Genotype Phenotype Correlation and Variability in Microcephaly Associated With Chorioretinopathy or Familial Exudative Vitreoretinopathy

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There have been multiple reports of congenital microcephaly and associated chorioretinopathy.1–6 Autosomal dominant microcephaly with or without chorioretinopathy, lymphedema, or mental retardation (MCLMR; OMIM #152950) is arguably the most thoroughly studied clinical entity and has been linked to mutations in KIF11.7,8 Autosomal recessive disease caused by mutations in TUBGCP4,9 TUBGCP6,10 and PLK4 have also been described.9–13 Long-term follow-up data in these patients are limited and the degree of disease progression is largely unknown.

In addition to chorioretinal atrophy, microcephaly can also rarely be seen in association with familial exudative vitreoretinopathy (FEVR), a disorder of abnormal retinal vascular development that can result in tractional retinal folds and detachments. Microcephaly with chorioretinopathy and microcephaly with FEVR have both been associated with mutations in KIF11, TUBGCP4, and TUBGCP6, and thus might represent a clinical spectrum rather than two distinct diagnoses.11–15 As with other genetic disorders with complex phenotypic overlap, it may be more accurate to refer to these diseases by genotype rather than phenotype. The present report describes the detailed phenotypes, molecular genetic findings, and available follow-up of 12 individuals from 9 families with microcephaly and fundus features of chorioretinopathy, FEVR, or both.
Table 1. Genetic and Demographic Data on Patients With Microcephaly and Chorioretinal Atrophy or Familial Exudative Vitreoretinopathy

| Patient | Local ID | Gene | Mutation | FHx of Retinal Disease | FHx of Microcephaly | Sex | Head Circumference | Age First Visit, y | Age Last Visit y | F/U y | Birth Weight (kg) | Intellectual Disability | Epilepsy | Growth Retardation | Lympedema | Additional Symptoms |
|---------|----------|------|----------|------------------------|---------------------|-----|-------------------|-------------------|-----------------|-------|------------------|-----------------------|----------|-------------------|-----------|---------------------|
| P1      | 30101    | KIF11 | c.620delA; p.K207Rfs*8 | +Father, brother    | +Brother            | M   | <1st percentile   | 0.3               | 1.1             | 0.8   | 5.49            | None                 | No       | No                | Yes       | None reported       |
| P2      | 20581    | KIF11 | c.620delA; p.K207Rfs*8 | +Father, brother    | +Brother            | M   | 2nd percentile    | 0.2               | –               | 0     | N/A              | None                 | No       | No                | Yes       | None reported       |
| P3      | 20581    | KIF11 | c.669_670dup, p.Ala224Valfs*5 | None            | None               | M   | NA                | 3                 | 29              | 26    | N/A              | Mild                 | No       | No                | No        | None reported       |
| P4      | 23778    | KIF11 | c.1159C>T; p.R387X | +Mother             | +Mother            | F   | <1st percentile   | 2                 | –               | 0     | 2.10            | N/A                  | Yes      | N/A               | No        | Congenital hip dislocation, constipation |
| P5      | 19762    | KIF11 | c.1159C>T; p.R387X | +Daughter           | +Daughter          | F   | 2nd percentile    | 11                | 24              | 13    | 2.80            | Mild                 | No       | No                | N/A       | None reported       |
| P6      | 29708    | KIF11 | c.2002-1G>T | +Mother and maternal grandfather | +Mother and maternal grandfather | F   | 2nd percentile (47 cm at 5 y) | 4                 | 15              | 11    | 2.27            | Mild                 | No       | No                | No        | None reported       |
| P7      | 51021    | KIF11 | c.2085_2095delinsG; p.C695Vfs*4 | None            | None               | M   | <1st percentile   | 0.3               | 1.3             | 1     | 2.97            | None                 | No       | No                | No        | None reported       |
| P8      | 32333    | KIF11 | c.2002_2009delp.C695Vfs*4 | None            | None               | M   | <1st percentile   | 16                | 20              | 4     | 2.70            | Mild                 | No       | No                | No        | Short-term memory deficits Epicanthal folds, flat nasal bridge, bulbous nose, long philtrum, micrognathia, mild kyphosis, pachygyia, scoliosis |
| P9      | 21364    | KIF11 | c.2507_2510del: p.S836X | None            | None               | M   | <1st percentile   | 0.8               | 24              | 23    | 2.10            | Severe               | N/A      | N/A               | N/A       | None reported       |
### Table 1. Continued

