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Case Report

Oculodentodigital Dysplasia: A Case Report and Major Review of the Eye and Ocular Adnexa Features of 295 Reported Cases

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Oculodentodigital dysplasia (OMIM #164200) is a rare disorder mainly characterized by abnormal craniofacial, dental, ocular, and digital development. The autosomal dominant form has been the most frequently reported inheritance pattern, although a few cases of autosomal recessive inheritance have been described [1–3]. Craniofacial abnormalities may include microcephaly, prominent columella, and underdeveloped nasal alae [2–4]. Dental abnormalities, such as hypoplastic enamel, small teeth, and premature loss of teeth, are often present [2–4]. Digit abnormalities may include syndactyly, camptodactyly, and midphalangeal hypoplasia [2–4]. Ophthalmic manifestations are common, such as microcornea and microphthalmia, and may involve a wide spectrum of eye and ocular adnexa structures, although previous analyses of prior cases show that full ocular physical exams were not performed on all patients [3, 5].

1. Introduction

Oculodentodigital dysplasia (OMIM #164200) is a rare disorder mainly characterized by abnormal craniofacial, dental, ocular, and digital development. The autosomal dominant form has been the most frequently reported inheritance pattern, although a few cases of autosomal recessive inheritance have been described [1–3]. Craniofacial abnormalities may include microcephaly, prominent columella, and underdeveloped nasal alae [2–4]. Dental abnormalities, such as hypoplastic enamel, small teeth, and premature loss of teeth, are often present [2–4]. Digit abnormalities may include syndactyly, camptodactyly, and midphalangeal hypoplasia [2–4]. Ophthalmic manifestations are common, such as microcornea and microphthalmia, and may involve
duct obstructions. We conducted an extensive literature review to summarize the eye features in patients with ODDD reported to date.

2. Case Report

The patient, an 8-month-old female, was born to a nonconsanguineous couple from a healthy 37-year-old mother of Native American descent and a healthy 30-year-old father of German and Irish descent. Family history is notable for an older sibling with cleft palate, paternal uncle with autism, paternal second cousin with congenital heart defect, and distant paternal great-great uncle with Down syndrome and webbed/fused 4th and 5th digits of one hand. A normal pregnancy was noted until the second trimester when an omphalocele was detected on ultrasound. A subsequent ultrasound revealed possible syndactyly of the hands. The patient was born at 39 weeks by vaginal delivery with induction. The birth weight was 3.552 kg (75th percentile), birth length was 50 cm (68th percentile), and birth head circumference was 34.5 cm (70th percentile). Apgar scores were 9 at both one minute and five minutes.

Multiple congenital anomalies noted at birth included an omphalocele that measured 4 cm at base and 3.5 cm across with intestines present in the sac, but no liver. The patient had a normocephalic head with sparse wispy hair, a small nose with hypoplastic alae, a prominent columella, small-appearing palpebral fissures, a small cornea, microphthalmia, a wide anterior fontanelle, and retrognathia (Figure 1). Syndactyly of digits 4 and 5 and webbing of digits 3 and 4 of the right (Figure 2) and left hands were present. Cardiac echocardiogram on the day of birth showed the presence of a mild patent ductus arteriosus, mild patent foramen ovale, and a normal aorta. Feeding difficulties were exacerbated by the presence of the omphalocele; surgical correction was performed on day 2 of life.

An ophthalmologic assessment at 4 months of age was notable for deep anterior chambers, bilateral nasolacrimal duct obstruction, microphthalmia, small 8 mm corneas, a blonde fundus, and moderate hyperopia in both eyes.

At her last examination at 8 months of age, the patient continues to have poor feeding with self-limiting volumes but has improved weight gain. The patient is at the 9th percentile for weight and 12th percentile for length. Cognitive and motor developments are delayed.

Sequencing of the GJA1 gene (transcript number: NM_000165.3) from patient genomic DNA revealed a heterozygous missense mutation in the GJA1 gene: c.65G>A (p.G22E). Deletion/duplication analysis of the GJA1 gene using the aCGH test was negative.

3. Methods

We performed a systematic review of the literature to summarize the ocular findings in individuals with ODDD. A PubMed/Medline search of “oculodentodigital syndrome” led us to find a total of 177 articles. No articles were excluded based on the year published. We reviewed the references to identify other articles that did not appear in our original search. 91 articles describing patients with a description consistent with the clinical syndrome, either with or without molecular confirmation of GJA1 pathogenic variants, were included. Within these selected articles, we identified 295 cases of ODDD with 73 different GJA1 mutations, including
have been observed. Ocular findings of microphthalmia and microcornea have been observed commonly in previous cases [2–4]. Craniofacial anomalies of microcephaly, poor hair growth, hypoplastic nasal alae, and prominent columella have been reported previously [2–4]. Bilateral syndactyly of the 4th and 5th digits is common [2, 3].

A systematic review of the published cases to date (ranging from 1963 to 2019) revealed 91 literature reports of 295 individuals with ODDD [1–91]. Table 2 [1–91] summarizes the sex distribution across all reviewed reports of ODDD. Patients with ODDD present with an approximately equal sex distribution (47% male and 53% female). Of the 295 individuals reported, 32 were clinically diagnosed with ODDD without molecular confirmation, 98 presented with features of ODDD and had a known relative with molecular confirmation of a GJA1 pathogenic variant, and 165 individuals had a molecularly confirmed GJA1 pathogenic variant.

