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RESEARCH REPORT

Ophthalmic manifestations in Costello syndrome caused by Ras pathway dysregulation during development

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ABSTRACT

Background: Costello syndrome (CS) is a multisystem developmental disorder caused by germline pathogenic variants in *HRAS* resulting in dysregulation of the Ras pathway. A systematic characterization of ophthalmic manifestations provides a unique opportunity to understand the role of Ras signal transduction in ocular development and guide optimal ophthalmic care in CS individuals.

Methods: Visual function, ocular features and genotype/phenotype correlations were evaluated in CS individuals harboring *HRAS* pathogenic variants, by cross-sectional and retrospective studies, and were recruited through the Costello Syndrome Family Network (CSFN) between 2007 and 2020.

Results: Fifty-six molecularly diagnosed CS individuals including 34 females and 22 males, ages ranging from 0.5 to 37 years were enrolled. The most common ophthalmic manifestations in the cross-sectional study were lack of stereopsis (96%), refractive errors (83%), strabismus (72%), nystagmus (69%), optic nerve hypoplasia or pallor (55%) and ptosis (13.7%) with higher prevalence than in the retrospective data (refractive errors (41%), strabismus (44%), nystagmus (26%), optic nerve hypoplasia or pallor (7%) and ptosis (11%)). Visual acuities were found to ranged from 20/25 to 20/800 and contrast sensitivity from 1.6% to 44%. *HRAS* pathogenic variants included p.G12S (84%), p.G13C (7%), p.G12A (5.4%), p.G12C (1.8%) and p.A146V (1.8%).

Conclusion: Majority of individuals with CS have refractive errors, strabismus, nystagmus, absent stereopsis, and optic nerve abnormalities suggesting that *HRAS* and the Ras pathway play a vital role in visual system development. Ptosis, refractive errors and strabismus are amenable to treatment and early ophthalmic evaluation is crucial to prevent long-term vision impairment and improve overall quality of life in CS.

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Costello syndrome; RASopathies; eye manifestations; strabismus; refractive errors; optic nerve hypoplasia

Introduction

Costello syndrome (CS) (1,2) is a genetic disorder with a prevalence of 1:300,000 to 1:1.25 million (ORPHA: 3071) and belongs to a class of neurodevelopmental disorders referred to as the RASopathies (3,4). Dominant *de-novo* mutations in the *HRAS* gene encoding a product of the Ras signal transduction pathway causes Costello syndrome (OMIM: # 218040) (5,6). Dysregulation of other genes in the Ras pathway result in similar syndromes having significant phenotypic overlap and include neurofibromatosis 1 (NF1), cardiofaciocutaneous syndrome (CFC), Noonan syndrome (NS), Noonan syndrome with multiple lentigines (NSML), and Legius syndrome (7). Costello syndrome is a multisystem disorder characterized by distinctive cranio-facial features, including macrocephaly, congenital heart defects, such as pulmonic stenosis, cardiac rhythm disturbances and hypertrophic cardiomyopathy, neurological features including hydrocephalus, syringomyelia, postnatal cerebellar overgrowth and neurocognitive impairment, dermatologic findings such as nasal papilloma, hemangiomas, keratosis pilaris, palmoplantar keratoderma, and, musculoskeletal features such as ulnar deviation, short Achilles tendon, hip joint problems and myopathies. A predisposition to neoplasia development, both benign and malignant has also been described (8–11). Although ocular findings such as dolichocilia (long eyelashes), strabismus, nystagmus, refractive errors and visual disturbances have been described in CS (12), these were collated using retrospective medical record analysis. A comprehensive standardized in-person study of ophthalmic manifestations has never been performed and reported in these individuals (12). Activating mutations in *HRAS*, the only gene of the Ras pathway associated with CS, results in hyperactivation of Ras pathway, a highly conserved key regulator of fundamental cellular functions such as cell differentiation, migration and proliferation (3). The role of Ras pathway in eye development has been reported in a number of *in vivo* studies in *Drosophila* (13,14), xenopus (15) and mouse models (16) as well as in *in vitro* models (17). Further, ERK, a downstream effector of the Ras pathway is reported to be a key factor in the synaptic plasticity

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of the visual cortex (18,19). Ocular manifestations have been reported in other RASopathies including NF1, CFC and NS (20–22). We sought to evaluate the visual function and ocular features of CS in a comprehensive manner in this study.

