

Ophthalmic Manifestations of NAA10-Related and NAA15-Related Neurodevelopmental Syndrome: Analysis of Cortical Visual Impairment and Refractive Errors

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Abstract

NAA10-related and *NAA15*-related neurodevelopmental syndrome, otherwise known as Ogden Syndrome, is known to present with varying degrees of intellectual disability, hypotonia, congenital cardiac abnormalities, seizures, and delayed speech and motor development. However, the ophthalmic manifestations of *NAA10* and *NAA15* mutations are not yet fully characterized or understood. This study analyzed the prevalence of six ophthalmic conditions (cortical visual impairment, myopia, hyperopia, strabismus, nystagmus, and astigmatism) in 67 patients with pathogenic mutations in the *NAA10* cohort (54 inherited, 10 de novo; 65 missense, 2 frameshift) and 19 patients with pathogenic mutations in the *NAA15* cohort (18 de novo; 8 frameshift, 4 missense, 4 nonsense, and 1 splice site). Patients were interviewed virtually or in-person to collect a comprehensive medical history verified by medical records. These records were then analyzed to calculate the prevalence of these ophthalmic manifestations in each cohort. Analysis revealed a higher prevalence of ophthalmic conditions in our *NAA10* cohort compared to existing literature (myopia 25.4% vs. 4.7%; astigmatism 37.3% vs. 13.2%; strabismus 28.4% vs. 3.8%; CVI 22.4% vs. 8.5%, respectively). No statistically significant

differences were identified between the *NAA10* and *NAA15* mutations. Our study includes novel neuroimaging of 13 *NAA10* and 5 *NAA15* probands, which provides no clear correlation between globe size and severity of comorbid ophthalmic disease. Finally, anecdotal evidence was compiled to underscore the importance of early ophthalmologic evaluations and therapeutic interventions.

Introduction

N-alpha-acetylation is one of the most common eukaryotic post-translational protein modifications. This process is partially facilitated by the NatA complex, which is composed of a N-acetyltransferase 10 (*NAA10*) catalytic subunit and the *NAA15* accessory protein¹⁻³. Ogden syndrome (OS), also known as *NAA10*-related and *NAA15*-related syndrome, was first characterized in 2011 as a pathogenic variant in the *NAA10* gene on the X-chromosome^{4,5}. Since then, there have been other *NAA10* and *NAA15* variants that have been identified with their phenotypic manifestations, including variable degrees of intellectual disability, hypotonia, congenital cardiac abnormalities, seizures, and delayed speech and motor development⁶⁻¹⁶. A large subset of individuals with *NAA10*, and to a lesser extent *NAA15*, mutations also present with visual abnormalities, including myopia, astigmatism, and cortical visual impairment (CVI)⁷. However, knowledge of the full extent of these ocular manifestations is relatively limited. A deeper understanding of the ophthalmic implications of these mutations is necessary to improve the clinical management of affected patients.

The aims of this study are to describe the ophthalmic manifestations of mutations in *NAA10* in order to compare it to previous findings in the field and to characterize the ophthalmic manifestations of *NAA15* mutations for the first time. We also sought to identify patterns on neuroimaging to correlate globe size to the severity of comorbid ophthalmic pathologies.

Methods

67 patients (56 females, 11 males) with a pathogenic mutation in *NAA10* and 19 individuals (5 females, 14 males) with a pathogenic mutation in *NAA15* were interviewed via secure video conferencing platforms or in-person at the Jervis Clinic between November 2019 and September 2022. A family of 3 patients with Met147Thr mutations in *NAA10* (OS_181, OS_187, OS_188) were not interviewed, but their medical records were provided and sufficiently thorough to include in our analysis. Thorough medical histories were collected, including genetic testing results, information on vision problems, and previous ophthalmic diagnoses. Interviews were 1-2 hours in length and information on all organ systems, as well as

social, cognitive, and developmental history, was gathered. Written consent was obtained for the collection of medical records. Google Sheets was used to organize and analyze prevalence data of ophthalmic conditions reported by interviewed participants. The most relevant conditions in patients with *NAA10* and *NAA15* mutations were cortical visual impairment, myopia, hyperopia, astigmatism, strabismus, and nystagmus. Other conditions were reported within the cohort, including anisometropia, eyelid myoclonus, glaucoma, and ptosis. These were not further analyzed due to low prevalence in the cohort and in previous literature.

A PubMed search was conducted to find the prevalence of cortical visual impairment, myopia, hyperopia, strabismus, astigmatism, and nystagmus in previously reported cases of Ogden Syndrome. Initial search criteria included the keywords “Ogden Syndrome” OR “*NAA10*” AND “ophthalmic OR vision OR visual”; and “Ogden Syndrome” OR “*NAA10*” AND “cortical visual impairment OR myopia OR hyperopia OR nystagmus OR astigmatism OR strabismus” to gather literature on known reports of visual impairment in patients with *NAA10* mutations. Data from the resultant relevant papers (n=106 probands) were organized and compared to data within our cohort. There was no pre-existing literature on the ophthalmic manifestations of *NAA15*, so our findings could only be compared to *NAA10*.

