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Nance-Horan Syndrome: Further Delineation of the Affected Male and the Female Carrier Phenotypes

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ABSTRACT

Nance-Horan syndrome (NHS; OMIM 302350) is a rare, X-linked syndrome characterized by bilateral congenital cataracts leading to profound vision loss, specific dental anomalies including characteristic screwdriver blade-shaped incisors, facial anomalies, and intellectual disability. It is caused by deleterious loss of function variants or deletions involving the *NHS* gene at Xp22.13. Heterozygous females often present with similar, but less severe features than affected males. We describe a relatively large cohort of eight new patients with NHS, including two patients with microdeletions including *NHS* who had classical presentations, and provide detailed descriptions of the clinical findings for both affected males and females. The spectrum of clinical features in NHS is variable and can be mild, in particular for females, and the condition can remain undiagnosed. This report contributes to the delineation of the phenotypic and genotypic findings associated with this condition.

1 | Introduction

Nance-Horan syndrome (NHS; Mendelian Inheritance in Man [OMIM] #302350; also known as cataract-otodental syndrome) was first described by Horan and Billson (1974) and Nance et al. (1974). NHS is a rare, X-linked disorder characterized by congenital cataracts with microcornea and strabismus, specific dental anomalies, and characteristic dysmorphic features with a long face, prominent nose, and mandibular prognathism (Nance et al. 1974). Ophthalmological findings in affected males include congenital, bilateral, severe dense stellate and nuclear cataracts that require surgery at an early age. Nystagmus may develop secondary to early visual deprivation from the cataracts. Despite early surgical removal of cataracts, visual acuity may remain poor, and retinal dysfunction is suspected based on pathological studies demonstrating marked retinal cystoid degeneration (Mathys et al. 2007; Ding et al. 2009). Microcornea, glaucoma, and microphthalmia have also been reported (Lewis 1989; Walpole

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et al. 1990). In females, lens opacities centered on the posterior Y-sutures are more frequent (Bixler et al. 1984; Zhu et al. 1990; Khan et al. 2012; Gómez-Laguna et al. 2018). These opacities are likely congenital and can be progressive, although females rarely need lens extraction in infancy (Fraccaro et al. 1967; Krill et al. 1969; Nance et al. 1974; Pavone et al. 1981; Bixler et al. 1984; Lewis 1989). The dental findings are distinctive, involving both primary and permanent dentitions in 100% of affected males, and are pathognomonic for NHS, either by their type or by their aggregation in the same individual (Sharma et al. 2017). Tooth anomalies include supernumerary teeth (mesiodens), tapering and screwdriver blade-shaped incisors, Hutchison incisors, a wide diastema, fused teeth, and molars that can be rounded, globular, and mulberry-shaped. Dental findings are seen in all males but are often present in a milder form among carrier females. There is a subtle, but recognizable pattern of distinctive facial features including large, anteverted and simple ear pinnae, a long and narrow face, a prominent nose and nasal bridge, and a pointed chin with prognathism. When examined carefully, female carriers also often share similar facial features with males (Walpole et al. 1990; Khan et al. 2012). Several families have also been reported to have shortening of the fourth and fifth digits (Lewis 1989; Walpole et al. 1990; Burdon et al. 2003). Intellectual disability is present in 30% of patients ranging from mild to severe (Walpole et al. 1990; Toutain et al. 1997) and autism has also been reported in rare cases (Toutain et al. 1997).

NHS is inherited as an X-linked, semi-dominant trait with high penetrance, with heterozygous females often manifesting similar, but less severe, features compared to affected males. However, female patients may have severe manifestations of the disease when skewed X-inactivation deviation is significant (Huang et al. 2023). NHS is caused by deleterious variants in *NHS* located at Xp22.13. This gene encodes a protein with four conserved nuclear localization signals that is a regulator of actin assembly and cell spreading (Gómez-Laguna et al. 2018). The NHS protein functions in the lens, dental primordia, craniofacial mesenchyme, and the brain during development (Burdon et al. 2003; Brooks et al. 2004, 2010).

To date, the number of reported cases of NHS remains relatively small and NHS is considered a rare condition. The spectrum of clinical findings, especially among female carriers, is not well-defined and although the aggregated features form a distinct and recognizable condition, one or more of the clinical findings are often not identified (Lewis 1989; Khan et al. 2012; Miller et al. 2021; Huang et al. 2023). Minor findings in heterozygous carriers and the variability of the dental findings, in addition to the subtlety of the craniofacial findings, likely lead to under ascertainment and reduced diagnosis of the syndrome. Herein we report the novel sequence variants and detailed clinical information for all eight affected males and female patients with NHS and provide a detailed literature review of the clinical features to improve the understanding of the phenotype associated with this condition.

2 | Clinical Reports

Genomic testing was performed as part of routine clinical care for most of these families and therefore institutional research ethics approval was not obtained. All families provided written permission for publication. The clinical findings have been summarized in Table 1.