Subjects and methods

All studies were performed under institutional IRB consent with approval obtained through the committee on Human Research at the University of California and adhered to the tenets of Declaration of Helsinki and are HIPAA compliant. Study participants were recruited through the Costello Syndrome Family Network (CSFN). All individuals in the study had positive molecular genetic testing with heterozygous pathogenic variants in *HRAS*. Participants voluntarily registered to be part of the study, and none declined or withdrew from the study after participation. Visual function testing and full ophthalmologic evaluations were performed in 29 individuals with CS at the International Costello Syndrome Family Network (CSFN) Conferences held at Berkeley, CA (2009, 23) and Chicago, IL (2011) and hereafter will be referred to as Group 1. Assessments of eye alignment, visual acuity, stereoacuity, color vision, and retinoscopy with and without cycloplegia were performed by DOB and TW. Behavior based measures of visual acuity, contrast sensitivity, color vision and stereopsis were obtained using 2-alternative forced-choice paradigms. The examiner presented the test card paired with a "blank card" using the modified "acuity card" procedure to judge the threshold for "seeing" the test target (24). Visual acuity was measured with children wearing their habitual refractive correction using either the Lea single symbols (with crowding bars at 100% spacing) and/or the University of California Berkeley Preferential Looking grating acuity cards (25). Contrast sensitivity was obtained using the Mr. Happy contrast test (25). Color vision was assessed using the Berkeley modified version of the F2 plate (25). Measures of stereopsis were attempted with the PASS test (26). Eye evaluations including ocular motility, retinoscopy with cycloplegia, handheld slit lamp and indirect ophthalmoscope assessments were performed by SS and TY. Retrospective medical record analysis was performed in 26 additional individuals and hereafter will be referred to as Group 2. Frequency and percentage, and general population prevalence were used for qualitative data. Fishers exact test was performed with R program to determine differences in prevalence among CS Group 1 and general population. Genotype and ocular phenotypic features were assessed for any correlation.

Results

Our cohort of 56 CS individuals, 29 in-person evaluations (Group 1) and 27 retrospective chart reviews alone with no in-person evaluation (Group 2), consisted of 34 females and 22 males (3:2 ratio), with ages ranging from 5 months to 37 years and all positive for *HRAS* pathogenic variants (Tables 1–3). The most common *HRAS* pathogenic variant was p.G12S in both groups, other variants being p.G13C, p.G12A, p.G12C and p.A146V (Table 1). The Majority (>90%) of the individuals in Group 1 had more than one ocular feature including reduced visual acuity, lack of stereopsis, strabismus, refractive errors, and/or nystagmus. Additional findings included ptosis, optic nerve hypoplasia and optic nerve pallor/atrophy (Figures 1 and 2). A significant number of individuals in Group 2 were also found to have strabismus, refractive errors, and nystagmus. A summary of our findings comparing the prevalence of ocular findings among CS individuals in Group 1, Group 2, previously reported eye findings in CS (12), and in the general population (27–34) are shown in Table 1. There was no significant genotype/phenotype correlation identified. Individual detailed eye examination findings for Group 1 and Group 2 are shown in Tables 2 and 3 respectively.

Visual function tests

Across all ages, 97% (28/29) of CS individuals were testable with either the Lea single symbols (with crowding bars at 100% spacing) and/or the University of California Berkeley Preferential Looking grating acuity cards. For children older than 4.9 years, visual acuity with the better seeing eye or with both eyes viewing ranged from 20/25 (logMAR = 0.1) to 20/152 (logMAR = 0.88); mean = 20/50 with the Lea symbols in 21 children. UCBSO PL grating acuity ranged from 20/20 (logMAR = 0) to 20/120 (logMAR = 0.78); mean = 20/42 in 18 children. Grating visual acuities for the six youngest children (0.5 to 2.4 years) was reduced from age matched norms and ranged from 0.48 to 1.68 logMAR; mean 1.1 logMAR (20/250). Contrast sensitivity was obtained using the Mr. Happy contrast test from 28/29 children. Of these, 23/28 (82%) were able to detect the face with the lowest available contrast for the test (1.6% Michelson contrast) indicating a good ability to detect subtle brightness differences. Five children showed reductions in contrast sensitivity ranging from 3.2% to 44% contrast as the lowest detectable contrast. Measures of stereopsis with the PASS test were attempted in 23 children, excluding the six children with a constant strabismus. Of these, only one child (1/23) demonstrated limited stereopsis (120 arc secs), three refused the stereo glasses required for testing, and 19/20 (95%) completed the demonstration plate indicating testability but were unable to appreciate the next test plate with 480 secs of stereoacuity. Color vision was assessed using the Berkeley modified version of the F2 plate. 19/23 (82%) showed normal color vision, two children were unable to complete the task and four were not tested. Of the four children with a mild red-green color vision deficiency (3 females, 1 male), the male and one female had accompanying optic nerve atrophy, one female had a normal fundus and the other had no fundus evaluation.

Ophthalmic features

Ptosis

Ophthalmologic exam revealed congenital ptosis in 4/29 (13.7%) individuals, this is higher than previously reported (8%) (12) and in the general population 0.0079% (13.7%, P = 2.81E-12) (27). The retrospective analysis data of 27 individuals revealed 3/27 (11%) individuals with ptosis.

Table 1. Demography, genotype and summary of ocular findings in CS.