| Patient | Local ID | Gene | Mutation | FHx of Retinal Disease | FHx of Microcephaly | Sex | Head Circumference | Age First Visit, y | Age Last Visit y | F/U y | Birth Weight (kg) | Intellectual Disability | Epilepsy | Growth Retardation | Lymphedema | Additional Symptoms |
|---------|----------|------|----------|------------------------|---------------------|-----|-------------------|-------------------|-----------------|------|-----------------|------------------------|----------|-------------------|------------|---------------------|
| P10     | 23879    | TUBGCP6 | c.3163G>A, p.H1055Y, c.3565G>A, p.G1189X | +Sister               | +Sister             | M   | <1st percentile (45 cm at 12 y) | 2                 | 17             | 15   | 2.89            | Severe                  | No       | Yes               | No         | None               |
| P11     | 23890    | TUBGCP6 | c.3163G>A, p.H1055Y, c.3565G>A, p.G1189X | +Brother              | +Brother            | F   | <1st percentile (46.5 cm at 17 y) | 9                 | 24             | 15   | 3.06            | Moderate                | No       | Yes               | Yes        | Broad, depressed nasal bridge, mild micrognathia, upslanting palpebral fissures, high arched palate, bifid uvula, secondary amenorrhea, urinary incontinence, constipation, mild kyphosis and lordosis, multiple pigmented nevi, increased muscle tone, decreased strength |
| P12     | 28924    | TUBGCP4 | c.1746G>A, p.Leu582G>A, c.1651C>T, p.Arg551* | None                  | None                | M   | <1st percentile (37 cm at 6 mo) | 0.4               | 6              | 5    | 2.59            | Mild                    | No       | No                | No         | Delay in gross and fine motor skills |

N/A: no information available. Head circumference percentile based on World Health Organization growth standards data.
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**Methods**

Individuals with microcephaly, defined as head circumference >2 standard deviations smaller than mean, and chorioretinopathy or FEVR were identified from the ophthalmic genetics clinics at Oregon Health and Science University, Children’s Hospital of Los Angeles, and S. Fyodorov Eye Microsurgery Federal State Institution. The study protocol followed the tenets of the Declaration of Helsinki and was approved by each participating center’s institutional review board. Data from available medical records, ophthalmic examination, fundus imaging, visual field testing, and electroretinography (ERG) were collected and analyzed. The initial presentation of some patients have previously been described (patients 5, 9, 10, and 11); additional molecular genetic and follow-up data on these patients are included in the present analysis. Assessment of posterior segment progression was completed for each subject by open review of all ophthalmic data and testing over the follow-up period. Full field ERG was conducted according to institutional protocol and International Society for Clinical Electrophysiology of Vision (ISCEV) standards. Kinetic visual fields were measured using the Goldmann perimeter or Octopus 900 perimeter (Haag Streit AG, Switzerland). The same full field ERG and visual field protocols were used in patients with serial testing.

Genetic testing methods were institution dependent. Methods included: (1) a targeted capture next generation sequencing research protocol assessing for mutations in retinal disease genes performed at the Laboratory for Molecular Diagnosis of Inherited Eye Disease (UTHealth, Houston, TX, USA) or Baylor College of Medicine, as previously described; (2) molecular diagnostic testing performed at the Center for Personalized Medicine at Children’s Hospital Los Angeles using a focused exome strategy targeting 286 eye disease genes (EyeDFX), and (3) targeted capture sequencing using the standard automated algorithm described at https://basespace.illumina.com and performed at the Research Centre for Medical Genetics (Moscow, Russia).