2.1 | Patient 1

A 10-year-old boy was referred for a genetic evaluation to determine the cause of his ophthalmological and dental findings. He was born at term. He had no red reflex bilaterally and was diagnosed with bilateral congenital cataracts that were extracted at age 5 weeks. He developed glaucoma following cataract surgery. Other eye findings comprised microphthalmia and wide amplitude nystagmus. He needs visual aids. He has a long face with a bulbous nose and a pointed chin (Figure 1). He has widely spaced teeth that were small and shaped similar to a "screwdriver blade." His hearing is normal, and he attends mainstream school without evidence of intellectual impairment. His developmental milestones were normal.

His mother was noted to have similar facial features, with a long, narrow face, prominent nose and distinctive dental anomalies including screwdriver blade-shaped incisors and a wide diastema between her teeth (Figure 1). The maternal grandmother also has similar facial findings (Figure 1). Both mother and grandmother wear glasses, but an ophthalmology examination, which was done after genetic testing, did not report cataracts or other abnormal eye findings in either woman. His mother has had cosmetic dentistry and his maternal grandmother uses dentures.

2.2 | Patient 2

An 8-year-old male was seen in follow-up in the Eye Genetics clinic for evaluation of microphthalmia, microcornea, aphakia, nystagmus and developmental delays. He was diagnosed with congenital cataracts after delivery at term. He underwent bilateral cataract extraction at the age of 7 weeks without intraocular lens placement. The patient subsequently developed aphakic glaucoma, which has been managed with topical medications. He had extropia and moderate vision loss from bilateral, deprivational amblyopia with a best-corrected visual acuity of 20/100 in both eyes. He walked at around 18 months of age but has had delays in expressive speech. At 5 years of age, he was able to converse in short sentences, ride a tricycle and hop. At 9 years of age, he was in fourth grade at school and had an individualized education plan (IEP) with speech therapy and a vision specialist for an hour each week. He has always required additional academic assistance at school and has also been evaluated for hyperactivity. He had a dental extraction for a fused tooth. He has been otherwise healthy with the exception of asthma treated with inhalers.

The patient was the only child born to his parents. Both parents were healthy. His mother has five brothers and three sisters, all with normal health per her report. There is no family history of congenital cataracts or abnormal dental findings, but the maternal grandmother had eye surgery in late adult life, possibly for age-related cataracts. The family was of Hispanic ethnicity with no known consanguinity.

TABLE 1 | Summary of clinical findings in eight patients with Nance Horan syndrome.

Patient	1	2	3	4	5	6	7	8
Sex	M	M	M	M	M	M	F	F
Age at reporting	10 y	8 y	14 m	9 y	15 m	3 y	14 m	7 y
Family history	Y	N	Y				Y	Y
Ocular findings								
Cataracts	Y; bilat.	Y; bilat.	Y; bilat.	Y; bilat.	Y; bilat.	Y; bilat.	Y; bilat.	Y; L eye
Glaucoma	Y	Y	Y	Y		Y	N	
Microphthalmia	Y	Y	N		Y	Y; bilat.	N	
Microcornea	Y	Y			Y		N	Y
Nystagmus	Y	Y	Y	Y			N	
Exotropia	N	Y		Y			N	Y
Reduced visual acuity	Y	Y	Y			Y	N	Y
Dental findings								
Wide-spaced teeth	Y	Y; ridged	Y		Y	—	—	
Small teeth/missing teeth	Y	—				Y	—	Y
Screwdriver shaped incisors	Y	—		Y		Y	—	Y
Wide diastema	Y	Y				—	—	
Fused/supernumerary teeth	—	Y		Y	Y	—	—	
Abnormally shaped teeth	Y			Y	Y			
Notched incisors				Y	Y			Y
Facial findings								
Brachycephaly ± plagiocephaly	—	Y	Y		Y	N	—	
Long face	Y	Y				—	—	Y
Bulbous nose	Y	—				—	Y	
Prominent, large ears	Y	Y		Y	Y	Y	—	Y
Short columella	Y	Y	Y			—	—	
Thin philtrum	Y	Y				—	—	
Everted lower lip	—	Y				—	—	
Small or pointed chin	Y	Y			Y	—	—	
Development								
Milestones	Normal	Delayed			Delayed	Delayed	Normal	
Developmental delay	N	Y		Y	Y	Y	N	Y
Autism	N	N		—			N	
Hypotonia	—				Y			
Impulsivity/lability					Y			
Other								
Hearing impairment	N	—					—	

(Continues)

TABLE 1 | (Continued)

Patient	1	2	3	4	5	6	7	8
Long and thin fingers	Y	Y					—	
Single palmar crease			Y				—	
Double hair whorls	—		Y				—	
Atrial septal defect	N		Y				—	
Cryptorchidism	—			Y				

On examination, the patient had brachycephaly with a long face and a relatively small jaw, epicanthic folds and low-set ears that were large, simple, and cupped (Figure 2). The left ear measured 6.2 cm at 8 years of age (+1 to +2SD). There were no ear pits or tags. He had a short columella, a thin philtrum, and an everted lower lip. He was in mixed dentition with an anterior crossbite and had a fused primary lower right central and lateral incisor. The other teeth in his lower jaw were ridged and widely spaced, and he had a wide diastema between his upper two incisor teeth. He had long and thin fingers, but the remainder of his examination and growth parameters were normal. Examination of his mother's eyes and teeth did not reveal the characteristic ocular and facial features of NHS and there were no Y-sutural opacities on slit lamp examination of the crystalline lenses.