Demography	Group 1	Group 2	Total		
Total study subjects	29	27	56		
Male	10	12	22 (40%)		
Female	19	15	34 (60%)		
Summary of pathogenic variants in HRAS					
Variant	**Group 1**	**Group 2**	**Total**		
p.G12S	23	24	47/56 (84%)		
p.G13C	4	0	4/56 (7%)		
p.G12A	0	3	3/56 (5.4%)		
p.G12C	1	0	1/56 (1.8%)		
p.A146V	1	0	1/56 (1.8%)		
Summary of ocular findings in Costello Syndrome					
Ocular findings	**Group 1**	**Group 2**	**Literature review**	**Population prevalence**	***P*- value**
Ptosis	4/29 (13.7%)	3/27 (11%)	8%	0.0079% [27]	2.81E −12
Strabismus—total	21/29 (72%)	12/27 (44%)	30.80%	3.3% [28]	< 2.2E-16
Orthophoria	8/29 (28%)	14/27 (52%)			
Exotropic disorders with or without HT or H (XT, X(T), X, HT, H(T))*	11/29 (38%)	2/27 (7.4%)		1.5% [28]	6.42E-12
Esophoric disorders with or without HT (ET, E(T), E, HT)**	10/29 (34.5%)	2/27 (7.4%)		1.8% [28]	5.49E-10
Nystagmus (jerk type, gaze evoked, horizontal)	20/29 (69%)	7/27 (26%)	38.30%	0.12% [29]	< 2.2E-16
24/29 individuals had cycloplegic refraction in group 1					
Total refractive errors	20/24 (83%)	15/27 (41%)			
Myopia (≤0.50DS)	1/24 (4%)	N/A	9.50%	22.9%[30]	.043
Total of High (−0.5 ≤ 5.0DS) and Degenerative Myopia (>5.0DS)	11/24 (46%)	11/27 (39%)		2.7% [30]	7.06E-11
Astigmatism (≥1.5DS)	6/24 (25%)	4/27 (15.0%)	4.20%	7.3% [35]	.004
Hyperopia (≥2.00DS)	2/24 (8%)	2/27 (7.0%)	2.10%	25.6% [35]	.1
27/29 individuals had slit lamp evaluation in group 1					
Anterior segment (Normal)	23/27 (85%)	27/27 (100%)			
Prominent corneal nerves	1/27 (3%)				
Iris freckles	1/27 (3%)				
22/29 individuals had fundus evaluation in group 1					
Optic nerve (Normal)	7/22 (32%)	25/27 (93%)			
Optic nerve hypoplasia	5/22 (23%)	2/27 (7.0%)	1.10%	0.017% [32]	6.55E-13
Optic nerve pallor/atrophy	6/22 (27%)		0.04%	0.08% [33]	1.58E-13
Wide optic discs	2/22 (9%)				
18/29 individuals alone peripheral retinal evaluation in group 1					
Retinal pigmentary changes	1/18 (5%)		3%	0.03% [34]	

Group 1(cross sectional evaluation), Group 2 (retrospective chart review.
*XT-Exotropia, X(T)-Intermittent exotropia, X-Exophoria, HT-Hypertropia, H(T)-Intermittent hypertropia, **ET-Esotropia, E(T)-Intermittent esotropia, E-Esophoria.

Figure 1. Two individuals with characteristic facial features of CS including broad forehead, bitemporal narrowing, hypertelorism, epicanthal folds, depressed nasal bridge, and exotropia. Individual in 1a corrected for degenerative high myopia, and baby in 1b showing sunset sign.

Strabismus and nystagmus

The in-person ocular motility and strabismus evaluations revealed strabismus in 21/29 (72%) individuals and is more than twice the number that was previously reported (30.8%) (12) and substantially greater than in the general population 3.3% (28) (72%, P = <2.2e-16). Exotropic disorders were more common with 11/29 (38%) having manifest exotropia XT, intermittent exotropia X (T), or exophoria X, with or without vertical phoria/tropia (Figure 1). With respect to esotropic presentations, 10/29 (34.5%) study subjects had esotropia ET, intermittent esotropia E (T), or esophoria E with or without vertical phoria/tropia. These occurrences were significantly higher than the general population prevalence for exotropic 1.5% (28) (38%, P = 6.42E-12) and esotropic 1.8% (28) disorders (34.5%, P = 5.49E-10). The retrospective medical record analysis data revealed strabismus reported in 12/27 (44%), however, the type of strabismus was specified only in four individuals—XT in 2/27 (7.4%) and ET in 2/27 (7.4%).

Nystagmus was identified in 20/29 (69%) individuals and noted to be jerk type, horizontal or gaze evoked nystagmus and was higher than previously reported (38.3%) (12) and in the general population 0.12% (29) (69%, P = <2.2E-16). Retrospective analysis of the data revealed nystagmus reported in 7/27 (26%) individuals with no details of the type of nystagmus.