There were 73 different GJA1 mutations identified from the 165 individuals that had a molecularly confirmed GJA1 pathogenic variant. Table 3 [1–3, 5–71, 92] summarizes the number of patients with each mutation. Patients with confirmed pathogenic variants and their relatives with no molecular confirmation but with features of ODDD were grouped separately. These two groups comprised 263 of the patients included in this study.

The eye features of all 295 patients are summarized in Table 4 [1–91]. The most common ophthalmic manifestations reported were microcornea (n = 111), microphthalmia (n = 110), short palpebral fissures (n = 56), and glaucoma (n = 51, 4 closed-angle and 1 open-angle).

Twenty-three patients presented with refractive error, of which isolated myopia was the most frequently noted (n = 14), followed by isolated hyperopia (n = 6), anisometropia (n = 2), and astigmatism (n = 1). Forty patients presented with eye movement disorders, with strabismus (n = 27, 9 esotropia, 1 exotropia) being the most common, followed by nystagmus (n = 8), amblyopia (n = 3), Duane syndrome (n = 2), and Brown syndrome (n = 1). Note that 1 patient had both nystagmus and esotropia [71]. Other common findings included epicanthus (n = 36), hypotelorism (n = 24), hypertelorism (n = 22), madarosis (n = 19), cataracts (n = 17), persistent pupillary membranes (n = 13), shallow anterior chambers (n = 12), pale/atrophic irides (n = 11), telecanthus (n = 11), and uveitis (n = 10).

A variety of abnormal findings for the retina and optic disc were noted (n = 18), with dysplasia of the retina/fundus (n = 3) and pale/atrophic optic discs (n = 3) being the most common documented findings.

Of the individuals with molecularly confirmed mutations, the most common mutations present were c.605G>A (p.R202H) (11%; with 1 patient also having a c.717G>A synonymous mutation), c.389T>C (p.I130T) (10%), and c.119C>T (p.A40V) (10%). Table 5 [2, 3, 12, 30, 40, 41, 66, 67, 92] summarizes the eye features present in the patients with these mutations.