Investigations for the patient included a normal male karyotype (46,XY), negative urine reducing substances and non-diagnostic urine amino acid testing. Testing for galactose-1-phosphate uridyl transferase and red blood cell galactose-1-phosphate was normal. At 2 months of age, testing was negative for Toxoplasmosis gondii, but positive for Varicella zoster IgM and Rubella. Array comparative genomic hybridization showed a small copy number gain at 6q11.1 (61,967,122–62,917,243) that was an estimated 0.95 Mb in size and contained one OMIM gene (*KHDRBS2*) and one other gene (*MTRNR2L9*). This CNV was reported as likely benign due to the finding of similar duplications that were inherited from normal parents in public databases (data not shown). His parents could not be tested for the same duplication.

2.3 | Patient 3

A 14-month-old boy was evaluated because of bilateral congenital cataracts and developmental delay. He was the third child born to unrelated Hispanic parents after a pregnancy complicated by gestational diabetes and hypertension. He weighed over 5 kg at term. As congenital cataracts had been diagnosed in his older brother in early infancy, the mother requested an ophthalmic examination shortly after his birth that revealed bilateral cataracts but no microphthalmia. He underwent bilateral cataract extraction at 1 month of age with placement of intraocular lenses. He developed glaucoma following cataract surgery that necessitated multiple surgeries. He has decreased visual acuity and secondary deprivational nystagmus. Examination at this time showed large ears (75%–97%) that protruded laterally and widely spaced teeth. He had a head circumference of 50.5 cm (+0.7SD). Brachycephaly and plagiocephaly with double occipital hair whorls were noted (Figure 3). His chin was prominent. Hand and foot measurements were normal although he had moderately broad thumbs, and great toes and somewhat broad fingertips with a unilateral single transverse palmar crease. An atrial septal defect was diagnosed in the newborn period but has not required surgical intervention.

His development has been delayed and he has had abnormal and challenging behavior. He sat at 9 months, crawled at 14 months, and walked at around 18 months of age. His language has been delayed and at 3 years, he spoke in brief phrases with echolalia. He was not toilet trained. He has had behavioral findings consistent with autism, with spinning, rocking, and screaming. His visual acuity was poor but has been difficult to assess accurately. He held toys close to his face to manipulate them but could navigate a room without difficulty.

The family history revealed that his parents are from Nicaragua and El Salvador, and he had Hispanic and Caucasian ancestry without any known consanguinity. The older brother (Figure 3) had bilateral congenital cataracts that were extracted in infancy without lens implantation. He does not have microcornea or nystagmus, but his best-corrected visual acuity is reduced. He has had delayed development, with walking at 13 months, delayed speech, and toilet training at 3 and a half years. He has had an IEP in school but is making satisfactory progress in a normal classroom with preferential classroom seating.

Craniofacial examination was remarkable for a long triangular face with a pointed chin. His head circumference at age of 3 years was 53 cm (+1.05 SD). The philtrum was short. His ears were large at 6.5 cm (> 97%) and laterally protruding. Dentition was remarkable for wide spaced teeth and a prominent midline diastema (Figure 3). The hands and feet were unremarkable, except for 4th toe clinodactyly. He has had progressive weight gain since about age 3 years.

The mother reported that she had been found to have small cataracts that have not needed extraction. She was significantly overweight, and there were no obvious facial anomalies. An 8-year-old sister has had normal development, but a unilateral cataract was noted at 5 years of age and surgery was planned. She had a long face with a prominent chin, but her ears were normal in size and did not protrude (Figure 3). The family history revealed that the boys' maternal grandmother died at age 29 years from cirrhosis, but was thought to have significant visual impairment from an unknown cause.