Refractive errors

Fifteen of 29 individuals (Group 1) presented at the conference without any habitual spectacle correction (14 were 10 years of age or younger, one was 20 years of age). Fourteen individuals had glasses, three between the ages

of 8 to 10 years had astigmatism ranging from 1.25 DC to 3.00 DC with a low spherical equivalent (SE) of ≤-0.65 DS to ≤ +1.75DS and the remaining 11 were older than 15 years of age with a SE ranging from −0.25 DS to −10.00 DS (mean = −5.00 DS) and, six had 1.00 DS of anisometropia or more. Twenty-four individuals (24/29 in Group 1) had cycloplegic refraction, of the five that had no refraction, four were less than 10 years of age, three of these had no glasses, and one 10-year-old had myopia with astigmatism and wore bifocals, another 34-year-old had myopia with astigmatism. Among the 24 individuals who had cycloplegic refraction, 13/24 were ≤10 years of age and had SE refractive errors ranging from −0.50 DS to +2.25 DS (mean = 0.37 DS) with or without astigmatism. Eleven of 24 were ≥15-years-old and had high myopia with SE≤5.00 DS or degenerative myopia with SE>5.00 DS with or without astigmatism (>1.50 DC in any axis). Overall, high myopia 4/24 (16%) and degenerative myopia 7/24 (29%) together were found in 11/24 (46%) individuals much greater than the previously reported myopia prevalence of 9.5% (12) in CS and in the general population 2.7% (30) (46%, P = 7.06E-11). Astigmatism (≥1.50 DC) was found in 6/24 (25%) CS individuals and was also much higher than previously reported in CS (4.2%) (12) and the general population prevalence of 7.3% (35) (25%, P = .004). Myopia ≤0.5 DS was found in 1/24 (4%) and was lower than in general population 22.9% (30) (4%, P = .043). Mild hyperopia ≤2.00 DS was found in 10/24 (41%) all younger than 10 years of age. Hyperopia (2.00DS to 4.00DS) was found in 2/24 (8%) individuals younger than 10 years of age and was much lower than in general population 25.6% (35) (8%, P = .1). Moderate to high hyperopia ≥4.0DS was not found in this cohort. Two individuals were found to require bifocal correction.

Anterior segment

Ophthalmic evaluation with a handheld slit lamp was normal in most individuals (23/27). Rare findings included prominent corneal nerves (1/27), large corneal diameter (1/27), iris freckles (1/27) and cortical cataract (1/27)—all with 3% prevalence. Cataracts were previously reported at a higher prevalence (6.4%) (12) in CS than what we found in this study, and was greater than the general prevalence of congenital and childhood cataracts ranging from 0.032 to 0.23% (31).

Posterior segment

Dilated fundus examinations were performed in 22/29 subjects using binocular indirect ophthalmoscopy and revealed a number of optic nerve abnormalities. Optic nerve hypoplasia (Figure 2) was found in 5/22 (23%) and was higher than previously reported (1.1%) (12) and in the general population (0.017%) (32) (23%, P = 6.55E-13). Optic nerve pallor or atrophy was noted in 6/22 (27%) also higher than previously reported (1.1%) (12) and in the general population 0.04% (33) (27%, P = 1.58E-13). Optic disc anomalies included peripapillary atrophy, tilted optic discs, and anomalous vessel on optic disc. Retinal pigmentary disturbance with RPE thinning and atrophy in the inferotemporal region of one eye was found in 1/18 (5%) individuals but with no other bone spicules or changes suggestive of retinal dystrophy.

Genotype/phenotype correlation

HRAS p.G12S (47/56, 84%) was the most common *HRAS* pathogenic variant in our cohort. Other variants included p.G13C (4/56, 7%) and p.G12A (3/56, 5%) and one patient each for p.G12C and p.A146V. This allelic distribution was similar to the published literature (36). All ocular findings including refractive errors, high and degenerative myopia, strabismus, nystagmus, and optic nerve hypoplasia or optic atrophy occurred in all genotypes. One individual with p.G13C had degenerative myopia, nystagmus, optic nerve hypoplasia and an area of RPE thinning and atrophy with hyperpigmentation in the inferotemporal region of one eye and another had nystagmus and mild hyperopia with astigmatism but had no fundus abnormalities. In Group 2 with retrospective chart review, one individual with p.G12A had nystagmus and the second individual with p.G12A had nystagmus, myopia and esotropia. Ocular features were variable in individuals with HRAS p.G12S, the most frequent pathogenic variant with no significant genotype-phenotype correlation noted.