Less common features of the phenotype observed in our presented case were also reported in other cases as well. These include nasolacrimal duct abnormalities (n = 2), pale/atrophic
| Sources | Multiple mutations? | GJA1 mutation | Individuals with a molecular confirmed GJA1 pathogenic variant | Untested individuals with both ODDD phenotype and known relative with molecular confirmation | Total individuals with the ODDD phenotype |
|----------|---------------------|---------------|-------------------------------------------------------------|-----------------------------------------------------------------|----------------------------------------|
| Cavusoglu et al. 2019 | No | c.168_169insT p.Q57SfsTer6 N/A | 1 0 0 0 1 100% 0 0% 1 | | |
| Aminabadi et al. 2009 & Aminabadi et al. 2010 | No | N/A | 2 1 3 75% 1 25% 4 | | |
| Dwarkanathan et al. 2015 & Furuta et al. 2012 | No | c.75G>T p.W25C (unspecified) N/A | 1 1 0 0 1 50% 1 50% 2 | | |
| Quick and Dobersen 2014; National Center for Biotechnology Information 2020 | Yes | c.605G>A p.R202H | 1 0 0 0 1 100% 0 0% 1 | | |
| Paznekas et al. 2003 & Paznekas et al. 2009 | No | c.605G>A p.R239R | 1 7 4 5 5 29% 12 71% 17 | | |
| Jamieson et al. 2010 | No | c.301C>T p.R101X p.G2fsX7 N/A | 1 0 0 0 1 100% 0 0% 1 | | |
| Jamieson et al. 2010 | No | c.301C>T p.R101X | 0 1 0 0 0 0% 1 100% 1 | | |
| Paznekas et al. 2009; Joss et al. 2008; & Richardson et al. 2006 | No | c.97C>T p.R33X* N/A | 0 2 0 0 0 0% 2 100% 2 | | |
| Paznekas et al. 2009; Richardson et al. 2004; Paznekas et al. 2003; & Gladwin et al. 1997 | No | c.93T>C p.I31M N/A | 0 0 4 4 4 50% 4 50% 8 | | |
| Wang et al. 2019 | No | c.91A>T p.I311P N/A | 1 0 0 0 1 100% 0 0% 1 | | |
| Paznekas et al. 2009 & van Steensel et al. 2005 | No | c.780_781delTG p.C260fsX306 N/A | 1 2 0 0 1 33% 2 67% 3 | | |
| Paznekas et al. 2009; Paznekas et al. 2003; & Gorlin et al. 1963 | No | c.68A>C p.K23T N/A | 1 0 0 0 1 100% 0 0% 1 | | |
| Dwarkanathan et al. 2015; Paznekas et al. 2009; & Vreeburg et al. 2007 | No | c.689_690delAT p.Y230fsX236 N/A | 0 3 1 0 1 25% 3 75% 4 | | |
| This study; Gumus 2018; Paznekas et al. 2009; Paznekas et al. 2003; & Traboulsi and Parks 1990 | No | c.65G>A p.G22E N/A | 0 3 0 0 0 0% 3 100% 3 | | |
| Wiest et al. 2006 | No | c.659C>A p.S220Y N/A | 0 1 0 0 0 0% 1 100% 1 | | |
| Paznekas et al. 2009; Paznekas et al. 2003; & Norton et al. 1995 | No | c.646G>T p.V216L N/A | 1 0 4 1 5 83% 1 17% 6 | | |
| Park et al. 2017; Paznekas et al. 2009; & Paznekas et al. 2003 | No | c.61G>A p.G21R N/A | 0 2 0 0 0 0% 2 100% 2 | | |
| Brice et al. 2013 | No | c.617A>G p.K206R N/A | 1 2 1 1 2 40% 3 60% 5 | | |
| Sources                                      | Nucleotide          | Protein    | Unspecified | Male | Female | Male | Female | Male | Female | Male | Female | Total |
|----------------------------------------------|---------------------|------------|-------------|-------|--------|-------|--------|-------|--------|-------|--------|-------|
| Paznekas et al. 2009                        | c.<602>C>T          | P.S201F    | NA          | 1     | 1      | 1     | 1      | 1     | 1      | 1     | 1      | 1     |
| Paznekas et al. 2009; de la Parra et al. 2007| c.<5G>T             | P.G2Y      | NA          | 0     | 0      | 0     | 0      | 0     | 0      | 0     | 0      | 0     |
| Paznekas et al. 2009; G et al. 2003 & Judisch| c.<581>C> T         | P.H149P    | NA          | 1     | 0      | 1     | 3      | 4     | 3      | 4     | 1      | 1     |
| Vitiello et al. 2018; Vingolo et al. 1994   | c.<504>C> T         | P.Y17S     | NA          | 0     | 4      | 0     | 1      | 4     | 1      | 4     | 1      | 1     |
| Wiest et al. 2006 & Thomsen et al. 1998     | c.<461>C> A         | P.R154Q    | NA          | 0     | 2      | 0     | 2      | 2     | 2      | 4     | 2      | 2     |
| Taşdelen et al. 2018                        | c.<442>C> T         | P.R154F    | NA          | 0     | 1      | 0     | 0      | 1     | 0      | 1     | 0      | 1     |
| Paznekas et al. 2009; Debeer et al. 2005    | c.<440>Y            | C.M147T    | NA          | 0     | 1      | 0     | 0      | 1     | 0      | 1     | 0      | 1     |
| Kogame et al. 2014                          | c.<427>C> T         | C.L11P     | NA          | 0     | 0      | 0     | 0      | 0     | 0      | 0     | 0      | 0     |
| Orosz et al. 2018                           | c.<413>G> A         | C.G138R    | NA          | 0     | 1      | 0     | 0      | 1     | 0      | 1     | 0      | 1     |
| Paznekas et al. 2009; Debeer et al. 2005 & Spaepen et al. 1991 | c.<412>G>C | P.R154H | NA | 1 | 0 | 1 | 4 | 5 | 4 | 9 | 9 |
| Kogame et al. 2014                           | c.<412>G> A         | C.G138S    | NA          | 0     | 2      | 0     | 0      | 2     | 0      | 2     | 0      | 2     |
| Paznekas et al. 2009; Debeer et al. 2005 & Spaepen et al. 1991 | c.<402>G>T | P.K134D | NA | 0 | 1 | 0 | 1 | 2 | 3 | 2 | 5 |
| Kogame et al. 2014                           | c.<400>Y            | G.K134E    | NA          | 0     | 1      | 0     | 0      | 1     | 0      | 1     | 0      | 1     |
| Nishat et al. 2005; Paznekas et al. 2009; & de la Parra et al. 1994, 2009, & Spaepen et al. 1991 | c.<389>T>C | P.C130T | NA | 7 | 4 | 5 | 1 | 12 | 71 | 5 | 29 |
| Paznekas et al. 2009; de la Parra et al. 2007 | c.<339>C>T         | C.P113P    | NA          | 2     | 2      | 1     | 0      | 3     | 60     | 2     | 40     | 5     |
| Paznekas et al. 2009; de la Parra et al. 2007 | c.<319>C>T         | C.P110D    | NA          | 2     | 3      | 1     | 2      | 3     | 38     | 5     | 63     | 8     |
| Paznekas et al. 2009; de la Parra et al. 2007 | c.<319>C>T         | C.P111P    | NA          | 0     | 1      | 0     | 0      | 0     | 0      | 0     | 0      | 0     |
| Paznekas et al. 2009; Debeer et al. 2005 & Spaepen et al. 1991 | c.<217>C>T | C.P114T | NA | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |