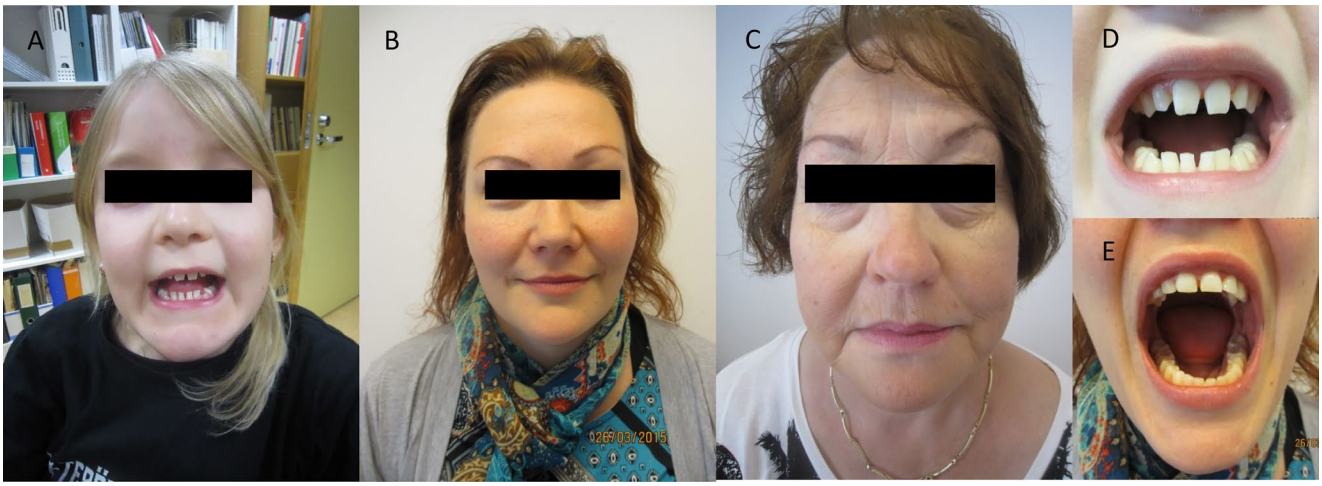

FIGURE 1 | Facial and dental features in the first patient (A), his mother (B) and maternal grandmother (C), showing along face with a bulbous nose and a pointed chin. Teeth are widespaced, screwdriver blade-shaped and diastema is clear (D and E).

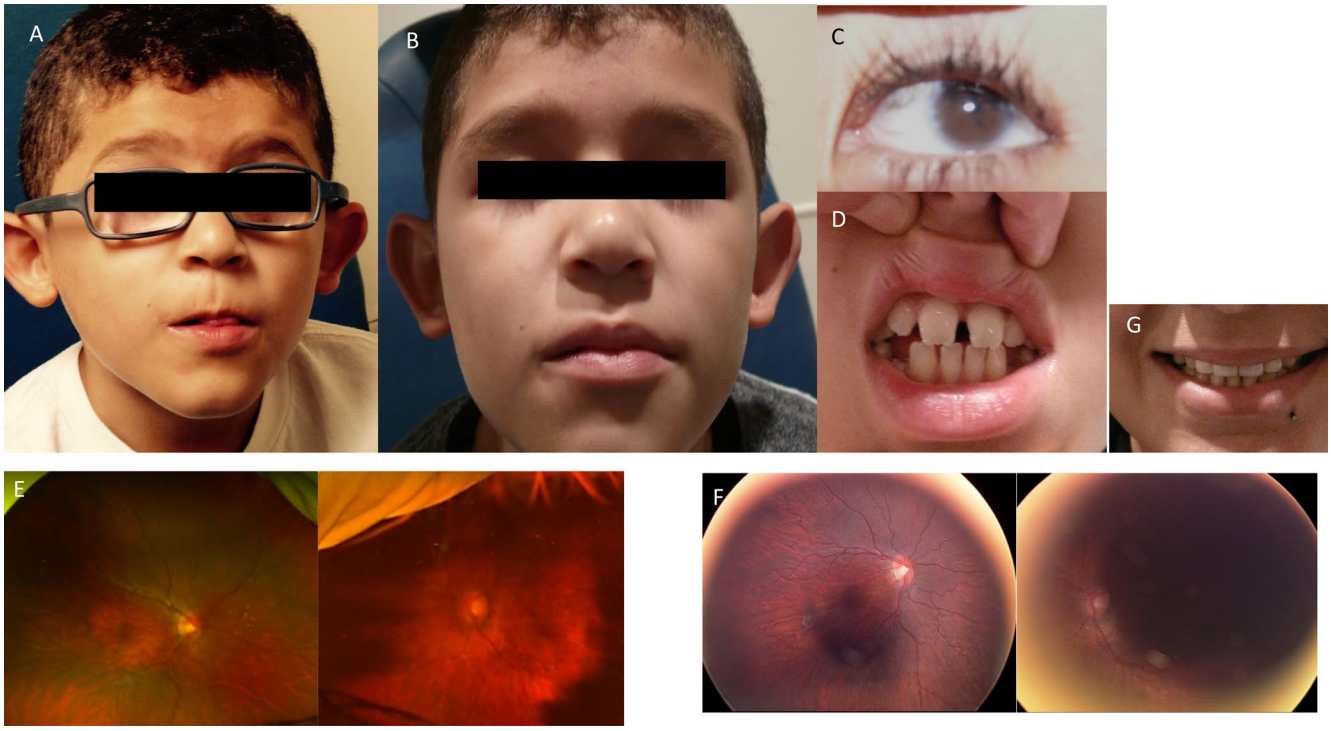

FIGURE 2 | Facial features in the second patient (A and B), with brachycephaly and a long face and relatively small jaw, epicanthic folds and low-set ears that were large, simple and cupped. Image of the left eye, showing microcornea (C). Images of the second patient's teeth, showing blade-shaped upper incisor teeth with a screwdriver appearance (D). Fundus photograph of the probands eye showing optic atrophy and possible tigroid fundus (E and F). Image of the mother's teeth, showing a normal dentition (G).

2.4 | Patient 4

A 9-year-old male was delivered at full term to nonconsanguineous parents of Irish, German, and Puerto Rican ancestry. Cataracts and bilateral cryptorchidism were noted in the newborn period, with subsequent lens removal and orchidopexy by 1 year of age. He later developed sensory deprivation nystagmus and glaucoma requiring medical treatment. He initially had mild language delays but was currently doing well in school, with no concerns regarding his speech articulation or vocabulary. Radiographs of his mouth showed supernumerary permanent teeth. The family history was negative for similar symptoms, and his mother wore glasses without concerns for any lens abnormalities. His physical exam showed normal growth parameters, nystagmus, left esotropia, protuberant ears, a narrow palate, a screwdriver-shaped left upper central incisor, a missing right upper central incisor, peg-shaped canine teeth, and notched lower incisors.