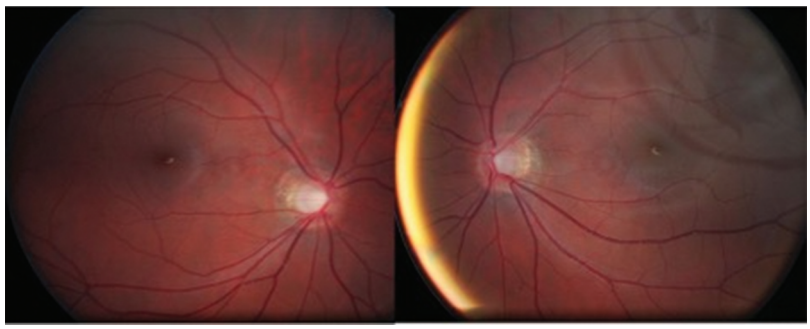

Figure 2. Fundus photos revealing small gray optic discs bilaterally with peripapillary atrophy and temporal crescents. Retina is otherwise normal in appearance with no pigmentary abnormalities.

Table 2. Cross-sectional eye exam data.

Data No.	Age in Years	Gender	Genetic defect	Current Glasses	Mr. Happy contrast Both eyes viewing	PASS Stereo (demo, 480, 240,120, 60 secs)	F2 square color test	Lea single symbols with crowding bars	PL grating acuity	Data No.	Ptosis	Strabismus	Nystagmus	Anterior segment	Optic nerve	Retina	Cycloplegic Retinoscopy
1	0.5	M	p.G12S	None	4.0%	N/A	Unable	N/A	OU sc 0.7/3	**1**	No	Orthophoria	No	N/A	N/A	N/A	N/A
2	1.1	F	p.G12S	None	63.0%	N/A	N/A	N/A	OUsc 0.5/24	**2**	No	100 XT	Present	NL	OU-pale optic discs	N/A	OD +0.50 DS; OS +0.50 DS
3	1.4	F	p.G12S	None	1.6%	Refused	Normal	N/A	OUsc 1/3	**3**	No	20 LX(T) @n, 40 LXT @d	Present	NL	OD- no view; OS- wide C:D 0.7 ratio	N/A	OD +0.75 DS; OS +0.75 DS
4	1.7	F	p.G12S	None	6.3%	N/A	N/A	N/A	OUsc 0.6/24	**4**	No	Orthophoria	Present	NL	OD-atrophy OS-appears large	NL	OD: -0.25 DS; OS: +0.75-1.00X180
5	2.1	F	p.G12S	None	1.6%	N/A	Training plate only	N/A	OUsc 0.5/3	**5**	No	20 X(T), H(T)	No	NL	N/A	N/A	OD +2.00 DS; OS +2.50-0.50 X160
6	2.4	F	p.G12C	None	5.0%	N/A	N/A	N/A	OUsc 1/3	**6**	Mild	X(T)	No	NL	NL	NL	OD +1.00-0.50X180; OS +1.50-1.00X180 (noncycloplegic)
7	4.9	M	p.G13C	None	1.6%	No stereo	Normal	ODsc 1.5/1.9 OSsc 1.5/2.4	ODsc 1.5/3 OSsc 1.5/3	**7**	No	RXT & RHT	Present: Jerk type	NL	OU-Small optic nerves	N/A	OD: +1.75 DS; OS: +1.75 DS
8	5.2	F	p.G13C	None	1.6%	Refused	Red-green deficit	unable to do	OUsc 0.5/3	**8**	No	60 XT, HT Alt	Present: right beating, jerk type	Cornea appears large	N/A	N/A	N/A
9	5.10	M	p.G12S	None	N/A	Refused	N/A	N/A		**9**	No	Orthophoria	Present	N/A	N/A	N/A	N/A
10	7	F	p.G12S	None	1.6%	No stereo	Normal	OUsc 0.5/1.9 Ossc 0.5/7.5	OUsc 0.6/1.5	**10**	No	Orthophoria	No	NL	OD-NL OS-Anomalous vessel on the disc	NL	OD +1.50-1.00x010; OS +1.50-1.00x160
11	7.5	M	p.G12S	None	1.6%	No stereo	Normal	OUsc 0.5/3.8	OUsc 0.7/1.5	**11**	No	R E(T)	Present: Latent, gaze evoked	NL	NL	NL	OD: +1.00 DS; OS: +1.50 DS
12	7.5	F	p.G12S	None	1.6%	No stereo	Normal	OUsc 1.5/3	OUsc 0.5/1.5	**12**	No	EP	Present	NL	OD NL, C:D 0.2, OS C:D 0.4 mild ON hypoplasia	NL	OU: + 1.00 DS
13	8.2	M	p.G12S	OD +1.75-1.25X035; OS +2.75-2.00X165	1.6%	No stereo	Normal	ODcc 1.5/3 OScc 1.5/3.8	ODcc 1.5/1.5 OScc 1.5/3	**13**	No	LXT, LH(T)	Present	NL	NL	NL	OD +2.75-1.25x035; OS +3.75-2.00x165

(*Continued*)

Table 2. (Continued).