Neuroimaging analysis was also conducted on 18 patients (13 *NAA10* and 5 *NAA15* probands) to assess structural abnormalities of the ocular globes, if present. These findings were analyzed to identify patterns between globe size, globe shape, and ophthalmic diagnoses.

Additionally, to better understand the direct impacts of early ophthalmic intervention, we collected quotes from patient families via email. Some quotes were edited by the authors due to some families not speaking English as their primary language. In these instances, the modified quotes were sent to the families for approval and subsequently approved. Original quotes are included in **Supplementary Table S1**.

Results

This study includes 67 individuals with *NAA10* variants and 19 individuals with *NAA15* variants. *NAA10* individuals come from 14 countries with a mean age of 10.8 years. *NAA15* individuals come from 4 countries with a mean age of 8.9 years. Within our cohorts, 61 *NAA10* patients (91.0%) and 18 *NAA15* patients (94.7%) were Caucasian. 57 *NAA10* patients (85.1%) and 18 *NAA15* patients (94.7%) were under the age of 18. **Table 1** and **Table 2** outline the demographic information of interviewed patients with *NAA10* and *NAA15* mutations, respectively.

Table 1. NAA10 demographic information of interviewed patients.

Characteristics	Study Participants (n=67) n (%)
Sex	
Male	11 (16.4%)
Female	56 (83.6%)
Race	
Caucasian	61 (91.0%)
Asian	5 (7.5%)
African American	1 (1.5%)
Ethnicity	
Hispanic	6 (9.0%)
Non-Hispanic	61 (91.0%)
Mean Age at Time of Video conference (y)	
Under 18 years of age	57 (85.1%)
Age Range	
	3.5 months - 56 years
Country of Residence	
USA	30 (44.8%)
United Kingdom	13 (19.4%)
Belgium	3 (4.5%)
Canada	3 (4.5%)
China	3 (4.5%)
Ireland	3 (4.5%)
Brazil	2 (3.0%)
France	2 (3.0%)
Germany	2 (3.0%)
Spain	2 (3.0%)
Australia	1 (1.5%)
Finland	1 (1.5%)
Holland	1 (1.5%)
Poland	1 (1.5%)

Table 2. NAA15 demographic information of interviewed patients.

Characteristics	Study Participants (n=19) n (%)
Sex	
Male	14 (73.7%)
Female	5 (26.3%)
Race	
Caucasian	18 (94.7%)

Asian	1 (5.3%)
Ethnicity	
Hispanic	1 (5.3%)
Non-Hispanic	18 (94.7%)
Mean Age at Time of Video conference (y)	
Under 18 years of age	18 (94.7%)
Age Range	
	2 years - 21 years
Country of Residence	
USA	14 (73.7%)
Australia	3 (15.8%)
United Kingdom	1 (5.3%)
Puerto Rico	1 (5.3%)

All patients were confirmed to have mutations in the *NAA10* or *NAA15* gene, as shown in **Table 3** and **Table 4**. All individuals were analyzed for pathogenicity using ACMG standards. For probands that possessed novel mutations that have not been characterized in the literature previously, we determined probable pathogenicity based on previous genetic analysis and ACMG standards (see **Supplementary Notes 1-6**) These are denoted with an asterisk (*).

The prevalence of the most common ophthalmic manifestations of OS in our cohort were compared to previously reported cohorts. **Table 5** compares the prevalence of CVI, myopia, astigmatism, strabismus, nystagmus, and hyperopia in our cohort to 106 previously reported cases, for a total of 173 individuals including those reported in this paper. Our cohort had significant overlap with the cohort reported previously⁷. However, the 37 probands from this paper who were not in our cohort were analyzed separately as seen in **Table 5**. Nystagmus and hyperopia were not analyzed in the prior paper, so the prevalence in our cohort was compared to 69 previously reported cases. This data is graphically depicted in **Figure 1**.

Table 3. *NAA10* Variants of Participants. For pathogenicity, P = known pathogenic, LP = likely pathogenic.