**Results**

Key demographics, molecular genetic data, and systemic phenotypes are summarized in Table 1 and ocular features are summarized in Table 2. Twelve patients with congenital microcephaly and chorioretinopathy or FEVR were included. Median age at initial ophthalmologic examination was 2 years (range = 0–16 years) and median follow-up was 8 years (range = 0–26 years). There were two sibling pairs (patients 1 and 2, and 10 and 11) and one mother-daughter pair (patients 4 and 5). The mother and maternal grandfather of patient 6 had a history of chorioretinal disease and microcephaly. The remaining five patients had no known family history of microcephaly or retinal disease; the suspected pathologic mutation was confirmed to be de novo in three patients (patients 3, 7, and 8) as both parents had negative genetic testing in these cases. A heterozygous mutation in the KIF11 was identified in 9 of 12 patients (5 nonsense, 5 frameshift, and 1 intronic splicing mutation). The sibling pair (patients 10 and 11) had compound heterozygous mutations in TUBGCP6 (one missense and one nonsense mutation). One individual (patient 12) had compound heterozygous mutations in TUBGCP4 (one nonsense mutation and one synonymous substitution previously reported in TUBGCP4-associated microcephaly and chorioretinopathy).

In addition to microcephaly, systemic features included developmental delay, growth retardation, congenital lymphedema of the lower limbs, and diverse dysmorphic facial features (Table 1). Although none of the patients had a history of preterm birth, three patients (patients 4, 6, and 9) with KIF11 mutations had a low birth weight of less than 2500 grams.

Visual acuity and refractive error were variable, and measurement was limited by age and developmental delay in some cases. Nystagmus was present in five patients. The most common presenting fundus features were areas of sharply demarcated chorioretinal dysplasia or atrophy, attenuated retinal vessels, and optic disc pallor (Table 2, Figs. 1–7). In keeping with the known spectrum of FEVR, some patients had vascular or vitreoretinopathy features ranging from peripheral retinal avascularity to tractional retinal folds or detachments. Incomplete vascularization of the peripheral retina was seen in patients 1, 2, and 11 and an absent inferior vascular arcade was present in one eye of patient 7. Tractional retinal folds (Figs. 7, 8) or retinal detachments (Figs. 1, 9) were also seen on initial presentation in five patients (patients 1, 2, 7, 10, and 12). Eight patients had ERG recordings and all demonstrated abnormal rod and cone dysfunction, ranging from mild to severe. Other ophthalmologic findings included strabismus (3 patients with exotropia and 1 with esotropia), cataract in four patients, iridocorneal dysgenesis in two patients, microphthalmia in three patients, and microcornea in three patients.

With a median of 8 years of follow-up, at least mild disease progression was detected in 9 of 12 patients. The degree of progression was highly variable; some patients had very mild expansion of the area of chorioretinal atrophy (patient 8; Fig. 2), however, examples of more significant progression were seen. Patient 5 had progressive macular atrophy and a drop in best corrected visual acuity from 20/80 in both eyes to 20/400 in the right and 20/300 in the left eye over a period of 13 years (Fig. 3). Despite chorioretinal atrophy being limited to the midperiphery on baseline imaging in patient 9 at 10 months of age, follow-up demonstrates progressive macular atrophy (Fig. 4). Serial imaging and visual field testing in patient 3 demonstrated that enlargement of chorioretinal atrophy can be associated with progressive outer nuclear and ellipsoid zone loss as well as expanding visual field deficits (Fig. 5). Patients 1, 10, and 12 had progression of their FEVR-like phenotypes with increased vitreous traction on retinal folds or detachments. Patient 10 presented with bilateral, severe temporal traction with detachments through the macula that progressed to complete funnel detachments in both eyes. Serial full field ERG testing was available in two patients (patients 3 and 5) and did not show significant decline.

