Ocular Manifestations of 22q11.2 Microduplication

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Purpose: To report a new ocular manifestation of the dup22q11 syndrome and explore involved genes that may offer insight to mechanisms of pathogenesis.

Design: Case series.

Participants: Two male patients with this syndrome diagnosed with dup22q11.2.

Methods: Medical records were reviewed. Duplication was detected in the oligo-single nucleotide polymorphism chromosomal microarray and duplicated genes within the segment where determined by literature and database review. Potential associations between the ophthalmologic manifestations and their physiopathology were investigated.

Main Outcome Measures: Microarray results and identification of candidate genes within the duplicated segment.

Results: Our patients demonstrate previously unreported findings of dup22q11.2, including Marcus Gunn jaw winking, Duane's retraction syndrome, and other abnormal eye movements consistent with a congenital cranial dysinnervation disorder (CCDD), retinal vascular tortuosity, and primary infantile glaucoma. The duplicated segment in case 1 includes *SNAP29*, which could be linked with the development of retinal vascular tortuosity, and *MAPK1*, which seems to play a role in axonal development through the semaphorin pathway, which may serve as a candidate gene for CCDD. In case 2, the *CLDN5* gene is within the duplicated segment. *CLDN5* could be involved in the pathophysiology of glaucoma.

Conclusions: Our cases expand the ocular phenotype for duplication of 22q11 and serve to identify potential candidate genes for the development of CCDD, retinal vascular tortuosity, and glaucoma. *Ophthalmology 2014;121:392-398 © 2014 by the American Academy of Ophthalmology.*

Chromosome 22q11 holds numerous region-specific low copy repeats that make it susceptible to DNA rearrangements.[1] This leads to several genetic disorders, including velocardiofacial syndrome/DiGeorge syndrome (DGS [Mendelian Inheritance in Man {MIM} 192430; MIM 188400]), cat-eye syndrome (CES [MIM 115470]), der(22) syndrome (MIM 609029), 22q11.2 distal microdeletion syndrome (MIM 611867), and 22q11.2 microduplication syndrome (dup22q11 [MIM 608363]).[2] Deletion of 22q11 is the most common chromosome aberration other than trisomy 21, with an incidence of 1 in every 4000−6000 live births.[3,4] Because interstitial duplications may be the reciprocal recombination product of deletions, it may be that the incidence of dup22q11.2 is similar to velocardiofacial syndrome/DGS, yet few cases have been reported, perhaps owing to underdiagnosis.[3,5]

The dup22q11 syndrome has broad phenotypic variability, ranging from no abnormalities to severe mental retardation with multiple congenital malformations. The most common systemic manifestations are developmental delay, growth retardation, and hypotonia (Table 1).[6] The most common reported ophthalmologic findings have included downslanting palpebral fissures, superior placement of the eyebrows, and ptosis (Table 2).[5−7]

We report the ophthalmic findings of 2 cases, which demonstrate previously unreported findings in the setting of dup22q11.2, including Marcus Gunn jaw winking, oculomotor abnormalities, retinal vascular tortuosity, and glaucoma.

Cases

The study involved human medical records. Our institutional review board did not require application for approval.

Case 1

A 7-year-old boy was born at term by cesarean delivery, large for his gestational age, to a 35-year-old mother with no prior pregnancies. The child was conceived with anonymous donor sperm. At birth, the patient presented with left ptosis and Marcus Gunn jaw wink phenomenon, which was surgically corrected at 25 months old by frontalis suspension. Physical examination was remarkable for macrocephaly (55 cm, 95th percentile at 3 years of age), prominent occiput, broad forehead, telecanthus, downslanting palpebral fissures, superior placements of eyebrows in the absence of ptosis, left postauricular pit with normal hearing, and a high arched palate with no cleft (Fig 1). He also had

ISSN 0161-6420/14/$ - see front matter
http://dx.doi.org/10.1016/j.ophtha.2013.06.040

Table 1. Phenotypic Manifestations of the 22q11.2 Microduplication Syndrome

Manifestation	%
Mental retardation/learning difficulties	97
Deficits of memory performance, perceptual organization, and verbal comprehension	
Attention deficit and hyperactivity disorder speech impairment	
Delayed psychomotor development	67
Growth retardation	63
Muscular hypotonia	43
Dysmorphic features	
Hypertelorism	70
Broad flat nose	53
Micrognathia	52
Velopharyngeal insufficiency	48
Dysplastic ears	45
Epicanthal folds	42
Downslanting palpebral fissures	41
Congenital heart malformations (tetralogy of Fallot, hypoplastic left heart, right sided aortic arch, interrupted aortic arch, ventricular septal defect)	22.5
Hearing impairment	48
Seizures	33
Microcephaly	7
Urogenital abnormalities	21