| GAI mutation | Total individuals with ODDD phenotype | Untested individuals with both ODDD phenotype and known relative with molecular confirmation | Individuals with a molecular confirmed GAI pathogenic variant |
|--------------|---------------------------------------|--------------------------------------------------|---------------------------------------------------------------|
|              | Nucleotide Protein Unspecified | Male | Female | Male | Female | Male | Female | Male | Female | Male | Female | Total |
| No            | c.<602>C>T                         | P.S201F    | NA          | 1     | 1      | 1     | 1      | 1     | 1      | 1     | 1      | 1     |
| No            | c.<5G>T                            | P.G2Y      | NA          | 0     | 0      | 0     | 0      | 0     | 0      | 0     | 0      | 0     |
| No            | c.<581>C> T                       | P.H149P    | NA          | 1     | 0      | 1     | 3      | 4     | 3      | 4     | 1      | 1     |
| Vitiello et al. 2018; Vingolo et al. 1994 | c.<504>C> T | P.Y17S | NA | 0 | 4 | 0 | 1 | 4 | 1 | 4 | 1 |
| Wiest et al. 2006 & Thomsen et al. 1998 | c.<461>C> A | P.R154Q | NA | 0 | 2 | 0 | 2 | 2 | 2 | 4 | 2 |
| Taşdelen et al. 2018 | c.<442>C> T | P.R154F | NA | 0 | 1 | 0 | 0 | 1 | 0 | 1 | 0 |
| Paznekas et al. 2009; Debeer et al. 2005 & Spaepen et al. 1991 | c.<412>G>C | P.R154H | NA | 1 | 0 | 1 | 4 | 5 | 4 | 9 | 9 |
| Kogame et al. 2014 | c.<412>G> A | C.G138R | NA | 0 | 1 | 0 | 0 | 1 | 0 | 1 | 0 |
| Paznekas et al. 2009; Debeer et al. 2005 & Spaepen et al. 1991 | c.<402>G>T | P.K134D | NA | 0 | 1 | 0 | 1 | 2 | 3 | 2 | 5 |
| Kogame et al. 2014 | c.<400>Y | G.K134E | NA | 0 | 1 | 0 | 0 | 1 | 0 | 1 | 0 |
| Nishat et al. 2005; Paznekas et al. 2009; & de la Parra et al. 1994, 2009, & Spaepen et al. 1991 | c.<389>T>C | P.C130T | NA | 7 | 4 | 5 | 1 | 12 | 71 | 5 | 29 |
| Paznekas et al. 2009; de la Parra et al. 2007 | c.<339>C>T | C.P113P | NA | 2 | 2 | 1 | 0 | 3 | 60 | 2 | 40 | 5 |
| Paznekas et al. 2009; de la Parra et al. 2007 | c.<319>C>T | C.P110D | NA | 2 | 3 | 1 | 2 | 3 | 38 | 5 | 63 | 8 |
| Paznekas et al. 2009; de la Parra et al. 2007 | c.<319>C>T | C.P111P | NA | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Paznekas et al. 2009; Debeer et al. 2005 & Spaepen et al. 1991 | c.<217>C>T | C.P114T | NA | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Sources | Multiple mutations? | GJA1 mutation | Individuals with a molecular confirmed GJA1 pathogenic variant | Untested individuals with both ODDD phenotype and known relative with molecular confirmation | Total individuals with the ODDD phenotype |
|---------|---------------------|---------------|---------------------------------------------------------------|---------------------------------------------------------------|------------------------------------------|
|         | Nucleotide | Protein | Unspecified | Male | Female | Male | Female | Male | Female | Total |
| Gabriel et al. 2011 & Jamsheer et al. 2009 | No | c.31C>T | p.L11F | N/A | 0 | 2 | 0 | 0 | 0 | 0% | 2 | 100% | 2 |
| Pornaveetus et al. 2017 | No | c.31C>A | p.L11I | N/A | 1 | 0 | 0 | 0 | 1 | 100% | 0 | 0% | 1 |
| Jamsheer et al. 2014 | No | c.317T>G | p.L106R | N/A | 2 | 0 | 0 | 0 | 2 | 100% | 0 | 0% | 2 |
| Paznekas et al. 2009 & Nivelon-Chevallier et al. 1981 | No | c.317T>C | p.L106P | N/A | 1 | 0 | 0 | 0 | 1 | 100% | 0 | 0% | 1 |
| Paznekas et al. 2009 & Paznekas et al. 2003 | No | c.306G>C | p.K102N | N/A | 1 | 2 | 0 | 0 | 1 | 33% | 2 | 67% | 3 |
| Paznekas et al. 2009; Paznekas et al. 2003; & Wooldridge et al. 1977 | No | c.293A>G | p.Y98C | N/A | 1 | 3 | 1 | 1 | 2 | 33% | 4 | 67% | 6 |
| Paznekas et al. 2009 | No | c.287T>C | p.V96A | N/A | 0 | 1 | 0 | 0 | 0 | 0% | 1 | 100% | 1 |
| Wiest et al. 2006 | No | c.287T>A | p.V96E | N/A | 0 | 1 | 0 | 0 | 0 | 0% | 1 | 100% | 1 |
| Paznekas et al. 2009 & Kjaer et al. 2004 | No | c.286G>A | p.V96M | N/A | 2 | 2 | 0 | 0 | 2 | 50% | 2 | 50% | 4 |
| Paznekas et al. 2009 & Honkaniemi et al. 2005 | No | c.284A>G | p.H95R | N/A | 0 | 1 | 0 | 1 | 0 | 0% | 2 | 100% | 2 |
| Paznekas et al. 2009; Paznekas et al. 2003; & Øjordsmoen and Nyberg-Hansen 1980 | No | c.268C>G | p.L90V | N/A | 4 | 0 | 3 | 2 | 7 | 78% | 2 | 22% | 9 |
| Jamsheer et al. 2014 | No | c.257C>A | p.S86Y | N/A | 0 | 1 | 0 | 0 | 0 | 0% | 1 | 100% | 1 |
| Pizzuti et al. 2004 | No | c.227G>A | p.R76H | N/A | 1 | 0 | 0 | 0 | 1 | 100% | 0 | 0% | 1 |
| Izumi et al. 2013 | No | c.226C>T | p.R76C | N/A | 1 | 0 | 0 | 0 | 1 | 100% | 0 | 0% | 1 |
| Paznekas et al. 2009; Paznekas et al. 2003; & Stanislaw et al. 1998 | No | c.226C>A | p.R76S | N/A | 0 | 2 | 0 | 2 | 0 | 0% | 4 | 100% | 4 |
| Choi et al. 2018 | No | c.221A>C | p.H74P* | N/A | 1 | 0 | 0 | 0 | 1 | 100% | 0 | 0% | 1 |
| Paznekas et al. 2009; Richardson et al. 2004; Paznekas et al. 2003; & Gladwin et al. 1997 | No | c.206C>A | p.S69Y | N/A | 0 | 0 | 2 | 5 | 2 | 29% | 5 | 71% | 7 |
| Paznekas et al. 2009 & Vasconcellos et al. 2005 | No | c.176C>A | p.P59H | N/A | 4 | 4 | 1 | 0 | 5 | 56% | 4 | 44% | 9 |
| Paznekas et al. 2009 | No | c.154_147dupCAG | p.Q49dup | N/A | 0 | 1 | 0 | 0 | 0 | 0% | 1 | 100% | 1 |
| Paznekas et al. 2009; Paznekas et al. 2003; Weintraub et al. 1975; & Gellis and Feingold 1974 | No | c.154_156dupTTT | p.F52dup | N/A | 1 | 0 | 1 | 1 | 2 | 67% | 1 | 33% | 3 |
| Hadjichristou et al. 2017 & Paznekas et al. 2009 | No | c.146A>C | p.Q49P | N/A | 1 | 1 | 0 | 0 | 1 | 50% | 1 | 50% | 2 |
| Izumi et al. 2013 | No | c.145C>G | p.Q49E | N/A | 0 | 1 | 0 | 0 | 0 | 0% | 1 | 100% | 1 |
| Paznekas et al. 2009 & Paznekas et al. 2003 | No | c.145C>A | p.Q49K | N/A | 3 | 2 | 0 | 0 | 3 | 60% | 2 | 40% | 5 |
Table 3: Continued.