**Discussion**

Multiple terms have been used to describe the phenotypic complex of microcephaly, chorioretinal atrophy, developmental delay, and other systemic features. The recognition that patients with similar systemic features and pathologic mutations can also have FEVR-like ocular findings adds to the phenotypic variability of these conditions. The present report, with analysis of 12 patients with molecular diagnosis achieved through targeted sequencing, further argues against distinct clinical entities and supports the
Table 2. Ophthalmological Features of Patients With Microcephaly and Chorioretinal Atrophy or Familial Exudative Vitreoretinopathy

| Patient | Nystagmus | Nyctalopia | BCVA at First Visit OD/OS | BCVA at Last Visit OD/OS | Refraction First Visit OD/OS | Refraction Last Visit OD/OS | CR Atrophy | Microophthalmia | Microcornea | Strabismus | Iris/Cornea Dysplasia | Cataract | Vitreous Veils | Retinal Folds | Retinal Detachment | ERG Progression |
|---------|-----------|------------|--------------------------|--------------------------|-----------------------------|-----------------------------|-------------|----------------|-------------|------------|----------------------|----------|--------------|---------------|----------------|------------------|
| P1      | Yes       | No         | LP FF                    | N/A                      | 0.00 + 0.50 × 90             | -                           | -            | -              | -            | -          | -                    | ET       | -            |               | N/A            | +                |
| P2      | Yes       | No         | LP FF                    | N/A                      | -                           | -                           | -            | -              | -            | -          | -                    | ET       | -            |               | N/A            | -                |
| P3      | No        | Yes        | 20/100 FF 20/60 20/50    | 20/60 20/50 -4.75 + 0.25 × 180 -4.00 + 1.25 × 180 | +                           | -                           | -            | -              | -            | -          | -                    | +        | -            |               | -              | R/C              |
| P4      | No        | Yes        | CSM N/A 20/400 20/300 20/50 | 20/400 20/300 -1.00 + 1.00 × 90 -1.00 + 1.50 × 90 | +                           | -                           | -            | -              | -            | -          | -                    | XT       | -            |               | -              | R/C              |
| P5      | No        | Yes        | 20/80 20/30 20/25 20/200 | 20/800 20/200 -2.00 + 2.00 × 078 -2.00 + 2.00 × 083 | +                           | -                           | -            | -              | -            | -          | -                    | XT       | -            |               | -              | R/C              |
| P6      | No        | No         | FF FF                   | FF FF                     | N/A                         | N/A                         | -            | -              | -            | -          | -                    | N/A      | -            |               | -              | R/C              |
| P7      | No        | No         | FF FF                   | FF FF                     | N/A                         | N/A                         | +            | +              | -            | -          | -                    | +        | +            |               | +              | +                |
| P8      | No        | Yes        | 20/200 20/200 20/200    | 20/200 20/200 -7.00 + 1.50 × 095 -7.00 + 2.00 × 100 | +                           | -                           | -            | -              | -            | -          | -                    | R/C      | +            |               | -              | +                |
| P9      | Yes       | Yes        | FF FF 20/200 20/200     | 20/200 20/200 +3.50 sphere +3.50 sphere | N/A                         | N/A                         | +            | +              | -            | -          | -                    | R/C      | -            |               | -              | +                |
| P10     | Yes       | Yes        | LP LP                   | LP LP                     | N/A                         | N/A                         | -            | -              | -            | -          | +                    | +        | -            |               | +              | +                |
| P11     | Yes       | Yes        | CSM FF 20/200 20/300    | 20/200 20/300 -2.50 + 0.50 × 110 -1.50 + 2.00 × 075 | +                           | +                           | -            | -              | -            | -          | -                    | R/C      | -            |               | -              | +                |
| P12     | No        | No         | LP LP                   | LP LP                     | N/A                         | N/A                         | -            | -              | -            | -          | -                    | R/C      | -            |               | +              | +                |

BCVA, best corrected visual acuity; LP, light perception; FF, fix and follow; CSM, central, steady, maintained; N/A, not available; CR, chorioretinal; ET, esotropia; XT, exotropia; PSC, posterior subcapsular cataract; R/C, rod/cone dysfunction.
FIGURE 1. Fundus images of a 1-year-old boy (patient 7) shows a tractional retinal detachment in the right eye (A) and foveal hypoplasia, inferior chorioretinal atrophy, and a severely attenuated inferior arcade in the left eye (B). Fluorescein angiography highlights the vascular malformation and attenuation (C, D).

FIGURE 2. Fundus images of a 16-year-old boy (patient 8) demonstrates optic disc pallor, chorioretinal atrophy, and marked vascular attenuation (A, B). Imaging at 20 years of age demonstrates mild expansion of chorioretinal atrophy. (C, D, white arrowheads).