Adapted from Wentzel C, Fernstrom M, Ohrner Y, Anneren G, Thuresson AC. Clinical variability of the 22q11.2 duplication syndrome. Eur J Med Genet 2008;51:501-10.

joint laxity, asymmetric shoulders, short clavicles, and a narrow chest. Echocardiogram was normal. He had a diagnosis of attention deficit disorder with hyperactivity but no cognitive delay. He is currently in therapy for speech and gross motor delays. Audiometric testing was normal. His younger brother, who was also conceived with the same donor sperm, had unremarkable systemic and ocular findings.

On ophthalmologic examination, visual acuity was 20/25 right eye and 20/30 left eye. Cycloplegic refraction showed hyperopic astigmatism (+3.00 +1.25 axis 90 right eye; +2.50 +2.00 axis 90 left eye). The left upper lid showed postoperative scars and the right upper lid was normal. He had a 15° right head tilt with normal cervical mobility. In primary position, he showed a left esotropia of 14 prism diopters with an A pattern and left hypotropia of 12 prism diopters, which increased in left head tilt, and right gaze. His horizontal eye movements were full, but he had difficulty generating these movements. On left gaze more than right gaze, he developed some degree of globe retraction, palpebral fissure narrowing, and upshooting of the adducting eye (Fig 2). He also had difficulty on upgaze and showed an acute "substitution movement" with a rapid convergence of both eyes. He exhibited <50% elevation of both eyes. On downgaze with some effort, the eye movements were full with the development of an exotropia (Fig 2). Slit-lamp examination was normal with prominent iris collarettes bilaterally. Goldmann intraocular pressures were normal. Fundus examination showed mild retinal vascular tortuosity.

Case 2

This 10-year-old boy was referred for evaluation of glaucoma. He had a prior diagnosis of autism. Primary infantile glaucoma was diagnosed at 15 months, for which a glaucoma tube shunt was placed in the right eye and 2 tube shunts were placed in the left eye. At 4 years of age, he developed bilateral retinal detachment and left eye cataract. He had pectus carinatum and bilateral preauricular pits, epicanthal folds, and superior placement of brows (Fig 3). The patient's paternal half-brother has autism.

On ophthalmologic examination, the patient showed no light perception in the right eye. The patient fixated with the left eye and was able to follow and reach for large objects. The right eye was phthisical with an opaque cornea and fibrotic anterior chamber. There was no view of the posterior pole and B-scan ultrasonography showed a flat retina. The left eye was buphthalmic with a deep and quiet anterior chamber. There was an old, patchy stromal corneal scar with no active stromal or epithelial edema. A patent peripheral iridectomy was seen superiorly. Tubes were in good position superionasally and superiotemporally. The left eye was aphakic. Eye movements were full with jerk nystagmus on horizontal gaze to either side. Intraocular pressure under general anesthesia was 18 mmHg (Tono-Pen; Reichert Technologies, Buffalo, NY). Corneal diameter measured 15.5 mm in the left eye with corneal pachymetry of 762 μm. The optic nerve had cupping of 0.7 with a healthy peripheral rim.

Results

Case 1

Oligo-single nucleotide polymorphism chromosomal microarray (Affymetrix 6.0), performed in a Clinical Laboratory Improvement Amendments (CLIA)-approved laboratory, using 1.8 million probes, including 900 000 single nucleotide polymorphism probes and 900 000 nonpolymorphic copy number probes with a median spacing of 0.7 Kb, showed a 1.44 Mb interstitial duplication from 22q11.21 to 22q11.22 (LabCorp, Philadelphia, PA). Thresholds for genome-wide screenings were set to 50 Kb for gains and losses within the clinically significant gene region, and >200 Kb for losses and >500 Kb for gains outside the clinically significant gene region. Comparative genomic hybridization array on the patient's mother and brother were negative for the 22q11.2 duplication. The donor sperm was not available for testing.