Data No.	Age in Years	Gender	Genetic defect	Current Glasses	Mr. Happy contrast Both eyes viewing	PASS Stereo (demo, 480, 240,120, 60 secs)	F2 square color test	Lea single symbols with crowding bars	PL grating acuity	Data No.	Ptosis	Strabismus	Nystagmus	Anterior segment	Optic nerve	Retina	Cycloplegic Retinoscopy
14	9.4	F	p.A146V	None	1.6%	No stereo	Normal	ODsc 1.5/1.9 OSsc 1.5/1.9	ODsc 1.5/1.5 OSsc 1.5/1.5	**14**	No	ET	No	NL	NL	NL	OD: +0.75 DS; OS: +0.75 DS
15	9.8	M	p.G12S	OD +0.75-2.75X030; OS +1.00-3.00X155	1.6%	120 secs	Normal	ODcc 1.5/1.9 OScc 1.5/2.4	N/A	**15**	No	Orthophoria	No	NL	OU: Optic nerve C:D 0.6	N/A	OD +0.25-2.75x030; OS +1.25-3.00x155
16	10	F	p.G13C	OD +1.00-1.75X180; OS +0.25–1.50X180 add + 3.25 OU	1.6%	No stereo	Red-green deficit	OUcc 1.5/3	OUcc 1.5/3	**16**	No	20 ET	Present: Latent, Horizontal	NL	NL	NL	N/A
17	10	F	p.G12S	None	1.6%	No stereo	Normal	OUsc 0.5/1.5	OUsc 0.5/1.5	**17**	No	Orthophoria	No	NL	OU-temporal pallor	NL	OU: Plano
18	15	F	p.G12S	OD −6.25 DS; OS −6.50 DS	1.6%	Constant ET, not tested	Red-green deficit	OUcc 0.5/1.9 OScc 0.5/2.4	OUcc 1.0/1.5	**18**	Mild	L ET small	Present:Gaze evoked	NL	OU-mild optic nerve pallor	NL	OD −5.50-1.00X170; OS −5.75-1.25X010
19	15.7	F	p.G12S	OD −6.75-1.50 X135; OS −2.75-1.00X60 +2.75 DS add	1.6%	No stereo	Normal	ODcc 1.5/6 OScc 1.5/7.5	ODcc1.5/3 OScc 1.5/3	**19**	No	Orthophoria	Present:Gaze evoked jerk type	prominent corneal nerve	OU -tilted discs; temporal pallor	NL	OD −7.75-1.00X130; OS −4.50-0.25X60
20	17.1	F	p.G12S	OD −5.00-1.50X045; OS −7.00-0.50x150	1.6%	No stereo	Normal	ODcc 1.5/2.4		**20**	No	20 ET	Present: Horizontal	NL	OU -ON hypoplasia	NL	OD −6.25-1.00x045; OS −7.75-0.50x150
21	18	M	p.G13C	OD −5.00-2.25X050; OS −7.75-1.25X150	1.6%	No stereo	Red-green deficit	ODcc 1.5/3.8	Odcc 1/3	**21**	No	ET Variable	Present: Left beating, jerk type	NL	OU-Optic atrophy	RPE atrophic change inferotemporal quadrant OS	OD −3.75-1.75X050; OS −6.00-1.25X150
22	18.4	F	p.G12S	OD −3.50-1.00X080; OS −3.00 DS	1.6%	No stereo	Normal	OUcc 1.5/3.8 ODcc 1.5/4.8 OScc 1.5/6.0	OUcc 1.5/3	**22**	No	30 R X(T)	Present: right beating, jerk type	NL	OU-ON hypoplasia	NL	OD −3.50-1.25X080; OS −2.75-0.50x090
23	19.8	F	p.G12S	OD −0.75-3.00X042; OS −2.00-2.00X140	1.6%	No stereo	Normal	ODcc 1.5/3 OScc 1.5/2.4	ODcc 1.5/3 OScc 1.5/1.5	**23**	No	20-40 ET	No	NL	N/A	N/A	OD −0.25-3.00x042 OS −2.00 −2.00x140
24	20	M	p.G12S	None	1.6%	No stereo	Normal	OUsc 3/3.8 ODsc 1.5/4.8	OUsc 0.5/3	**24**	No	40 R XT	Present: Left beating, jerk type	NL	OD-Optic nerve hypoplasia OS> OD	NL	OD +0.50-1.00x020; OS plano-1.00x165

(*Continued*)

Table 2. (Continued).