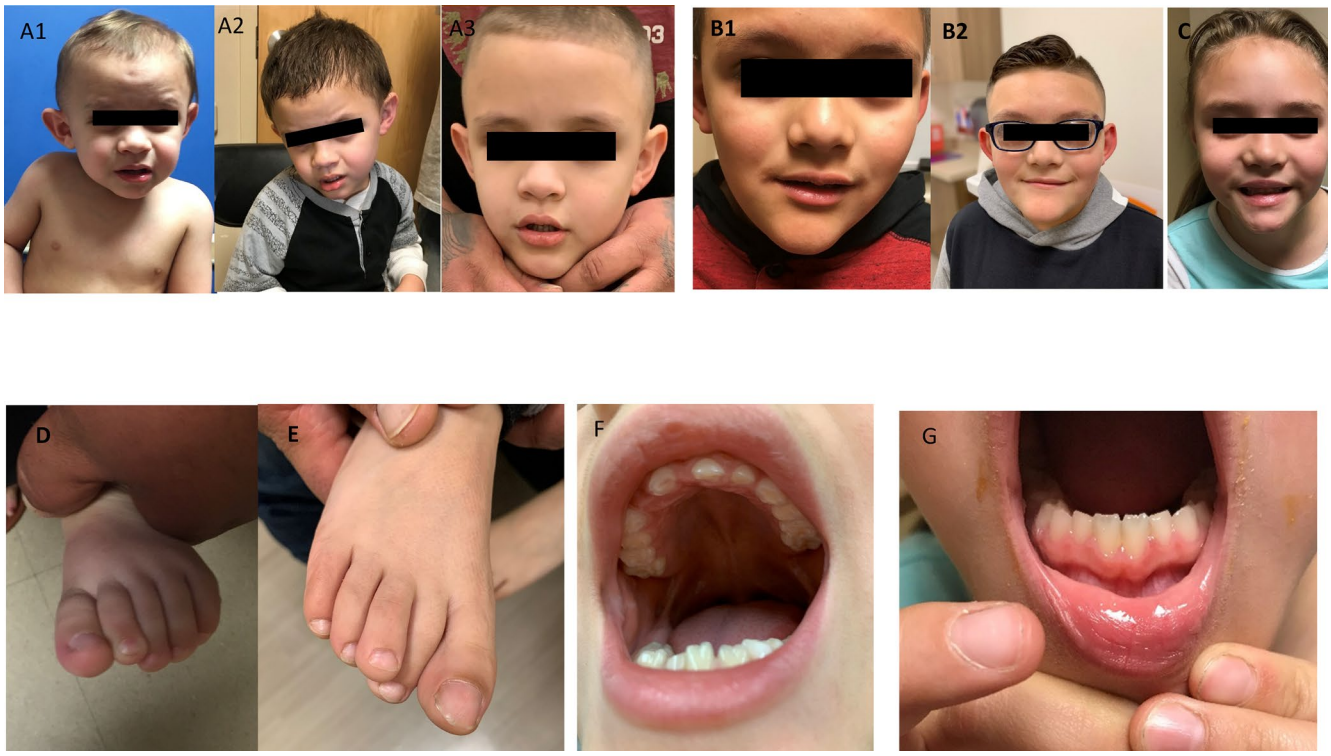

FIGURE 3 | Facial and dental features of the third patient (A1–A3) and siblings (B1–C), showing typical facial features long face with pointed chin, cupped ears, overlapping toes (D and E) and small teeth that are widely spaced (F and G).

2.5 | Patient 5

A 15-month-old male was born at full term to nonconsanguineous parents of Mexican ancestry. He was diagnosed with bilateral congenital cataracts, microphthalmia, and microcornea soon after birth. He has had a language delay and increased activity levels. The family history was non-contributory. His physical exam showed normal growth parameters, plagiocephaly with flattening of his left occiput, microphthalmia with short palpebral fissure lengths, protuberant helices, a pointed chin, widely spaced teeth with notches in his incisors, and mildly decreased truncal tone. At 27 months of age, his expressive language was delayed, with minimal spontaneous speech (three words), and he had significant impulsiveness and emotional lability.

2.6 | Patient 6

A 3-year-old male presented with bilateral congenital cataracts. He was delivered by C-section due to maternal hypertension during the 3rd trimester at 40 weeks of gestation and had a birthweight of 3700 g. Lens opacities were first detected in the left eye at 6 months of age and he underwent cataract extraction with intraocular lens placement at 12 months of age for the left eye and at 15 months for the right eye. He was diagnosed with amblyopia and strabismus. He had normal motor milestones, but was initially described as having speech delays; although at 3 years of age, parents reported that he had "too many words to count." He has not had any intervention services and has had no other medical concerns. The family history was significant for refractive error in the father, but there was no history of cataracts. The mother had one miscarriage prior to this baby and was healthy apart from a history of hypertension. Parents were both of Nepalese descent, and consanguinity was denied.