Case 2

CYP1B1 gene sequencing, including all coding exons with ≥50 base pairs of flanking intron sequences, revealed no biologically significant mutation (eyeGene Network, National Eye Institute, Bethesda, MD). Direct genomic sequencing with ABI BIG DYE chemistry and an ABI 3100 automated sequencer in both directions was used to sequence the gene (reference mRNA sequence NM_000104). Array-based comparative genomic hybridization containing DNA oligonucleotides in, or flanking, all exons of the *CYP1B1* gene (ExonArrayDx) revealed no deletion or duplication. The same single nucleotide polymorphism chromosomal microarray (Affymetrix 6.0) revealed a 2.107-Mb interstitial duplication of 22q11.21. The patient's parents were not available for testing.

For a gene map of the duplicated segments go to: http://genome.ucsc.edu/cgi-bin/hgGateway?hgsid=337162421&clade=mammal&org=Human&db=hg18 (accessed June 3, 2013) and search chr22:19,259,677−20,803,906 for case 1 and chr22:17,256,416−19,363,588 for case 2.

Discussion

The 22q11.2 microduplication syndrome demonstrates wide phenotypic variability. The first reported cases were described as a variation of the "cat-eye" syndrome[8−11] until Edelmann et al[1] and Ensenauer et al[2] recognized it as a newly emerging syndrome. Subsequent case reports have established the systemic manifestations (Table 1). The most commonly reported oculofacial manifestations are downslanting palpebral fissures (35%), hypertelorism (34%), epicanthal folds (26%), hyperopia (22%), superior placement of eyebrows (20%), and ptosis (10%) (Table 2). Our 2 cases with dup22q11 syndrome demonstrate some of the previously reported findings, including downslanting palpebral fissures, superior placement of eyebrows, strabismus, hyperopia, and ptosis in case 1 and superior placement of eyebrows and epicanthal folds in case 2.

Previously unreported ophthalmologic manifestations were also found in our patients. In case 1, we found retinal vascular tortuosity and Marcus Gun jaw winking phenomenon with an oculomotor abnormality. Marcus Gunn jaw wink is seen in approximately 2%−13% of patients with congenital ptosis.[12,13] Therefore, this may not be a primary manifestation of the chromosomal aberration.

In the duplicated segment of case 1, we found many genes that play important roles in molecular pathways. The *SNAP29* gene and *EDH1* (MIM 605888) interact with each other and form a complex with insulin-like growth factor-1 (IGF1) receptor. It has been suggested that IGF1 receptor and IGF1 play an important role in the subretinal neovascularization of age-related macular degeneration because they are expressed in capillary endothelial and fibroblast-like cells of choroidal neovascular membranes.[14] It has also been established that IGF1−IGF1 receptor signaling contributes to upregulation of vascular endothelial growth factor in vasculogenesis in embryonic tissue.[15] Increased levels of vascular endothelial growth factor[16,17] or IGF1[18] may be related to retinal vascular tortuosity. Perhaps, alterations in dosage of *SNAP29* could potentially alter vascular endothelial growth factor and IGF1, leading to the tortuous retinal vasculature seen in our patient. Tortuous retinal vessels are present in 34% of patients with 22q11 deletion syndrome.[19]

Case 1 has unusual eye movements consistent with a congenital cranial dysinnervation disorder (CCDD) of the abnormalities on lateral gaze, suggesting a form of Duane's retraction syndrome (DRS). In association with Marcus Gun jaw wink, DRS has been previously reported, and both are considered part of the CCDD spectrum.[20−24] It has been postulated that the CCDDs are a result of mutations in genes essential to normal axonal development.[25] The *MAPK1* (mitogen-activated protein kinase 1) gene is a member of the MAP kinase family proteins, also known as extracellular signal-regulated kinases. The extracellular signal-regulated kinase pathway is important for experience-dependent plasticity and for long-term potentiation of synaptic transmission in the developing visual cortex.[26] The MAP kinase signaling pathways have also been associated with the activation of the protein semaphorin 7A, a membrane-anchored member of the semaphorin family of guidance proteins, which enhance central and peripheral axon growth and are required for proper axon tract formation during embryonic development.[27] Although none of the reported CCDD-causing genes have been related to the MAP kinase pathway, there is a report that relates semaphorin signaling with the development of DRS.[28] Duane's