Data No.	Age in Years	Gender	Genetic defect	Current Glasses	Mr. Happy contrast Both eyes viewing	PASS Stereo (demo, 480, 240,120, 60 secs)	F2 square color test	Lea single symbols with crowding bars	PL grating acuity	Data No.	Ptosis	Strabismus	Nystagmus	Anterior segment	Optic nerve	Retina	Cycloplegic Retinoscopy
25	21	M	p.G12S	OD +0.25-1.00x175; OS plano-0.75X180	1.6%	No stereo	Normal	OUcc 1.0/3	OUcc 1.0/1.5	**25**	Mild	E(T), HT Alt	Present: Right beating, jerk type	NL	OU-small discs	NL	OD −0.25-1.00x175 OS −0.50-0.75x180
26	25	F	p.G12S	OD −8.50-1.00X035; OS −9.50-1.25X135	1.6%	No stereo	Normal	ODcc 1.5/3 OScc 1.5/3.8	ODcc 1.5/1.5 OScc 1.5/3	**26**	No	2 XP @distance and near	Present: gaze evoked, jerk type	NL	OU-tilted, OS-mild hypoplasia	NL	OD −8.50-1.00X035; OS −9.50-2.00X135
27	33	M	p.G12S	OD-3.00-1.00x010; OS −4.50 DS	1.6%	No stereo	Normal	OUcc 1.5/3		**27**	No	Orthophoria	Present: Jerk type	OS: cortical cataract	NL	NL	OD −3.25–1.75x010; OS −5.25–0.75x090
28	34	F	p.G12S	OD −1.25-1.50X090; OS +0.50-1.25X030 doesn't wear	1.6%	No stereo	Normal	OUsc 1.5/4.8 ODsc 1.5/6.0 OSsc 1.5/6.0	OUsc 1.5/6	**28**	Mild OS only	10 XT HT Alt	Present	freckles on iris	N/A	N/A	N/A
29	35	F	p.G12S	OD −6.00-3.50x100; OS −6.00-4.50x090	3.2%	No stereo	Normal	OUcc 1.5/6	N/A	**29**	No	ET	No	NL	N/A	N/A	OD −6.00-2.75x100; OS −6.50-4.25x090

E-Esophoria, ET-Esotropia, E(T)-Intermittent esotropia, XT-Exotropia, X(T)-Intermittent exotropia.
X-Exophoria, HT-Hypertropia, H(T)-Intermittent hypertropia.
ONH-optic nerve hypoplasia, N/A-not available, NL- normal, DS-Diopters Sphere.

Table 3. Retrospective chart review data.

Data No.	Age in Years	Gender	Genetic defect	Refractive error; Glasses Measurement	Strabismus	Ptosis	Nystagmus	Data No.	Anterior segment	Optic nerve	Retina
1	2	F	p.G12S	None	No	No	Yes	**1**	NL	NL	NL
2	3	M	p.G12S	Hyperopia-no glasses	No	No	No	**2**	NL	NL	NL
3	6	F	p.G12S	None	Yes	No	No	**3**	NL	NL	NL
4	6.5	F	p.G12S	Anisometropia	Yes-XT	No	Yes	**4**	NL	ONH	NL
5	7	M	p.G12S	Myopia, OD: -12.0 DS; OS: -12DS	Yes	No	Yes	**5**	NL	NL	NL
6	8	F	p.G12S	Myopia	No	No	No	**6**	NL	NL	NL
7	10	F	p.G12S	None	Yes	No	No	**7**	NL	NL	NL
8	10	F	p.G12S	None	No	No	No	**8**	NL	NL	NL
9	10	M	p.G12S	None	No	No	Yes	**9**	NL	NL	NL
10	10	F	p.G12A	None	No	Yes	No	**10**	NL	NL	NL
11	11	F	p.G12S	None	No	No	No	**11**	NL	NL	NL
12	11	M	p.G12S	None	No	No	No	**12**	NL	NL	NL
13	12	M	p.G12S	Wears Glasses	Yes	No	No	**13**	NL	NL	NL
14	12	F	p.G12S	Hyperopia-no glasses	Yes-intermittent	No	No	**14**	NL	NL	NL
15	12	M	p.G12S	Myopia & astigmatism	No	No	No	**15**	NL	NL	NL
16	16	F	p.G12S	Myopia	No	No	No	**16**	NL	NL	NL
17	16	F	p.G12S	Myopia & astigmatism	No	No	No	**17**	NL	NL	NL
18	17	F	p.G12S	Astigmatism	Yes X(T)	No	Yes	**18**	NL	NL	NL
19	18	F	p.G12S	Myopia	Yes	No	No	**19**	NL	OS -ONH	NL
20	20	M	p.G12A	Myopia		No	No	**20**	NL	NL	NL
21	22	M	p.G12S	Myopia, OD: -11.0 DS; OS: -13.7 DS; + 3 Add for near	Yes	No	No	**21**	NL	ONH	NL
22	22	F	p.G12S	None	Yes -ET OS	No	No	**22**	NL	NL	NL
23	25	M	p.G12S	Myopia	Yes	Yes	Yes	**23**	NL	NL	NL
24	26	F	p.G12S	Astigmatism	No	No	No	**24**	NL	NL	NL
25	27	M	p.G12A	Myopia	Yes -ET OS	No	Yes	**25**	NL	NL	NL
26	32	M	p.G12S	Myopia; bifocals	No	No	No	**26**	NL	NL	NL
27	37	M	p.G12S	Wears glasses	No	Yes	No	**27**	NL	NL	NL

ET-Esotropia, XT-Exotropia, X(T)-Intermittent exotropia.
ONH-optic nerve hypoplasia, NL- normal, DS-Diopters Sphere.