On examination, height was 102.1 cm (57th centile; $Z = 0.16$) and weight was 16.5 kg (56th centile; $Z = 0.15$). He was normocephalic with an OFC of 53 cm (94th centile; $Z = 1.53$). He had mild, bilateral microphthalmia, and aphakia. His ears were prominent and cupped. He had small and screwdriver-shaped lower teeth with multiple capped teeth due to dental caries. His mother did not demonstrate similar facial or dental findings and an eye examination did not reveal any evidence of cataracts.

2.7 | Patient 7

A 14-month-old female was referred for genetic testing due to bilateral congenital cataracts and nystagmus. The pregnancy was complicated by echogenic bowel detected on a 20-week ultrasound scan and maternal cholestasis. The cataracts were treated with left and right extracapsular cataract extractions. Other eye findings included a secondary membrane in the left eye, left miotic pupil, conjunctival irritation with override to the right cornea, right nasolacrimal duct obstruction, sensory exotropia and glaucoma. She was otherwise well and her development was normal; she was able to cruise, babble and had two single words. On examination at 12 months of age, height was 73.8 cm (43rd centile; Z score −0.17), weight was 8.07 kg (17th centile; Z score −0.94) and OFC was 44 cm (24th centile; Z score −0.7). She had mild facial asymmetry with a smaller left side, mild midface hypoplasia and a broad nasal tip. Her primary dentition appeared normal.

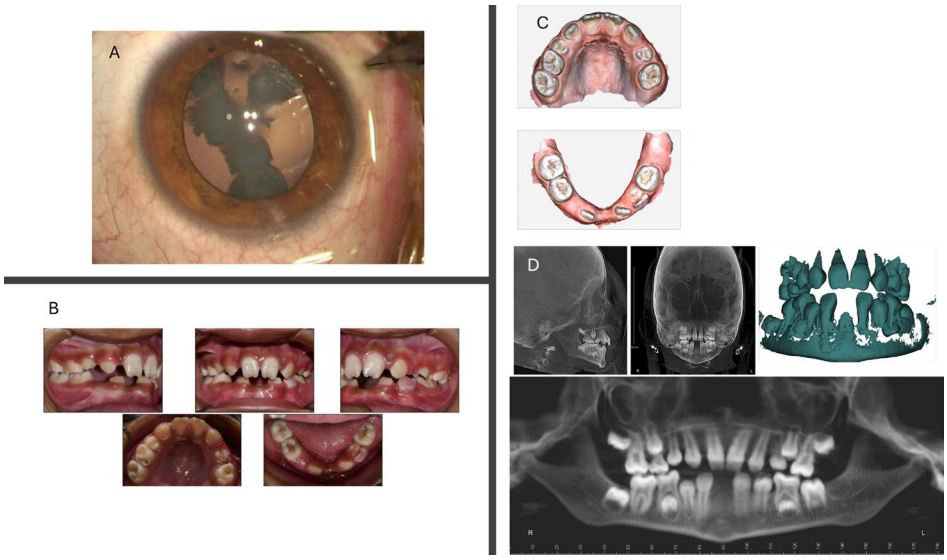

FIGURE 4 | Sutural cataract in the left eye of a seven-year Asian female (A). Intra oral examination revealed late mixed dentition (B). Dental models revealed that her central incisors teeth were typical Hutchinson incisors in upper arch with screwdriver shape and vertical notches. Radiological findings of the same patient depict multiple missing permanent teeth i.e. upper lateral incisors, lower central and lateral incisors. Taurodontism was also present in maxillary permanent first molars and there were no supernumerary teeth in either of the jaws (C and D).

Her mother was 20 years of age and had a history of juvenile cataracts diagnosed at 5 years of age after a failed vision screen at school. She had surgery in her left eye only and has right, mild nuclear opacities/small flecks, posterior subcapsular opacities, optic nerve cupping, large talon cusps with an impression of screwdriver-shaped upper incisors, and attention deficit hyperactivity disorder. Testing revealed that she was heterozygous for the same likely pathogenic variant in *NHS* as her daughter. There was no other family history of congenital cataracts and no additional family members were tested. Screening for TORCH infections showed cytomegalovirus (CMV) IgG positive with negative CMV polymerase chain reaction at 2 months of life.

2.8 | Patient 8

A 7-year-old Asian female child presented with left upper lid ptosis and decreased visual acuity of the left eye since early childhood. On ocular examination, visual acuity was 20/40 (LogMar 0.5) in the right eye and 20/200 (LogMar 0.8) in the left eye. She had mild ptosis with an exotropia of 15 prism diopters, microcornea and sutural cataract in the left eye (Figure 4). The right eye had a few lenticular opacities and the rest of the examination was unremarkable. Axial length was 21.14 mm (normal range) and 19.38 mm (consistent with microphthalmia) in the right and left eyes, respectively. She had facial anomalies with prominent external ears and the upper third of the face was longer than the middle and lower thirds. Intraoral examination revealed late mixed dentition (Figure 4). The upper lateral incisor and lower central and lateral incisors were absent and there was a tendency toward an anterior open bite. Digital imaging revealed that her central incisor teeth were typical Hutchinson incisors in the upper arch with screwdriver-shaped and vertical notches (Figure 4). The maxillary permanent first molars and retained deciduous second molar on the right side revealed additional cusps, giving the typical bud molar appearance. Her lower canines were also screwdriver-shaped and had vertical notches. Radiological findings as revealed in the cone beam computed tomogram (CBCT; Figure 4) showed multiple missing permanent teeth including the upper lateral incisors and the lower central and lateral incisors. Taurodontism was also present in the maxillary permanent first molars. There were no radiological signs of third molars in both jaws. In addition, she had vertebral segmentation defects including a short neck, scoliosis, and short stature. The patient underwent left eye cataract surgery with intraocular lens implantation. Her father, paternal uncle and grandmother's two brothers also had bilateral microcornea with cataracts. Father's examination revealed bilateral microcornea, and absorbed membranous cataract. The patient's younger brother had a normal ocular examination.