Table 2. Summary of Ophthalmic Manifestations of Present and Previously

Manifestations	Knoll et al[10]	Ensenauer et al[5]	Hassed et al[45]	Portonoi et al[7]	Yobb et al[33,*]	de La Rochebrochard et al[46]	Alberti et al[31]
Cases reported (n)	1	12	3	2	7	1	1
Sex	M	7M/5F	2F/1M	1M/1F	2M/5F	F	F
Downslanting palpebral fissures	+	8/12	3/3	0/2	1/1	+	+
Upslanting palpebral fissures	−	2/12	0/3	0/2	0/8	−	−
Epicanthal folds	+	2/12	0/3	0/2	2/2		+
Superior placement of eyebrows	−	8/12	0/3	0/2	0/8	+	−
Hypertelorism	+	8/12		2/2	3/3	−	
Short palpebral fissures				2/2	0/8	−	
Ptosis	−	3/12		0/2	0/8		
Strabismus	−	1/12		0/2	0/8		+
Hyperopia	−	2/12		0/1	0/8		+
Myopia	+	0/12		0/1	1/8		−
Nystagmus	−	0/12		0/1	1/8		−
Chorioretinal coloboma					1/8		
Retinal vascular tortuosity							
Marcus Gunn jaw wink							
Primary infantile glaucoma							

+ = feature present; − = feature absent; M = male; F = female; n/m = not measured. Blank cell indicates unknown.
*Includes patient from Edelmann et al.[1]

Figure 1. Case 1. Note broad forehead, telecanthus, downslanting palpebral fissures, and superior placements of eyebrows. He has a right head tilt and left ptosis.

syndrome has been previously reported in a case of 22q11.2 duplication.[29] Although strabismus is present in 10% of the reported cases of dup22q11,[5,30–32] the specific type of strabismus is not often described.

Case 2 presented with primary infantile glaucoma. Nystagmus was seen, but likely as a secondary manifestation of vision loss owing to glaucoma. Nystagmus has been reported in only 1 case of 22q11 duplication as an isolated primary finding.[33] The *PRDOH* and *DGCR6* genes are located within the duplicated segment of case 2. *PRODH* is involved in the degradation of the amino acid proline. Mutations to the *PRODH* gene result in hyperprolinemia type I[34] and predispose to a susceptibility to schizophrenia.[35] Deletion of *DGCR6* and *PRODH* and mild hyperprolinemia have been found in high frequency in individuals with autism.[36,37] Although there is still controversy regarding the deleterious effects of hyperprolinemia, it is believed that any genetic defect producing modest increases in proline could have significant effects on the central nervous system during its critical periods of development.[37] High levels of proline have also been found in patients with velocardiofacial syndrome.[38,39] The only report associating hyperprolinemia with glaucoma describes a family with aniridia.[40] One individual had buphthalmos owing to infantile glaucoma. Whether duplication of the gene would cause a pathologic perturbation in proline levels, and whether this could affect the eye, is unknown.

CLDN5, which encodes the protein claudin-5, is also found in the duplicated region of case 2. Claudins are integral membrane proteins and components of tight junction strands. Rho-associated coiled-coil–forming protein kinase inhibitors have been studied as a potential new treatment for glaucoma.[41] Rho-associated coiled-coil–forming protein kinase inhibitor Y-27632 causes retraction and rounding of human trabecular meshwork cell bodies, disruption of filamentous actin, impairment of focal adhesion formation, and decreased myosin light chain phosphorylation in trabecular meshwork cells and Schlemm's canal endothelial cells, resulting in a significant decrease in intraocular pressure and an increase in the facility of aqueous outflow.[42–44] In a study of Schlemm's canal endothelial cells in monkeys, after administration of Y-27632 there was a decreased claudin-5 expression in conjunction with depolymerization of filamentous actin.[43] This suggests a possible involvement of

Reported Cases of 22q11.2 Microduplication Syndrome

Engels et al[47]	Courtens et al[48]	Laitenberger et al[32]	Ou et al[30]	Yu et al[49]	Wentzel et al[6]	Case 1	Case 2	Total Results (%)
3	7	1	9	2	2	1	1	53
1M/2F	4M/3F	1M	4M/5F	2F	1M/1F	1M	1M	
0/3	1/7	–	3/9	0/2	0/2	+	–	19/53 (35.8)
0/3	0/7	–	5/9	0/2	0/2	–	–	7/53 (13.2)
2/3	2/7	–	1/9	0/2	2/2	–	+	14/52 (26.9)
0/3	0/7	–	0/9	0/2	0/2	+	+	11/53 (20.7)
	2/7		0/9	0/2	1/2	n/m	n/m	15/43 (34.8)
						n/m	n/m	2/11 (18.1)
0/3	0/7		0/9	0/2	1/2	+	–	5/48 (10.4)
0/3	0/7	+	2/9			+	–	5/46 (10.1)
3/3	0/7					+	–	7/32 (21.9)
0/3	2/7					–	–	4/32 (12.5)
0/3	0/7					–	+	1/32 (3.1)
						–	–	1/53 (1.9)
						+	–	1/53 (1.9)
						+	–	1/53 (1.9)
						–	+	1/53 (1.9)