FIGURE 3. Fundus images of an 11-year-old girl (patient 5) show perifoveal pigment mottling, optic disc pallor, and inferior chorioretinal atrophy (A, B). Imaging at 24 years of age demonstrates progression of atrophy in the mid periphery and macula (C, D).

The notion that ocular disease in these patients fall along a spectrum from well-demarcated chorioretinal atrophy to FEVR-like vascular and vitreoretinal changes. Additionally, the long-term follow-up included in this study demonstrates that both the chorioretinal atrophy and vitreoretinopathy seen in these patients can be slowly progressive over time.

In this series, all patients had reduced visual function and most presented in infancy or early childhood, however, examples of later presentations were also observed. Visual acuity testing was often limited by age and developmental delay, but there was a general correlation between visual function and fundus features, including degree of macular chorioretinal atrophy and retinal attachment status. Although the fundus features associated with microcephaly often fall into one of two major categories, chorioretinal atrophy or FEVR, others have reported phenotypic overlap, particularly in patients with KIF11 mutations.12–15 The present series included examples of phenotypic overlap, either within a single individual or within families, in diseases caused by KIF11, TUBGCP4, and TUBGCP6.
mutations. For example, patient 7 presented with features of FEVR, including peripheral avascular retina and leakage in both eyes and a tractional retinal detachment in the right eye as well as well demarcated mid peripheral chorioretinal atrophy in the left eye (Fig. 1). The sibling pair (patients 10 and 11), with mutations in the TUBGCP6 gene, demonstrate there can be phenotypic variation between family members with the same mutations. The older female (patient 11) had a predominantly chorioretinal phenotype with well demarcated, dysplastic-appearing lesions, whereas the younger male (patient 10) presented with temporal nonperfusion and tractional retinal detachments. Patient 12, with heterozygous TUBGCP4 mutations, presented with chorioretinal dysplasia, temporal tractional retinal detachments, and persistent fetal vasculature with a vascular stalk from the optic nerve to the posterior lens capsule in both eyes. This phenotypic variability is less surprising in patients with KIF11 mutations, which has been identified as a common cause of nonsyndromic autosomal dominant FEVR.19 Cases of autosomal recessive TUBGCP6 and TUBGCP4 disease are less common, and, to our knowledge, have not been reported in cases of isolated FEVR without microcephaly. These cases,
along with others in the literature, demonstrate how specific mutations in KIF11, TUBGCP6, and TUBGCP4 can all cause fundus features of both chorioretinal atrophy and FEVR.

There appears to be variable expressivity in at least one KIF11 mutation. Patients 4 and 5 (a mother and daughter pair) had a KIF11 mutation, c.1159C>T, that had been previously described in 3 unrelated families with autosomal dominant MCLMR.7,20 There is inter- and intra-familial variation of the ocular phenotype in the previously reported families with some affected individuals having no evidence of chorioretinal atrophy. Compared with her mother, patient 4 presented at a younger age and had a more severely diminished ERG, with no recordable scotopic response and a severely subnormal photopic response. To our knowledge, only a chorioretinopathy phenotype, without features of FEVR, has been seen in association with this specific KIF11 mutation. The mechanism for both variable penetrance and expressivity is unknown, but may be similar to the complex gene-gene interactions seen in other genetic ciliopathies.21,22

Retinal disease progression was common but variable in severity in this cohort. With a median of 8 years of follow-up, we identified at least mild disease progression in 9 of 12 patients. Two primary types of progression were observed, including (1) increase in chorioretinal atrophy area and (2) increase in vitreoretinal traction resulting in retinal folds or detachments.