3 | Results

The genetic testing results from the eight patients are summarized in Table 2. All patients had variants or copy number variants that fulfilled at least one very strong and one moderate criterion for pathogenicity according to the Standards and Guidelines for the Interpretation of Sequence Variants (Richards et al. 2015). The first patient underwent next generation sequencing (NGS) testing with a congenital cataract panel that revealed a heterozygous variant, c.3808C>T, p.(Gln1270*), in exon 6 of the *NHS* gene. The variant was verified by Sanger sequencing and subsequently identified in the mother and maternal grandmother. The p.(Gln1270*) variant predicts premature truncation of the NHS protein and had not previously been reported.

The second patient underwent exome sequencing as a research test according to prior methods (Krall et al. 2019). The results showed a single nucleotide deletion, c.1038delG predicting p.(Pro346fs) in *NHS* (NM_001291867). This sequence variant was verified in a clinical laboratory (GeneDx Inc.). We were unable to perform genetic testing on his mother due to insurance limitations.

TABLE 2 | Summary of genetic testing results in eight patients with Nance Horan syndrome.

Patient	Nucleotide variant (Transcript is NM_001291867 unless stated)	Protein variant	Zygosity	Inheritance	gnomAD 4.1/ClinVar	ACMG[a] criteria
Patient 1	c.3808C>T	p.(Gln1270*)	Hemizygous	Maternal	Absent/Absent	PVS1[b], PM2[c]
Patient 2	c.1038delG	p.(Pro346fs)	Hemizygous	Not done	Absent/Absent	PVS1, PM2
Patient 3	c.1399_1402delGACA	p.(Asp.467Lysfs*10)	Hemizygous	Maternal	Absent/Absent	PVS1, PM2
Patient 4	Del Xp22.13 (chrX:17,731,096-17,883,090; GRCh 37/hg19)	—	Hemizygous	De novo	NA	PVS1, PM6[d]
Patient 5	Xp22.13 (chrX:17,291,222-17,838,885; GRCh 37/hg19)	—	Hemizygous	De novo	NA	PVS1, PM6
Patient 6	c.3222del	p.(His1074Glnfs*4)	Hemizygous	Maternal; possible mosaicism	Absent/Absent	PVS1, PM2
Patient 7	c.3237del	p.(Lys1079Asnfs*20)	Heterozygous	Maternal	Absent/Absent	PVS1, PM2
Patient 8	c.2472T>A	p.(Cys824*)	Heterozygous	Paternal	Absent/Absent	PVS1, PM2, PP1[e]

[a]SACMG = standards and Guidelines for the Interpretation of Sequence Variants: A Joint Consensus Recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (Richards et al. 2015). PVS1.
[b]Predicted null variant in gene where loss of function is a known mechanism of disease; PM2.
[c]Absent from disease databases; PM6.
[d]De novo (without paternity and maternity confirmation); PP1.
[e]Co-segregation with disease in multiple affected family members.

In the third family, a 30-gene cataract panel was performed in the proband in a commercial laboratory and revealed a frameshift variant in exon 6, c.1399_1402delGACA, p.(Asp.467Lysfs*10), of *NHS*. This variant was confirmed in his brother, mother and sister. No other family testing has been possible to date.

The fourth patient had an Affymetrix SNP 6.0 cytogenomic microarray (Santa Clara, CA) that showed a 158-kb, contiguous, hemizygous deletion of Xp22.13 (chrX: 17,731,096–17,883,090; GRCh 37/hg19 coordinates) involving the 3′ region of *NHS* (exons 4–8), *SCML1*, and *RAI2*. Maternal cytogenomic microarray testing was negative for the deletion.

For the fifth patient, an Affymetrix SNP 6.0 cytogenomic microarray revealed a 548-kb contiguous deletion of Xp22.13 (chrX: 17,291,222–17,838,885; GRCh 37/hg19 coordinates) involving all of *NHS* and *SCML1*, as well as the 3′ exon of *RAI2*. Maternal fluorescence in situ hybridization using a bacterial artificial chromosome (BAC) clone from the deleted region (RP11-201 N18) showed a normal hybridization pattern.

For the sixth patient, a cataract panel showed that he was hemizygous for c.3222del, p.(His1074Glnfs*4) in *NHS*. Testing of his mother showed that she was heterozygous for the same variant and the sequence data suggested that she was a possible mosaic; however, confirmation of mosaicism with a secondary method was not performed.

For the seventh patient, a cataract panel with 113 genes showed that the proband was heterozygous for a maternally inherited, truncating variant, c.3237del, p.(Lys1079Asnfs*20) in *NHS*. The variant was classified as likely pathogenic by the testing laboratory.

