in conjunction with clinical phenotyping. However, genetic testing is not intended to replace other ancillary tests, and clinical judgment is needed to determine the appropriate workup for INS depending on the clinical context (eg, an MRI is indicated in a child with nystagmus, severe developmental delay, and optic atrophy). The role of genetic testing may continue to evolve with the emergence of novel gene therapies.

Future research on the clinical utility of genetic testing for patients with INS requires high-quality, larger prospective trials using standardized and well-defined inclusion and exclusion criteria. Additionally, standardization of the technology employed for genetic analysis and genes included in panel testing is essential. The use of newer technologies and more comprehensive testing, such as whole-exome sequencing or whole-genome sequencing, should also be evaluated. The continued improvement and refinement of genetic testing in conjunction with clinical phenotyping may support its future inclusion in the everyday evaluation and treatment practice patterns for patients with INS.

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Table 1.

Summary of results

Authors	No. patients	Mean age, years (range)	Family history of nystagmus, no. (%)	Genetic testing	Genes tested	Gene variants identified	Diagnostic yield	Diagnosis reclassified (no.)
Choi et al[13]	37	36.3 ± 16.9 (6-72)	10/37 (27)	NGS	98 gene panel	*PAX6* *FRMD7* *GPR143* *CACNA1F* *CNGA3* *GUCY2D*	35% (13/37) overall *Key points* Family history 80% (8/10) Foveal hypoplasia alone: 69.2% Combined family history or foveal hypoplasia:84.6%	30% (4)[a]
O'Gorman et al[16]	81	0-18	No	NGS	31 gene panel	*HPS5* *PAX6* *TYR* *OCA2* *CACNA1A* *CACNA1F* *FRMD7(2)* *MLPH* *TULP1* *SACS* *SLC24A5*	43.2% (35/81) overall in patients with nondiagnostic ERG findings *Key points* Clinically idiopathic nystagmus (groups 1 and 2, 12/33 [36.3%]) vs patients with suspected albinism (groups 3 and 4, 23/48 [47.9%])	7.4% (6)[b]
Rim et al[14]	48	9.2 ± 10.3 (0.3-39.8)	8/48 (17)	NGS	113 gene panel	*GUCY2D* *NMNA T1* *RPGR1P1* *CEP290* *CRB1* *CRX* *WDR1* *GPR143* *PAX6* *CNGB3* *FRMD7* *CACNA1F*	58.3% (28/48) overall *Key points* Family history: 88% (7/8) Idiopathic group: 53.3% (8/15) had a confirmed or possible molecular diagnosis	21% (10)[a]
Thomas et al[15]	15	24.4 (1-58)	15/15 (100)	NGS	336 gene panel	*FRMD7* *CACNA1F* *TYR* *CRYBA1* *TYRP1*	80% (12/15) overall with clinical features (including BCVA, refraction, color vision, nystagmus characteristics, iris transillumination defects, and fundus appearance) *Key point* 60% (9/15) when masked to clinical features	20% (3)[b]

BCVA, best-corrected visual acuity; *ERG*, electroretinography; *NGS*, next-generation sequencing.

[a]Reclassified from initial clinical diagnosis, which did not include ERG findings.

[b]Reclassified from clinical diagnosis, which could include ERG findings.