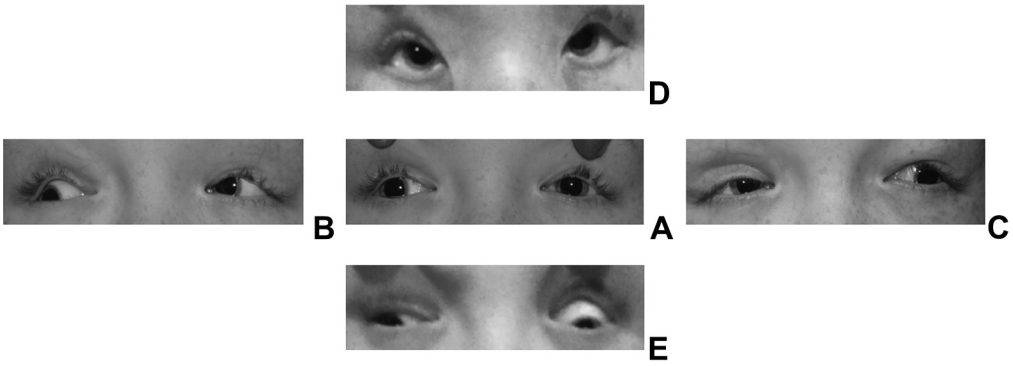

Figure 2. Case 1. In primary position (**A**), the patient is esotropic with left hypotropia. On left gaze (**B**) more than right gaze (**C**), he develops some degree of globe retraction, palpebral fissure narrowing, and upshooting of the adducting eye. On upgaze (**D**), he has rapid convergence of both eyes. On downgaze (**E**), he develops exotropia.

claudin-5 in the pathophysiology of glaucoma. We report novel ocular manifestations in association with the dup22q11.1 syndrome in 2 children. These manifestations may be related to the duplication of specific genes and may offer clues to new pathways for the development of CCDD and glaucoma.

Literature Search

MEDLINE (1950—present) was used for the literature search. We used the following keywords: *22q11.2 duplication*, *ophthalmology*, *eye manifestations*, *retina*, *glaucoma*, *Marcus Gunn jaw wink*, *congenital cranial dysinnervation disorder*, *congenital glaucoma*, *infantile glaucoma*, and *Duane's retraction syndrome*. Keywords were used with word *22q11* and *chromosome 22* to find any previous reports. We also used articles cited in the reference lists of cited articles.

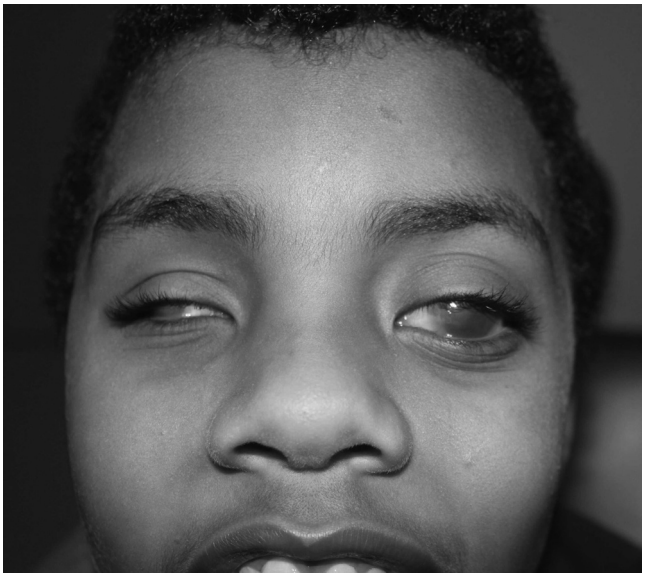

Figure 3. Case 2. Note epicanthal folds and superior placement of brows. Phthisical right eye and buphthalmic left eye with old patchy stromal corneal scar.

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Footnotes and Financial Disclosures

Originally received: March 29, 2013.
Final revision: June 3, 2013.
Accepted: June 20, 2013.
Available online: August 21, 2013.
Manuscript no.: 2013-519.

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Financial Disclosures:
The authors have no commercial or proprietary interest in any materials discussed in this article.

Funded in part by the Foerderer Fund (to A.V.L.) and the Alcon Ocular Genetics Fellowship (K.A.S.) The sponsor or funding organization had no role in the design or conduct of this research.

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