Discussion

This is the first systematic in person visual function and ocular examination performed in a cohort of molecularly diagnosed individuals with CS. We show reduced best corrected visual acuity, decreased contrast sensitivity and absent stereopsis suggesting that optimal vision is compromised in majority of CS individuals. Previous reports of eye findings in Costello syndrome had little information on visual function tests. The prevalence of strabismus, refractive errors, nystagmus, ptosis and optic nerve anomalies were significantly higher than identified by retrospective chart analysis and published cases (12). The type of strabismus has not been reported in past, here we show that XT, ET and/or HT can occur. Although myopia has been reported, we show for the first time a very high prevalence of degenerative high myopia requiring regular eye checks including dilated eye exams. Both optic nerve hypoplasia and optic atrophy were identified in greater numbers than previously in our cohort. Although, retinal dystrophy has been reported in two individuals in the past (12), the retinal pigmentary change found in one individual among our cohort was nonspecific RPE atrophy with no bone spicules and unlikely to be of functional significance. The sample size and a single mutation in *HRAS* accounting for majority of the pathogenic variants limit the power to detect any significant genotype/phenotype correlations.

The above findings in CS of ptosis, refractive errors, strabismus, optic nerve abnormalities and rare instances of retinal dystrophy have also been reported in other RASopathies including NF1, CFC and NS (20–22,37) suggesting the potential role of *HRAS* and other Ras genes in ocular and vision development. Ocular development begins at day 21 to 25 of gestational age with evagination of the optic vesicles bilaterally from the neuroectoderm of the developing brain reaching the surface ectoderm around day 30 (38,39). This surface ectoderm along with the underlying mesenchyme forms the anterior parts of the eye and the neuroectoderm forms the retina and optic nerve (38,39). This is a complex process involving multiple transcription factors and signaling pathways including the Ras pathway (39,40). The role of Ras signaling pathway in ocular development is further substantiated by data showing expression of these genes in the developing brain and eye in addition to *in vitro* and *in vivo* studies in *Drosophila*, xenopus, and mouse models (13–17,41,42). The Ras pathway plays a key role in cell growth, differentiation and migration and is crucial to the development of cornea, lens, retina and retinal pigment epithelium. The FGF-Ras-Erk pathway has been shown to be essential for optic fissure and optic nerve development (40). Additionally, the downstream effectors of HRAS in the Ras pathway, ERK 1 and 2 are implicated in the development of visual recognition memory and the synaptic plasticity of the visual cortex (18,19,43). These studies suggest that the ophthalmic manifestations in CS of optic nerve hypoplasia and optic atrophy, decrease in visual acuity, absent binocular function, strabismus, and nystagmus may be caused by disruption of normal neuronal and synaptic development beginning in the embryonic period. However, the greater prevalence of high and degenerative myopia in CS individuals ≥15 years allude to a continuing role of the Ras pathway in ocular development through the teen age years.

Studies have shown that in children with developmental delays and complex medical needs, vision related problems are more prevalent although vision issues may not receive immediate attention with other health needs taking higher

precedence (44). However, delayed visual responses can be an indication of visual system deficits and need to be identified early. Visual learning is vital as a form of essential developmental information and communication and it is crucial to address these problems at an early age (36). The child's vision and quality of life can be improved greatly by simple interventions such as corrective glasses and/or, corrective treatment/surgery for ptosis or strabismus. Similarly, making small changes in living spaces to aid individuals with poor vision to facilitate easy movement and prevent accidents are important low vision mobility services that can be provided to families. Orientation and mobility instruction from a teacher of children with visual impairments can assist individuals to rely on monocular clues to depth as the binocular clue to depth (stereopsis) was absent in all but one of the children. Additionally, there are emerging treatments such as low dose atropine, orthokeratology, scleral crosslinking and others to slow the progression of myopia that may also be effective in individuals with CS (45). Further, a number of investigations on therapeutics such as MEK inhibitors targeting the Ras pathway are underway (46,47). Availability of potential treatment strategies in these rare disorders during development may pave the way for treatment of more common eye conditions such as strabismus and refractive errors.

Conclusions

Ocular abnormalities are seen in majority of individuals with Costello syndrome highlighting the significant role of Ras pathway in normal ocular and visual pathway development including emmetropization, ocular alignment, binocular function, and stereopsis. It is crucial to identify ocular conditions that are treatable either structurally and/or functionally to prevent vision loss and improve quality of life at the earliest possible opportunity. Routine, early ophthalmic evaluation at the time of diagnosis of CS with regular follow-up appointments (as recommended by the child's eye care providers) are necessary to improve the visual outcome.

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