Proband Identifier	Age Range (y)	Sex	Protein Change	cDNA Change	Inheritance	Pathogenicity
OS_102	5-9	F	Asp10Glu	c.30C>G	De novo	P
			Pro08Ser	c.22C>T	De novo	P
OS_103	15-19	F	His16Pro	c.047A>C	De novo	P
OS_104	0-4	F	Tyr31Cys	c.92A>G	De novo	P
OS_107	55-59	F	Tyr43Ser	c.128A>C	De novo	P
OS_108	30-34	M	Tyr43Ser	c.128A>C	Maternal	P
OS_109	25-29	M	Tyr43Ser	c.128A>C	Maternal	P
OS_110	5-9	M	Ile072Thr	c.215T>C	Maternal	P
OS_111	5-9	M	Ile072Thr	c.215T>C	Maternal	P
OS_112	5-9	F	Arg83Cys	c.247C>T	De novo	P
OS_113	5-9	F	Arg83Cys	c.247C>T	De novo	P
OS_114	5-9	F	Arg83Cys	c.247C>T	De novo	P
OS_115	10-14	F	Arg83Cys	c.247C>T	De novo	P
OS_116	10-14	F	Arg83Cys	c.247C>T	De novo	P
OS_117	10-14	F	Arg83Cys	c.247C>T	De novo	P
OS_118	35-39	F	Arg83Cys	c.247C>T	De novo	P
OS_119	10-14	F	Arg83Cys	c.247C>T	De novo	P
OS_120	15-19	F	Arg83Cys	c.247C>T	De novo	P
OS_121	10-14	F	Arg83Cys	c.247C>T	De novo	P
OS_122	0-4	F	Arg83Cys	c.247C>T	De novo	P
OS_123	5-9	F	Arg83Cys	c.247C>T	De novo	P
OS_124	15-19	F	Arg83Cys	c.247C>T	De novo	P
OS_125	25-29	F	Arg83Cys	c.247C>T	Maternal	P
OS_126	0-4	F	Arg83Cys	c.247C>T	De novo	P
OS_127	0-4	F	Arg83Cys	c.247C>T	De novo	P
OS_128	10-14	F	Arg83Cys	c.247C>T	De novo	P
OS_129	5-9	F	Arg83Cys	c.247C>T	De novo	P
OS_130	5-9	F	Arg83Cys	c.247C>T	De novo	P

OS_132	5-9	F	Arg83Cys	c.247C>T	De novo	P
OS_133	0-4	F	Arg83Cys	c.247C>T	De novo	P
OS_135	5-9	F	Arg83Cys	c.247C>T	De novo	P
OS_136	0-4	F	Arg83Cys	c.247C>T	De novo	P
OS_137	0-4	F	Arg83Cys	c.247C>T	De novo	P
OS_138	10-14	M	Arg83Cys	c.247C>T	De novo	P
OS_139	15-19	F	Ala087Ser	c.259G>T	Do novo	P
OS_140	0-4	F	Ala087Ser	c.259G>T	De novo	P
OS_141	15-19	F	Ala87Ser	c.259G>T	De novo	P
OS_142	10-14	F	Ala104Asp	c.311C>A	De novo	P
OS_143	15-19	F	Arg116Trp	c.346C>T	De novo	P
OS_144	20-24	F	His120Pro	c.359A>C	De novo	P
OS_146	15-19	F	Leu121Val	c.361C>G	De novo	P
OS_147	0-4	F	Ser123Pro	c.367T>C	De novo	P
OS_148	0-4	F	Phe128Ser	c.383T>C	De novo	P
OS_149	0-4	F	Phe128Leu	c.384T>G	De novo	P
OS_150	5-9	F	Phe128Leu	c.384T>G	De novo	P
OS_151	0-4	F	Phe128Leu	c.384T>G	De novo	P
OS_152	5-9	F	Phe128Leu	c.384T>G	De novo	P
OS_153	20-24	F	Phe128Leu	c.384T>G	De novo	P
OS_154	10-14	F	Phe128Leu	c.384T>G	De novo	P
OS_155	0-4	F	Phe128Leu	c.384T>G	De novo	P
OS_156	10-14	F	Met147Thr	c.440T>C	De novo	P
OS_157	5-9	F	Met147Thr	c.440T>C	De novo	P
OS_159	0-4	M	Thr152Argfs*6	c.455_458del	Maternal	P
OS_160	0-4	M	Glu181Alafs*67	c.542_551del	De novo	P
OS_162	10-14	F	Arg83Cys	c.247C>T	De novo	P
OS_163	35-39	F	Met147Thr	c.440T>C	De novo	P
OS_164	5-9	M	Arg149Trp	c.445C>T	De novo	P
OS_165	5-9	F	Arg116Trp	c.346C>T	De novo	P
OS_166	0-4	F	Arg83Cys	c.247C>T	De novo	P
OS_167	0-4	F	Arg116Gln	c.347G>A	Unknown	LP*

OS_168	0-4	M	Arg116Gln	c347G>A	Maternal	LP*
OS_169	10-14	F	Arg116Trp	c.346C>T	Unknown	P
OS_170	0-4	M	His34Tyr	c.100C>T	De novo	LP*
OS_171	20-24	F	His120Pro	c.359A>C	De novo	P*
OS_172	5-9	F	Arg83Cys	c.247C>T	De novo	P
OS_181	35-39	F	Met147Leu	c.439A>T	Maternal	LP*
OS_187	0-4	F	Met147Leu	c.439A>T	Maternal	LP*
OS_188	0-4	M	Met147Leu	c.439A>T	Maternal	LP*

Table 4. NAA15 Variants of Participants. For pathogenicity, P = known pathogenic, LP = likely pathogenic.