For patient 8, targeted exome sequencing revealed a novel variant, c.2472T>A, p.Cys824*, in the *NHS* gene along with a pathogenic, 0.52 Mb deletion on chromosome 16p11.2 that was confirmed by chromosomal microarray. The chromosome 16 deletion is known to cause the growth delays, intellectual disorders and vertebral segmentation defects that were seen in this patient. Testing of the father revealed that he was heterozygous for the same likely pathogenic variant in *NHS* as the proband.

4 | Discussion

We present eight families with clinical and molecular genetic findings consistent with NHS that had truncating variants or gene deletions that predict loss of function for *NHS*. NGS-based testing with the ability to detect copy number variants is needed for diagnostic testing. In the future, genome sequencing will show us the proportion of deep intronic variants that are causal for the phenotype. All males had "classical" findings, with bilateral congenital cataracts and at least one additional finding of secondary glaucoma, microphthalmia, microcornea, nystagmus and strabismus (Table 1). Dental findings included the characteristic wide-spaced teeth, screwdriver-shaped incisors and fused or supernumerary teeth. Facial features in males and females were similar and included brachycephaly with or without plagiocephaly, a long face, bulbous nose, prominent and large ears, short columella, and a small or pointed chin. Additional clinical features in single cases were long and thin fingers, a single palmar crease, double hair whorl, atrial septal defect, and cryptorchidism, but it is unclear if these features are associated with the *NHS* variants. Four out of the six males had developmental delays and one patient had hypotonia impulsivity, and emotional lability. There were no instances of autism or hearing loss and growth was normal in these patients.

Females had a milder, highly variable phenotype that was consistent with prior findings in the literature (Li et al. 2018). Interestingly, the mother and maternal grandmother in the first family had similar facial features to the affected male patient without the classical lens opacities centered around the posterior Y-suture (Khan et al. 2012).

NHS is caused by pathogenic variants in the *NHS* gene located at chromosome Xp22.13 (Burdon et al. 2003; Toutain et al. 2002). While Nance-Horan syndrome typically involves multiple body systems, some patients may present with only ophthalmologic findings and X-linked cataracts have been described as an allelic disorder for NHS (Coccia et al. 2009). The gene is alternatively spliced and encodes at least five isoforms (Brooks et al. 2010; Sharma et al. 2009). The *NHS* gene has three different isoforms; one comprises nine coding exons and one contains at least 10 exons, with exon 6 representing about 60% of the *NHS* coding region (Florijn et al. 2006; Tug et al. 2013). The gene encodes a protein with four conserved nuclear localization signals that is a regulator of actin assembly and cell spreading (Brooks et al. 2010, 2004; Burdon et al. 2003; Khan et al. 2012). The NHS protein is highly conserved across vertebrate species and has an important regulatory role, both spatially and temporally, in the development of the central nervous system, eyes (mainly the lens, and to a lesser degree, the retina), teeth, and heart (Huang et al. 2006; Sharma et al. 2008). *NHS* encodes a functional WAVE homology domain and is part of a complex that is critical for actin remodeling and cell morphology, migration, motility, and adhesion (Brooks et al. 2010).

Deleterious variants associated with NHS have included truncating variants conferring loss of function, including nonsense variants and small deletions (Li et al. 2018). The deleterious variants have been located throughout the gene; nonetheless the exon-intron 1 region, along with exon 6, constitutes the most frequently affected regions (Gómez-Laguna et al. 2018). There has been no obvious genotype–phenotype correlation, although it has been speculated that intellectual disability is more common among patients with pathogenic variants in the 2nd, 6th or 8th exons. In our series, patients four and five had de novo microdeletions involving *NHS* together with *SCML1*, and *RAI2*, a relatively rare pathogenic mechanism for NHS (Lopez Martinolich et al. 2022). These two patients appeared to have typical presentations of NHS, without demonstration of the skeletal findings previously noted in other patients with larger microdeletions including the *NHS* gene (Liao et al. 2011; Lopez Martinolich et al. 2022).

In our series, patient 8 was diagnosed due to the clinical suspicion of the patient's dentist and had dual diagnoses, with an additional microdeletion of chromosome 16p11.2. Her family history was extensive and consistent with multiple affected individuals who had not been diagnosed with NHS. Similarly, the mother of

the seventh patient was also affected with juvenile cataracts and dental findings and yet remained undiagnosed until her daughter came to medical attention. As medical knowledge improves and genetic testing becomes more widespread, it can be hoped that more patients will receive a timely diagnosis in the future.

In conclusion, we report eight new patients with NHS, all of whom have variants or copy number variants predicting loss of function for the *NHS* gene. Two patients had microdeletions that included *NHS*, but had typical presentations and were without the skeletal findings that have been observed in NHS patients with larger deletions. The spectrum of clinical features in NHS is variable and in particular, can be subtle in females to the extent that only minor facial anomalies are present. This report adds to the spectrum of phenotypic and genotypic information available for NHS patients and their families.

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Ethics Statement

Consent for publication was obtained from all patients and families. All procedures followed were in accordance with the Helsinki Declaration of 1975, as revised in 2000.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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