| Sources                                                                 | Multiple mutations? | GJA1 mutation | Individuals with a molecular confirmed GJA1 pathogenic variant | Untested individuals with both ODDD phenotype and known relative with molecular confirmation | Total individuals with the ODDD phenotype |
|------------------------------------------------------------------------|---------------------|---------------|---------------------------------------------------------------|---------------------------------------------------------------------------------|-------------------------------------|
|                                                                         | Nucleotide          | Protein       | Male              | Female             | Male              | Female             | Male | Female | Total |
| Amano et al. 2012; Feller et al. 2008; Paznekas et al. 2009; & Itro et al. 2005 | No                  | c.142G>A      | p.E48K            | N/A                | 3                 | 0                  | 0    | 0      | 3     |
| Jamsheer et al. 2014                                                   | No                  | c.139G>C      | p.D47H            | N/A                | 0                 | 3                  | 0    | 0      | 3     |
| Tumminelli et al. 2016                                                 | No                  | c.125G>C      | p.E42Q            | N/A                | 1                 | 0                  | 0    | 0      | 1     |
| Gabriel et al. 2011                                                    | No                  | c.120delGGTT  | p.V41L            | N/A                | 0                 | 1                  | 1    | 2      | 4     |
| Paznekas et al. 2009 & Kellermayer et al. 2005                         | Yes (compound heterozygous with GJB2 mutation) | c.121G>C  | p.R127H (GJB2 mutation) | N/A                | 0                 | 1                  | 0    | 0      | 1     |
| Park et al. 2019; Hayashi et al. 2014; Paznekas et al. 2009; Debeer et al. 2005; & Paznekas et al. 2003 | No                  | c.119C>T      | p.A40V            | N/A                | 6                 | 4                  | 4    | 3      | 10    |
| Wittlieb-Weber et al. 2015                                              | No                  | c.175C>T      | p.S59S            | N/A                | 1                 | 2                  | 0    | 0      | 1     |
| Attig et al. 2016                                                       | No                  | c.396_398delAAA | p.I132_ K133delinsM | N/A                | 3                 | 2                  | 0    | 0      | 3     |
| Paznekas et al. 2009                                                    | No                  | c.19T>G       | p.L77V            | N/A                | 1                 | 0                  | 0    | 0      | 1     |
| Himi et al. 2009                                                        | No                  | c.13A>T       | p.S5C             | N/A                | 0                 | 1                  | 0    | 0      | 1     |
| Pace et al. 2019                                                        | No                  | c.287T>G      | p.V96G            | N/A                | 0                 | 1                  | 0    | 0      | 1     |
| Totals                                                                |                     |               |                   |                    | 72                | 93                 | 52   | 46     | 124   |