Proband Identifier	Age Range (y)	Sex	Protein Change	cDNA Change	Inheritance	Pathogenicity
NAA15_001	5-9	M	p.Arg27Gly (AGA>GGA)	c.79A>G	De novo	P
NAA15_002	5-9	M	p.His080Argfs*17	c.0239_0240del	De novo	P
NAA15_003	10-14	M	p.His80Arg fsX17	c.239_240delAT (frameshift)	De novo	P
NAA15_004	10-14	F	p.Trp0083X	c.248G>A	De novo	P
NAA15_005	0-4	M	p.Glu173AsnfsX54	c.517delG	De novo	P
NAA15_006	5-9	M	p.Glu173*	c.517G>T	De novo	P
NAA15_007	5-9	F	p.L329fs*22	c.986dupT	De novo	P
NAA15_008	15-19	F	p.Thr351Profs*3	c.1051delA	De novo	P
NAA15_009	5-9	M	p.ENST00000296543.5 splice site variant	c.1753+1G>A	Unknown	LP*
NAA15_010	5-9	M	p.Asn623Ilefs*	c.1868del	De novo	P
NAA15_011	20-24	M	p.Asn0864Ser	c.2591A>G	De novo	P
NAA15_012	10-14	M	p.Asp0335Glu fs*7	c.1005-1008del	De novo	P
NAA15_013	10-14	F	p.Arg782X	c.2344C>T	De novo	P
NAA15_014	0-4	M	p.Ala719Thr (GCA>ACA)	c.2155G>A in exon 17	De novo	P
NAA15_015	0-4	M	p.Ala585Thr	c.1753G>A	De novo	P
NAA15_016	10-14	M	p.Ala678Cysfs*3	c.2031dupT	De novo	P
NAA15_017	0-4	M	p.Asn362MetfsX36	c.1083del	De novo	P
NAA15_018	5-9	M	p.Gln0621*	c.1861C>T	De novo	P
NAA15_019	10-14	F	p.N/A intronic	c.1087+2T>C	De novo	LP*

Table 5. Comparison of Ophthalmic Manifestations in Current Cohort vs. Previous Literature

Condition	Current Cohort (n=67) (%)	Lyon et al., 2023 ⁷ (n=37) (%)	Cheng et al., 2019 ¹⁵ (n=22) (%)	Gupta et al., 2019 ¹⁷ (n=39) (%)	McTiernan et al., 2022 ⁶ (n=8) (%)	Weighted total across literature (not including our cohort)	Prevalence including our cohort
CVI	n=15 (22.4%)	n=1 (2.7%)	n=5 (22.7%)	n=3 (7.7%)	n=0 (0%)	9/106 (8.5%)	24/173 (13.9%)
Myopia	n=17 (25.4%)	n=0 (0%)	n=1 (4.5%)	n=3 (7.7%)	n=1 (12.5%)	5/106 (4.7%)	22/173 (12.7%)
Astigmatism	n=25 (37.3%)	n=0 (0%)	n=8 (36.4%)	n=6 (15.4%)	n=0 (0%)	14/106 (13.2%)	39/173 (22.5%)
Strabismus	n=19 (28.4%)	n=1 (2.7%)	n=2 (9.1%)	n=1 (2.6%)	n=0 (0%)	4/106 (3.8%)	23/173 (13.3%)
Nystagmus	n=4 (6.0%)	Not reported	n=1 (4.5%)	n=1 (2.6%)	n=0 (0%)	2/69 (2.9%)	6/136 (4.4%)
Hyperopia	n=10 (14.9%)	Not reported	n=2 (9.1%)	n=4 (10.3%)	n=2 (25.0%)	8/69 (11.6%)	18/136 (13.2%)