Slow enlargement of chorioretinal atrophy was seen in both the mid periphery and macula. In some cases, this expansion was minimal and unlikely to be visually significant. In other cases, progression was associated with worsening visual fields, outer nuclear and ellipsoid zone loss, and decline in visual acuity. Importantly, as demonstrated in Figure 4, individuals can have progressive macular atrophy even when punched out atrophic lesions are limited to the mid periphery at initial presentation. Britel et al. have also reported progression of chorioretinal atrophy in a patient with a KIF11 mutation, and similarly demonstrated how fundus autofluorescence (FAF) imaging can show an
**Figure 7.** Fundus images from a sibling pair with microcephaly and different ocular phenotypes. The brother has falciform retinal folds in both eyes (patient 10) (A, B) whereas the sister has slightly attenuated retinal vessels and patches of chorioretinal dysplasia (patient 11) (C, D). Images reproduced with permission: Trzupek KM, Falk RE, Demer JL, Weleber RG. Microcephaly with chorioretinopathy in a brother-sister pair: evidence for germ line mosaicism and further delineation of the ocular phenotype. *Am J Med Genet A.* 2007;143A(11):1218-22. © 2007 Wiley-Liss, Inc.

**Figure 8.** Fundus images of a one-year-old boy (patient 1) with retinal folds originating from the nerves and diffuse retinal dysplasia (A, B). Fluorescein angiography highlights severe retinal vascular attenuation (C, D).
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FIGURE 9. Fundus images of a 5-month-old boy (patient 12) with diffuse chorioretinal dysplasia, complete tractional retinal detachments, and persistent fetal vasculature (A, B). There is increased traction on follow-up at 6 years of age (C, D).

increased area of reduced autofluorescence with a corresponding shift of the hyperautofluorescent border as the disease progresses. All eight patients with ERG recordings had some degree of both rod and cone dysfunction. There was no evidence of ERG decline when serial testing was available, however, there may be a floor effect in patients with severely diminished readings and those with chronic tractional retinal detachments. Worsening of vitreoretinal traction was also observed in patients with FEVR-like changes and resulted in retinal detachment in some cases.

To date, according to the Human Gene Mutation Database (HGMD), there have been 95 pathologic mutations identified in the KIF11 gene. Prior studies have been unable to identify correlations between affected protein domain or mutation type and KIF11-associated ocular phenotype. We describe 7 KIF11 mutations, 6 of which are novel, in the current study; c.1159 C>T has been previously described. Importantly, a family history is not required for diagnosis of KIF11 related disease; 3 of the 9 cases with KIF11 mutations were confirmed to be de novo, a rate similar to that reported by Schloge et al. The phenotypic overlap of chorioretinopathy and FEVR fits with the known functions of KIF11, which encodes a kinesin-like motor protein involved in mitosis and cilia function. In the retina, KIF11 has been localized to the inner segments and ciliary compartments of photoreceptors and in the retinal pigment epithelium. Additionally, in vitro blockage of KIF11 function has been found to inhibit endothelial cell proliferation and migration. KIF11 knockdown also results in developmental vascular defects in zebrafish and chick embryos. KIF11-associated disease likely represents a systemic ciliopathy that disrupts photoreceptor development and retinal angiogenesis. Many of the previously described KIF11 mutations, as well as those identified in the current study, are spread across various protein domains, further suggesting that haploinsufficiency is the most likely mechanism.

TUBGCP4 and TUBGCP6 are both necessary for microtubule nucleation at the centrosome and TUBGCP6 is a phosphorylation target of PLK4, another gene that has been associated with microcephaly and chorioretinopathy. Knockdown of PLK4 in a zebrafish model resulted in impaired response to visual stimuli and reduced number of cells containing cilia in the photoreceptor layer. The underlying pathogenesis in TUBGCP4- and TUBGCP6-associated disease is still unknown but cilia function and abnormal photoreceptor development may be involved.

This series highlights the variety of fundus features associated with microcephaly and mutations in KIF11, TUBGCP4, and TUBGCP6. Some mutations can have significant phenotypic variability; one family member may have prominent chorioretinal atrophy while another has a typical FEVR phenotype. Similar variability can be seen between eyes in a single individual. There is also evidence of variable expressivity with some mutations in regard to visual potential and ERG severity. Although progression of posterior segment disease is minimal in many cases, new or enlarging areas of atrophy or worsening of vitreoretinal traction can result in visual function decline in some patients. Patients should have long-term follow-up and be connected with low-vision specialists when appropriate.

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