*Unknown which specific individuals tested.
| Table 4: Eye and ocular adnexa features reported in ODDD. |
|---------------------------------------------------------|
| **Orbit**                                               |
| Anterior chamber                                       |
| Microphthalmia                                         |
| (110/37%)                                              |
| Hypotelorism                                           |
| (24/8%)                                                |
| Hypertelorism                                          |
| (22/7%)                                                |
| Short axial length                                     |
| (4/1%)                                                 |
| Shallow anterior chamber                               |
| (12/4%)                                                |
| Deep anterior chambers                                 |
| (2/<1%)                                                |
| **Cornea**                                             |
| Microcornea                                            |
| (111/38%)                                              |
| Thick corneas                                          |
| (4/1%)                                                 |
| Corneal opacities                                      |
| (3/1%)                                                 |
| Corneal farinata                                       |
| (1/<1%)                                                |
| Band keratopathy                                       |
| (1/<1%)                                                |
| Corneal keratosis                                      |
| (1/<1%)                                                |
| Abnormal Descemet’s membrane                           |
| (1/<1%)                                                |
| Anteriorly deviated Schwalbe’s line                    |
| (1/<1%)                                                |
| **Sclera**                                             |
| Blue sclera                                            |
| (1/<1%)                                                |
| Persistent pupillary membranes                         |
| (13/4%)                                                |
| **Pupil**                                              |
| Eccentric pupils                                       |
| (3/1%)                                                 |
| **Lens**                                               |
| Cataracts                                              |
| (17/6%)                                                |
| Lens opacities                                         |
| (2/<1%)                                                |
| White retrolental masses                               |
| (1/<1%)                                                |
| **Uvea** (iris, ciliary body)                          |
| Pale/atrophic irides                                   |
| (11/4%)                                                |
| Uveitis                                                 |
| (10/3%)                                                |
| General iris abnormalities                             |
| (7/2%)                                                 |
| Synchiae                                               |
| (4/1%)                                                 |
| Hypoplastic anterior iris stroma                       |
| (3/1%)                                                 |
| Ciliary body cysts                                     |
| (2/<1%)                                                |
| Flat iris                                              |
| (1/<1%)                                                |
| Iridoschisis                                           |
| (1/<1%)                                                |
| Inferior iris coloboma                                 |
| (1/<1%)                                                |
| Dysplastic iris                                        |
| (1/<1%)                                                |
| **Uvea** (choroid)                                     |
| Thick choroid                                          |
| (2/<1%)                                                |
| Thin choroid                                           |
| (1/<1%)                                                |
| Persistent hyperplastic primary vitreous               |
| (1/<1%)                                                |
| Vitreous membrane attachment to optic nerve and lens    |
| (1/<1%)                                                |
| **Vitreous**                                           |
| Vitreous degeneration                                  |
| (1/<1%)                                                |
| **Retina/fundus**                                      |
| Dysplastic retina/fundus                               |
| (3/1%)                                                 |
| Pale retina/fundus                                     |
| (2/<1%)                                                |
| Thread-like retinal vasculature                        |
| (2/<1%)                                                |
| Dystrophic retinal epithelium                          |
| (1/<1%)                                                |
| Hypoplastic macula                                     |
| (1/<1%)                                                |
| Absent fundal glow with B-scan ultrasound               |
| (1/<1%)                                                |
| **Optic disc**                                         |
| Pale/atrophic optic disc                               |
| (3/1%)                                                 |
| Dysplastic optic disc                                  |
| (2/<1%)                                                |
| Ellipsoid optic disc                                   |
| (1/<1%)                                                |
| Optic disc hypervascularity                            |
| (1/<1%)                                                |
| Ocular adnexa | Eyelid | Short/narrow palpebral fissures (56/19%) | Epicanthus (36/12%) | Telecanthus (11/4%) | Ptosis (7/2%) | Blepharophimosis (1/1%) | Entropion (1/1%) | Ectropion (1/1%) | Epiblepharon (1/1%) | Mucosal hypertrophy (1/1%) |
|--------------|--------|------------------------------------------|---------------------|---------------------|--------------|--------------------------|-----------------|-----------------|---------------------|--------------------------|
| Eyebrow/eyelash | Madarosis (19/6%) | Flared eyebrows (3/1%) (2 medially flared) | Synophrys (1/1%) |
| Nasolacrimal duct abnormalities | Hypolacrimation (1/1%) |

**Refractive errors**
- Myopia (16/5%) (2 anisometropic)
- Hyperopia (8/3%) (2 anisometropic)
- Astigmatism (1/1%)

**Eye movement disorders**
- Strabismus (27/9%) (9 esotropic, 1 exotropic)
- Nystagmus (8/3%)
- Amblyopia (3/1%)
- Duane syndrome (2/1%)
- Brown syndrome (1/1%)