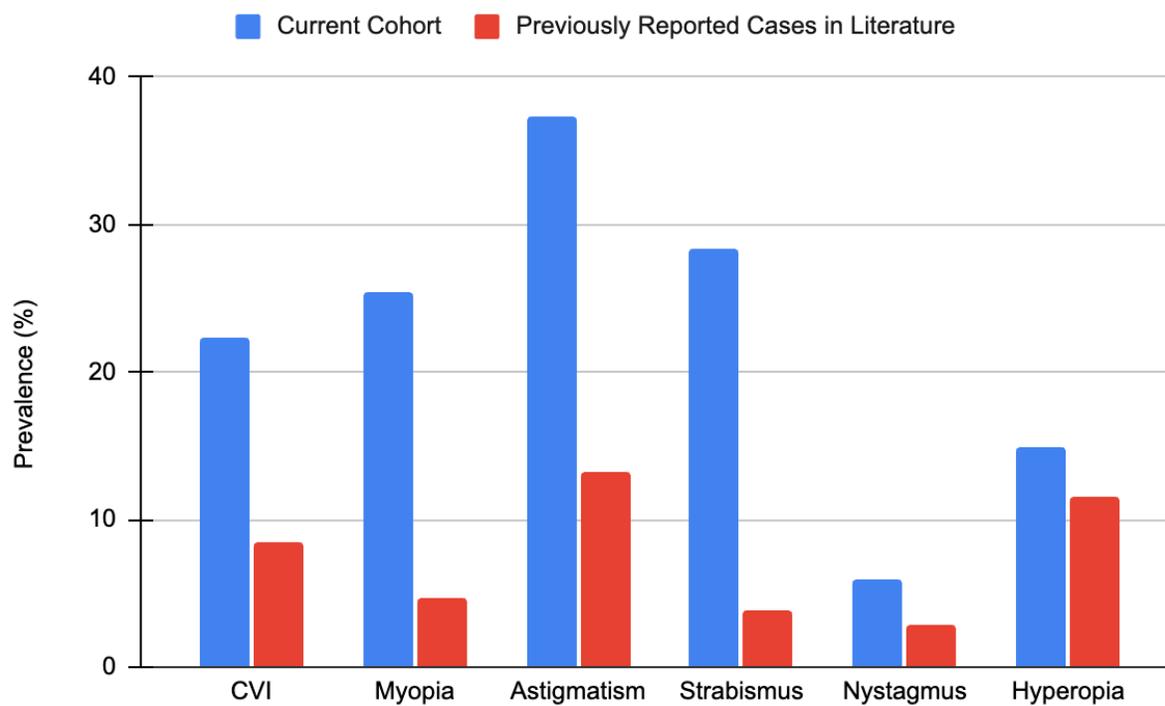


Figure 1. Comparison of Ophthalmic Manifestation Prevalence (%) in Current *NAA10* Cohort versus Previous Literature.

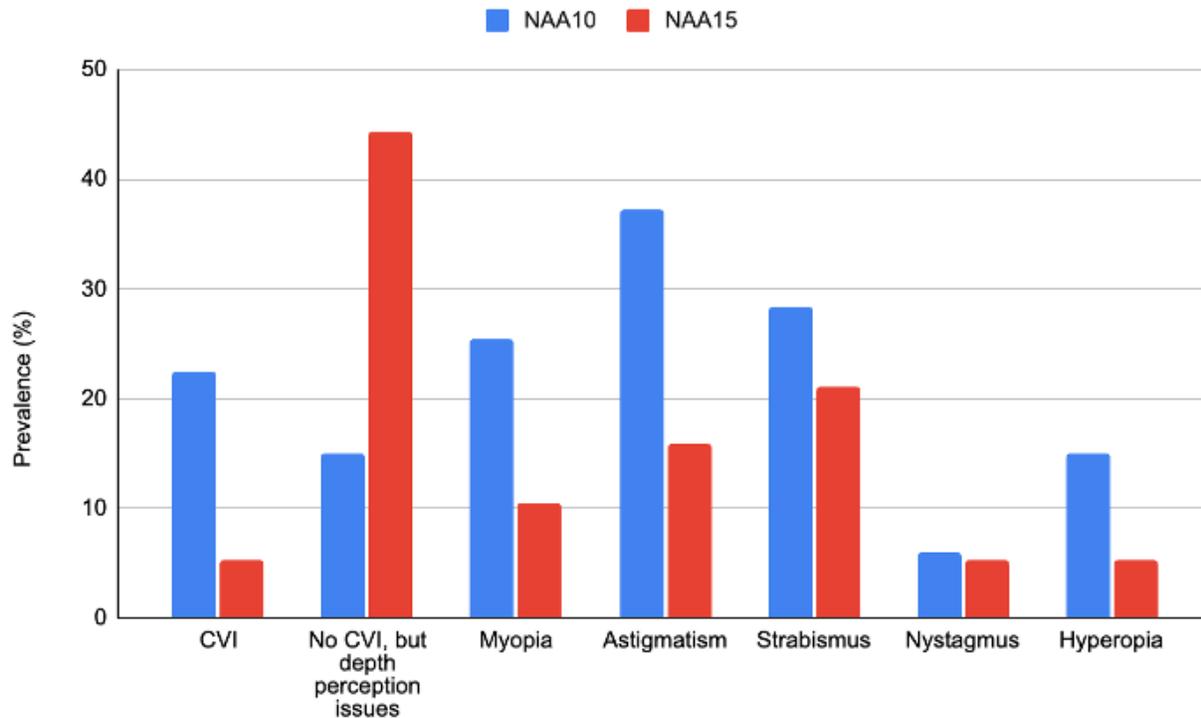


Figure 2. Comparison of ophthalmic manifestation prevalence in *NAA10* versus *NAA15* cohorts

In comparing the prevalence of CVI, astigmatism, myopia, hyperopia, strabismus, and nystagmus in our *NAA10* versus *NAA15* cohorts, we were unable to ascertain any statistical significance, likely due to small sample size. However, **Figure 2** shows that *NAA10* generally has higher prevalence of ophthalmic manifestations in every formal ophthalmic diagnosis category. Notably, in the absence of a CVI diagnosis, trouble with depth perception was mentioned more frequently in patients with *NAA15* mutations (44.4%, n=8), compared to those with *NAA10* (19.2%, n=1) (**Figure 2**).