**Additional eye disorders**
- Glaucoma (51/17%) (4 closed-angle, 1 open-angle)
- Paracentral scotoma (1/1%)

**ERG/neurological**
- Abnormal ERG (2/1%)
- Delayed visual evoked responses (2/1%)
- Occipital subcortical white matter changes (1/1%)
retina/fundus \((n = 2)\), and deep anterior chambers \((n = 2)\). Additionally, including this study, the three patients with the p.G22E mutation have the following findings: microphthalmia \((n = 3)\), cataracts \((n = 1)\), microcornea \((n = 2)\), blonde fundus \((n = 1)\), persistent pupillary membrane \((n = 1)\), deep anterior chamber \((n = 1)\), hyperopia \((n = 1)\), strabismus \((n = 2, 1\) esotropic), amblyopia \((n = 1)\), glaucoma \((n = 1)\), short palpebral fissures \((n = 1)\), nasolacrimal duct abnormalities \((n = 1)\), and epicanthus \((n = 1)\) \([2, 3, 21, 22]\).

Some unique genotype-phenotype correlations were noted upon further analysis. Three patients presented with eccentric pupils, but only 2 of these patients were reported with an associated mutation. Both mutations (p.Q49dup and p.Q49P) seem to affect the same amino acid in connexin-43 \([3, 61, 72]\). Additionally, uveitis was reported in 10 patients, 9 of which were associated with similar mutations. Eight of these patients were within the same study and had the p.H194P mutation, another patient had no molecular confirmation of a GJA1 mutation, and the other patient was reported with a missense mutation on exon 2 \([4, 9, 10, 27, 28]\). However, since the majority of these patients were reported within the same study, the apparent genotype-phenotype correlation of p.H194P and uveitis might be due to underreporting of uveitis from other sources with different pathogenic variants or may be due to other factors of the family not identified within the study.

Further analysis of the genotype-phenotype correlation was conducted by pairing the phenotypic manifestations of each mutation with the corresponding defects in the connexin-43 domains. The domains were defined by the amino acid ranges provided on UniProt (P17302–CXA1_HUMAN) \([93]\). Table 6 \([1–3, 5–71, 92, 93]\) provides a summary of the phenotypes associated with mutations from each domain.

The domains most commonly affected by GJA1 mutations are the extracellular-1 loop and the cytoplasmic-1 loop of connexin-43, accounting for 19 and 20 mutations, respectively. Disruptions in the extracellular-1 loop presented primarily as microphthalmia \((n = 32)\) and microcornea \((n = 30)\). A similar pattern can be seen in the cytoplasmic-1 loop, as the most common presentations were microphthalmia \((n = 20)\) and microcornea \((n = 18)\). Other clinical findings, however, may be able to distinguish mutations resulting from these domains. The next most common findings associated with mutations in the extracellular-1 loop were glaucoma \((n = 15)\) and hypertelorism \((n = 11)\), as opposed to short palpebral fissures \((n = 14)\) and hypertelorism \((n = 14)\) for the cytoplasmic-1 loop.

Mutations affecting the cytoplasmic N-terminus and the transmembrane-1 domain shared similar features to the ones in the extracellular-1 and cytoplasmic-1 domains, as microphthalmia and microcornea were the most common clinical findings. However, the mutations in the cytoplasmic N-terminus and transmembrane-1 domain presented with microcornea \((n = 17\) and \(n = 21\), respectively) more frequently than microphthalmia \((n = 5,\) and \(n = 14,\) respectively). The opposite pattern is true for the extracellular-1 and cytoplasmic-1 domains.

The mutations in the extracellular-2 loop demonstrate a different phenotypic pattern, as microphthalmia \((n = 14)\) occurs the most frequently, while microcornea is less frequent \((n = 4)\). Mutations in the transmembrane-2 domain also display a unique pattern, with hypertelorism \((n = 5)\) being the most frequent clinical finding. Other domains listed in Table 6 also demonstrate some unique clinical patterns, but this may be due to variability from the small number of samples. The patterns mentioned previously, however, still provide insight into the role of different connexin-43

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**Table 5: Common GJA1 mutations with associated eye features.**

| Sources | Multiple mutations? | GJA1 mutation | Individuals with GJA1 mutation (confirmed and affected relatives) | Associated eye features |
|---------|----------------------|---------------|---------------------------------------------------------------|-------------------------|
| Quick and Dobersen 2014; National Center for Biotechnology Information 2020 | Yes | c.605G>A p.R202H | 1 | Microphthalmia (1) |
| Paznekas et al. 2009; Paznekas et al. 2003 | No | c.605G>A p.R202H | 17 | Microphthalmia (1), microcornea (2) |
| Nishat et al. 2012; Paznekas et al. 2009; Paznekas et al. 2003; and Amador et al. 2008 | No | c.389T>C p.I130T | 17 | Microphthalmia (9), hypertelorism (3), short axial length (4), cataract (1), microcornea (8), thick cornea (4), macular hypoplasia (1), shallow anterior chamber (4), myopia (4), strabismus (6) (1 esotropic), glaucoma (6), and epicanthus (3) |
| Park et al. 2019; Hayashi et al. 2014; Paznekas et al. 2009; Debeer et al. 2005; and Paznekas et al. 2003 | No | c.119C>T p.A40V | 17 | |
| GJA1 mutation | Protein domain (amino acid range) (obtained from UniProt-P17302) | Associated phenotype (no. of individuals) |
|---------------|---------------------------------------------------------------|------------------------------------------|
| p.G2fsX7 (with p.R101X) | Cytoplasmic N-terminus (1-13) | Microcornea (7), microphthalmia (5), epicanthus (4), strabismus (3) (1 esotropic), short palpebral fissures (2), telecanthus (2), amblyopia (1), dysplastic fundus (1), optociliary vein (1), dysplastic optic disc (1), pale/atrophic optic disc (1), persistent pupillary membrane (1), myopia (3), hyperopia (1) (anisometropic), glaucoma (1), ptosis (1), entropion (1), madarosis (1), hypertelorism (1), and cataract (1) |
| p.G2V | | |
| p.L11P | | |
| p.L11F | | |
| p.L11I | | |
| p.L7V | | |
| p.SSC | | |
| p.W25C | Transmembrane-1 (14-36) | Microcornea (21), microphthalmia (14), short palpebral fissures (11), persistent pupillary membrane (6), iris stroma hypoplasia (3), hypertelorism (2), cataract (2), iris abnormalities (2), blonde fundus (1), iridoschisis (1), deep anterior chamber (1), hyperopia (2), strabismus (7) (3 esotropic), amblyopia (1), nystagmus (1), ptosis (1), epiblepharon (1), nasolacrimal duct obstruction (1), and flared eyebrows (1) (medially flared) |
| p.R33X | | |
| p.I31M | | |
| p.K23T | | |
| p.G22E | | |
| p.G21R | | |
| p.S18P | | |
| p.Y17S | | |
| p.L26P | | |
| p.Q57SfsTer6 | Extracellular-1 (37-76) | Microphthalmia (32), microcornea (30), glaucoma (15) (2 closed-angle, 1 open-angle), hypertelorism (11), epicanthus (10), strabismus (9) (3 esotropic), short palpebral fissures (9), iris atrophy (peripupillary) (8), cataract (6), shallow anterior chamber (6), hypertelorism (5), short axial length (4), myopia (4), corneal farinata (4), telecanthus (3), iris abnormalities (2), eccentric pupils (2), persistent pupillary membrane (2), dysplastic fundus (1), dysplastic optic (1), macular hypoplasia (1), synchiae (1), ciliary body cysts (1), deep anterior chamber (1), hyperopia (1), ptosis (1), blepharophimosis (1), madarosis (1), nasolacrimal duct abnormalities (1), and low-voltage ERG (1) |
| p.R76H | | |
| p.R76C | | |
| p.R76S | | |
| p.H74P | | |
| p.S69Y | | |
| p.P59H | | |
| p.Q49dup | | |
| p.F52dup | | |
| p.Q49P | | |
| p.Q49E | | |
| p.Q49K | | |
| p.E48K | | |
| p.D47H | | |
| p.E42Q | | |
| p.V41_A44del | | |
| p.V41L (with p.R127H (GJB2 mutation)) | | |
| p.A40V | | |
| p.P59S | | |
| p.Y98C | Transmembrane-2 (77-99) | Hypertelorism (5), microcornea (2), microphthalmia (3), glaucoma (3), strabismus (2) (1 esotropic), short palpebral fissures (2), eyelid mucosal hypertrophy (1), telecanthus (1), epicanthus (1), optic disc atrophy (1), hyperopia (1), myopia (1), strabismus (1), paracentral scotoma (1), madarosis (1), and delayed visual evoked potentials (1) |
| p.V96A | | |
| p.V96E | | |
| p.V96M | | |
| p.H95R | | |
| p.L90V | | |
| p.S86Y | | |
| p.V96G | | |
domains in providing phenotypic variability among patients with ODDD.

In conclusion, this report provides a comprehensive review of the eye and ocular adnexa abnormalities that are currently known to be associated with the ODDD phenotype. Limitations of this report include the possibility of an incomplete ophthalmologic evaluation and/or lack of reporting of eye features in all of the evaluated case reports or misdiagnosis in the individuals with the ODDD phenotype without molecular confirmation. As such, it is possible that the reported common eye features within this summary may be over or underrepresented. Ophthalmic manifestations are commonly associated within the phenotype, and a wide spectrum of eye and ocular adnexa structures may be affected. The rarity of this condition provides further incentive to further investigate the phenotype.

Consent

Consent has been obtained.
Conflicts of Interest

Virang Kumar and Arti Pandya declare that they have no conflicts of interest. Natario L. Couser, MD, MS, is a principal investigator at the Virginia Commonwealth University site of Retrophin, Inc., and book editor in Elsevier.

Supplementary Materials

Supplementary Material 1: all GJA1 mutations with associated eye and ocular adnexa features. This dataset groups patients with ODDD by GJA1 mutation and reports the associated eye and ocular adnexa features. (Supplementary Materials)

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