Neuroimaging

Neuroimaging was analyzed for 13 individuals in the *NAA10* cohort (probands OS_110, OS_111, OS_115, OS_126, OS_132, OS_150, OS_152, OS_153, OS_155, OS_162, OS_163, OS_168, and OS_172) and 5 individuals in the *NAA15* cohort (NAA15_007, NAA15_008, NAA15_010, NAA15_013, and NAA15_019) by a neuroradiologist. Probands' globes were rated 1-4, where 1 is normal, 2 is bilateral dysmorphia, 3 is bilateral dysmorphia and macrophthalmia, and 4 is macrophthalmia, as depicted in **Figure 3**. **Table 6** shows the globe ratings of the 13

assessed *NAA10* probands and **Table 7** shows the globe ratings of the 5 assessed *NAA15* probands, as well as other ophthalmic diagnoses that these patients had at the time of imaging.

Table 6. Globe Size and Ophthalmic Diagnoses in *NAA10* Mutation Cohort.

Proband Identifier	Globe size rating (1-4)	Other Ophthalmology Diagnoses at Time of Imaging
OS_168	1	None
OS_126	1	Astigmatism Strabismus (R Esotropia)
OS_172	1	Hyperopia Astigmatism CVI
OS_162	1	Myopia CVI Strabismus
OS_111	1	None
OS_110	1	Strabismus (R esotropia)
OS_152	1	Bilateral cortical blindness Astigmatism Myopia Nystagmus Intermittent alternating exotropia
OS_155	1	CVI Strabismus Blindness
OS_115 (a)	2	Myopia CVI
OS_132	2	Microphthalmia Optic nerve aplasia Optic nerve hypertrophy CVI Myopia Ptosis
OS_163	3	Severe myopia Strabismus (R exotropia)
OS_150 (c)	3	Nystagmus CVI Oculomotor apraxia Strabismus (intermittent exotropia) Hyperopia
OS_153 (b)	4	Myopia Strabismus CVI

Table 7. Globe Size and Ophthalmic Diagnoses in *NAA15* Mutation Cohort.

Proband Identifier	Globe Size Rating (1-4)	Other Ophthalmology Diagnoses at Time of Imaging
NAA15_007	1	Astigmatism
NAA15_010	1	Normal
NAA15_013	1	Amblyopia Astigmatism
NAA15_019	1	Esotropia
NAA15_008 (d)	4	Cortical Visual Impairment (CVI) Myopia Pale Optic Nerve Strabismus Nystagmus Progressive Vision Loss Astigmatism

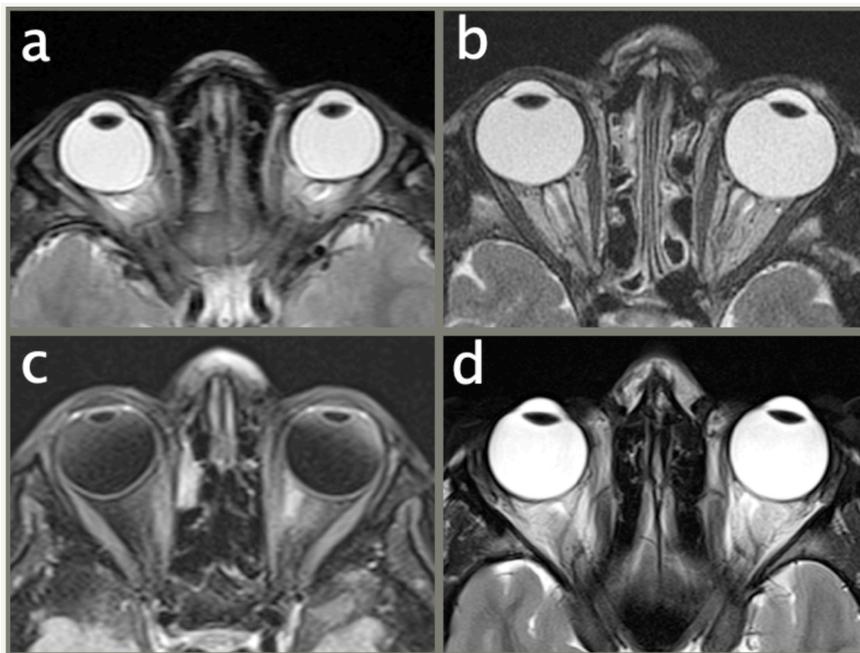


Figure 3. Brain MRI collage depicting ocular globe abnormalities in 4 different patients with Ogden syndrome. (a) axial T2WI (OS_115) shows bilateral globe dysmorphia; (b) axial T2WI (OS_153) shows bilateral macrophthalmia and mild dysmorphia; (c) axial fat-sat T2 FLAIR (OS_150) depicting bilateral macrophthalmia and mild dysmorphia; (d) axial T2WI (patient NAA15_008) shows bilateral macrophthalmia.

To better understand the impact of early ophthalmic interventions in patients with Ogden Syndrome, we reached out directly to patient families for quotes (**Table 8**). These underscore the importance of early and regular ophthalmology screening and intervention to optimize mobility, intellectual development, social development, and overall quality of life for patients with *NAA10* and *NAA15* mutations. Full quotes are available in **Supplementary Table S1**.

Table 8. Quotes from *NAA10* and *NAA15* Families.

Proband	Quote
NAA10_OS_103	The only thing we had was glasses. There was never any vision therapy. I wish we would have known about CVI when she was younger.
NAA10_OS_151	After the glasses came into the picture, [X] really started to use her hands to interact much more, which opened up a whole new world for her and was so important to increasing her quality of life. Prior to glasses she was kicking at everything instead because she could see at that distance better than what was in range of her arms. Over the years we have just seen improvement over improvement in [proband's] vision.
NAA10_OS_153	At [0-4] years old, she had surgery on one of her eyes to correct strabismus. She is near-sighted and wears glasses intermittently for distance activities. When she was school age, her teacher did report that she seemed more engaged and attentive when wearing her glasses during a school lesson/activity.
NAA10_OS_163	As a teenager, she did have a functional vision assessment by an optometrist who specialized in people with IDD. Although he could not get a refraction, he was very patient and observant during his creative assessment and was able to tell that she was using her left eye and getting her best vision about six inches from her face. Also, due to the corneal scarring, she sees best in the lower periphery.
NAA15_008	In early childhood, [her reduced visual acuity and visual field] manifested as a fear of heights or irregular surfaces which at the time we attributed incorrectly to anxiety. The initial issues with vision became apparent around [5-9] yrs of age when lack of depth vision was noted and corrected with glasses. B has received highly beneficial treatment from Occupational Therapists and Speech Pathology which commenced when she was [0-4 years] of age due to delays in these

	areas. B completed high school successfully and has entered a Bachelor's degree at university now.
NAA15_009	My son had surgery to correct his strabismus 4 years ago and still visits his ophthalmologist annually. He needs glasses for school, but has not needed another intervention. When I was first told he needed surgery, I was skeptical, thinking it was only an aesthetic intervention. However, this intervention has had a positive impact on his future, his learning process, and even his mobility.
NAA15_013	As a child, the most positive intervention that was utilized was eye patching when she was [0-4] and [5-9] years old to correct the amblyopia. The deficit in her depth perception showed some improvement in the years following the correction but it remains limited.
NAA15_019	When she was younger, she was afraid of surfaces that changed or stairs due to her depth perception issues. We have also used neurodevelopmental strategies to strengthen her peripheral vision and her non-dominant eye. When her vision increased and became stronger, it helped her in her schoolwork and able to do dance classes.

Discussion

Mutations in the *NAA10* and *NAA15* genes affect the development of multiple organ systems, including the eyes^{11,12,15}. Literature on *NAA10*- and *NAA15*-related neurodevelopmental syndromes to date has not focused on the specifics of ophthalmologic manifestations in a large cohort. We described common ophthalmic conditions in both *NAA10* and *NAA15* individuals including CVI, astigmatism, myopia, hyperopia, strabismus, and nystagmus. The prevalence of all studied conditions was higher in our cohort compared to previous literature (CVI 22.4% vs. 8.5%; myopia 25.4% vs. 4.7%; astigmatism 37.3% vs. 13.2%; strabismus 28.4% vs. 3.8%, respectively). This suggests that many of these conditions may be under-reported and thus underdiagnosed in patients with Ogden Syndrome.

In Western countries, CVI is a leading cause of pediatric bilateral visual impairment^{18,19}. It is diagnosed when children exhibit abnormal visual responses that are not caused by the eye itself. As this affects visual processing, it can have far-reaching effects on a patient's ability to learn and interact with their surroundings. Difficulties with depth perception, face processing,

and discernment of contrast are often functional manifestations of CVI^{20,21}. It has been suggested that up to 10.5% of children with developmental disabilities have CVI, though many remain undiagnosed^{22,23}. Our data support the suggestion that CVI is underdiagnosed, as we found a high prevalence of trouble with depth perception in both *NAA10* and *NAA15* individuals in the absence of a confirmed CVI diagnosis (19.2% (n=1) and 44.4% (n=8), respectively). Further, trouble with depth perception could serve as a metric to better understand visual abnormalities in patients with OS. Examination by an ophthalmologist is recommended upon diagnosis, but further exploration of the characteristics of CVI as it relates to OS could help further guide patient care, ensure early intervention of treatable ocular conditions during development, and provide valuable insights into the underlying mechanisms and development of visual processing.

Previous literature suggests that *NAA10* individuals present with more severe phenotypes than *NAA15* individuals⁷. In terms of the ophthalmic phenotypes, we found no significant differences between *NAA10* and *NAA15* presentations. However, it is important to note the small sample size of the *NAA15* cohort, so this needs to be validated in a larger cohort in the future. Though it was not significant, a higher proportion of *NAA15* patients also had trouble with depth perception with no documented CVI diagnosis. This may be a result of milder phenotypic presentations with *NAA15* mutations, but it may also point to a greater need for screening and assessment for CVI in this patient population.

Interestingly, in comparing presentations across demographics, we found that *NAA10* males were significantly less likely to have astigmatism compared to *NAA10* females ($p < 0.05$) (**Supplementary Figure S1e**). This significance is likely due to a small sample size of males, as mutations in *NAA10* are more lethal in males⁷. Perhaps *NAA10* males who would have had ophthalmologic manifestations died due to more serious systemic dysfunction. We also analyzed mutation patterns with regards to ophthalmologic manifestations of interest. We found that p.Phe128Leu had a higher prevalence of nystagmus ($p < 0.05$) (**Supplementary Figure S2h**). Again, this may be due to small sample size, but it may also be suggestive of mutation-specific impacts on phenotype. Further research is necessary, as these phenotypic manifestations of specific mutations may aid in guiding screening processes or clinical decision making to improve quality of care for *NAA10* and *NAA15* individuals.

Neuroimaging assessment for structural abnormalities of the ocular globes was performed on a select number of *NAA10* (n=13) and *NAA15* (n=5) individuals. There is no clear correlation between globe size/shape and ocular phenotypes, but it is interesting to note that, overall, the *NAA15* individuals had milder ophthalmic manifestations and fewer neuroimaging abnormalities compared to *NAA10* individuals, with the exception of one *NAA15* individual (p.Thr351Profs*3) who had a more severe ocular presentation than the other *NAA10* individuals. Further neuroimaging and data collection should be done to better understand the functional consequences of ocular globe MRI phenotypes (macrophthalmia and/or dysmorphia) in patients with *NAA10* and *NAA15*-related neurodevelopmental syndromes.

The specific function of *NAA10* and *NAA15* in visual system development are not fully clear. Previous literature has suggested that *NAA10* may be involved in retinoic acid signaling, which is critical for ocular development^{12,24}. The critical role of *NAA10* in eye development was further supported by a study on zebrafish, wherein *NAA10* knockdowns produced small, underdeveloped eyes²⁵. *NAA15* has been shown to play a critical role in neuron generation and differentiation²⁶, which could also contribute to the visual abnormalities seen in patients with mutations in this protein. Further research is necessary to investigate the connection between *NAA10/NAA15* and detrimental alterations in ocular development and function.

Limitations

A major limitation of this study was that it was conducted through video conferencing and chart review. We were fortunate to have access to thorough medical records for most probands. However, some were not fully comprehensive or did not include records from an ophthalmologist or optometrist. In these instances, we relied on information gathered from interviews with the patients' parents, who may not always recall details of medical information. As a result of this, we are likely under-reporting the prevalence of the ophthalmic manifestations studied.

Additionally, our cohorts contained some novel mutations, which made it difficult to classify some proband mutations as pathogenic versus likely pathogenic versus VUS. However, this was greatly aided by recently published material on *NAA10* and *NAA15* mutation pathogenicity⁷. Further, there are mutations, such as p.Ser123Pro, that have been previously published as "likely pathogenic," but biochemical analysis has not been performed. We used ACMG criteria by Richards et al. to classify mutations that have not been reported or classified previously²⁷. These classification justifications are available in **Supplementary Notes S(1-6)**.

Conclusions

NAA10-related and *NAA15*-related neurodevelopmental syndrome is classically characterized by intellectual disability, congenital cardiac anomalies, and delayed development. However, our analysis underscores the importance of considering the ophthalmic phenotypes that are common in this condition. The prevalence of CVI, myopia, astigmatism, strabismus, nystagmus, and hyperopia were higher in our cohort of 67 patients with *NAA10* mutations than previously reported in literature. To our knowledge, this is the first cohort analysis of the ocular manifestations of *NAA15* mutations. Our analysis suggests that many of these conditions are likely being underdiagnosed in this patient population, specifically CVI. More research with larger cohorts and functional assays is certainly needed to better understand the role that these mutations play in altering visual development. This would help promote prompt screening, assessment, and intervention by an optometrist or ophthalmologist upon diagnosis of Ogden syndrome and improve the quality of life for these patients.

Author Contributions

GJL conducted all virtual interviews with participants and was responsible for primary data collection, with assistance by EM. RP was responsible for data analysis and project conception, along with GJL. MW was responsible for neuroimaging analysis. The first draft of the manuscript was written by RP and AP, with critical revision performed by GJL, AG, and MW at several points.

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Ethical Approval

Both oral and written patient consent were obtained for research and publication, with approval of protocol #7659 for the Jervis Clinic by the New York State Psychiatric Institute - Columbia University Department of Psychiatry Institutional Review Board.

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Competing Interests

The authors declare that they have no competing interests or personal relationships that could have influenced the work reported in this paper.

Supplementary Information

Figures S1(a-h). Prevalence of the Ophthalmic Manifestations of NAA10 Mutations by Demographic (n=67).

Figures S2(a-h). Prevalence of the Ophthalmic Manifestations of NAA10 Mutations by Mutation (n=50). Note that only mutations with ≥ 3 probands were included in the analysis.

Table S1. Full quotes from select *NAA10* and *NAA15* families.

Notes S(1–6). NAA10 Mutations - Arg116Gln, His120Pro, His034Tyr, Met147Leu.
NAA15 Mutation - p.ENST00000296543.5 splice site variant c.1753+1G>A

Supplementary Dataset S1. Excel file: NAA10 Summary

Supplementary Dataset S2. Excel file: NAA15 Summary

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