Ophthalmic features of retinitis pigmentosa in Cohen syndrome caused by pathogenic variants in the VPS13B gene

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ABSTRACT.

Purpose: The aim of this study is to report on the phenotype and genotype of five patients diagnosed with Cohen syndrome, an extremely rare autosomal recessive disorder manifesting with mental and physiological defects.

Methods: Five patients from three German families and one Syrian family underwent a comprehensive ophthalmological examination. The scheduled visual acuity measurements, fundus ophthalmoscopy, spectral domain optical coherence tomography (OCT), full-field electrophysiological recordings of scotopic and photopic electroretinograms (ERGs) and colour vision testing could not be carried out in all subjects, because of the mental and physical retardation. The genetic diagnosis was achieved by next-generation sequencing.

Results: The ophthalmic and systemic phenotype of the patients is typical for Cohen syndrome including myopia, night blindness, photophobia, fundus pigmentary changes and bull’s eye maculopathy. Electroretinograms (ERGs) were extinguished in the four patients, whose recording was possible. Genetic testing revealed homozygous or two heterozygous bi-allelic mutations in the VPS13B (COH1) gene in all five patients, with five different allelic variants observed. The homozygous mutation c.6055_6056delGA; p.Asp2019Glnfs*15 in two sibling patients as well as the homozygous nonsense mutation c.8112C>G; p.Tyr2704* have not previously been reported.

Conclusions: The phenotype of the five patients reported here is typical for Cohen syndrome; however, their genotype is heterogeneous. Two new allelic variants were found to be the causative mutation.

Key words: allele – Cohen syndrome – genotype – phenotype

Introduction

Cohen syndrome (MIM 216550) is a rare autosomal recessive disorder (Cohen et al. 1973; Carey & Hall 1978). Diagnosis is based on the typical clinical picture of intellectual disability, obesity, muscular hypotonia, facial, oral, ocular and limb abnormalities and low levels of leucocytes (neutropenia) (Alavi et al. 1993; North et al. 1995; Kivitie-Kallio & Norio 2001; Kolehmainen et al. 2004), but the clinical findings are variable (Hennies et al. 2004). Ocular signs and symptoms can be high myopia, retino-choroidal dystrophy, heremalopia (decreased vision in bright light), night blindness, strabismus, constricted visual fields and/or nystagmus (Norio et al. 1984; Kivitie-Kallio et al. 2000; Chandler et al. 2002; Taban et al. 2007). Deterioration in vision can occur from early childhood up to 40 years of age, and vision is generally severely impaired. A bull’s eye macula is seen in most patients (Norio et al. 1984; Resnick et al. 1986; Kivitie-Kallio et al. 2000).

It has been estimated that the incidence of patients with Cohen syndrome is fewer than 1000 people worldwide (US National Library of Medicine 2018). More than 200 cases have been described (Wang et al. 2016), the largest cohort of 29 patients being reported from Finland (Norio 2003). It is also overrepresented in Greek/Mediterranean (Bugiani et al. 2008), Amish (Falk et al. 2004) and Irish traveller populations (Murphy et al. 2007). In Finnish patients, the phenotype is highly homogeneous, but in non-Finnish patients there is considerable phenotypic variability (Kivitie-Kallio & Norio 2001; Hennies et al. 2004; Kolehmainen et al. 2004;
Katzaki et al. 2007; Chandler & Clayton-Smith 2010; Douzgou & Petersen 2011).
The responsible gene, VPS13B (COH1), has been mapped to chromosome 8 at locus 8q22.2 (Tahvanainen et al. 1994; Kolehmainen et al. 2003) and encodes for a protein which is thought to play a role in the intracellular transport of proteins. Seifert et al. (2015) identified VPS13B as a Golgi-enriched scaffold protein which augments the structure and function of the Golgi complex. The disturbance in the Golgi apparatus leads to alterations in protein glycosylation and endosomal-lysosomal trafficking (Duplomb et al. 2014). There is a large degree of allelic heterogeneity, and over 200 different variant mutations in the VPS13B gene have been found in individuals with Cohen syndrome to date (Sfari Gene, 2018.11: https://gene.sfari.org/database/human-gene/VPS13B/variants-tab, HGMD Professional, 2018.3 http://www.hgmd.cf.ac.uk/ac/index.php).

We report here on the ophthalmic, systemic and genetic characteristics in five patients with Cohen syndrome caused by homozygous or two heterozygous mutations in the VPS13B gene, who attended the Centre for Ophthalmology, Tubingen for examination. In view of the rareness of the disease, we sought to confirm and expand knowledge about the phenotype of patients with the VPS13B gene.

Materials and Methods
We examined five patients (four females and one male), aged between 9 and 38 years, from three German families and one Syrian family. Two patients were siblings. The data were collected retrospectively from medical records.

Ophthalmic examinations were not comprehensive or possible in all patients because some patients were not amenable or could not understand the instructions because of mental retardation. The ophthalmic examination included, if possible, visual acuity measurement using Snellen or Lea charts, fundus ophthalmoscopy and spectral domain optical coherence tomography (SD-OCT) using a single line scan protocol for a horizontal cross section through the fovea (Spectralis HRA+ OCT; Heidelberg Engineering Inc., Heidelberg, Germany). Further, full-field scotopic and photopic electroretinograms (ERGs) were recorded according to ISCEV standards (McCulloch et al. 2015a,b) (Diagnosys; Lowell, MA, USA), and colour vision testing (Ishihara or Lea) was carried out, if feasible. Visual field testing and retinal imaging with fundus autofluorescence were not possible in any patient.

Genomic DNA was isolated from peripheral blood according to standard procedures. Genetic testing for all genes associated with syndromic and non-syndromic retinitis pigmentosa was conducted applying next-generation sequencing as reported previously (Glöckle et al. 2013; Weisschuh et al. 2016).

The study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of the University of Tuebingen. Written informed consent was obtained for the research study, as well as for the diagnostic genetic testing, from all patients or their parents/guardians if underage or mentally retarded.

Results
In Table 1, the ophthalmic and clinical features of the five patients are listed. The likely causative VPS13B genotypes are given at the bottom of the Table. Figure 1 shows the fundus photographs and the OCT results.

In all patients, the ophthalmic examination revealed myopia, night blindness, photophobia, hemeralopia, fundus pigmentary changes and bull’s eye maculopathy. Astigmatism was also present in all patients, as was night blindness, hemeralopia and photophobia. The age of onset of first ophthalmic symptoms (night blindness or photophobia) was between 1 and 8 years (see Table 1). Four of the five patients had optic nerve pallor. In addition, the OCT scan (Fig. 1) showed macular oedema in three patients and small cystoid lesions in two patients, with atrophy of the outer retinal layers. Quantification of layer thickness therefore could not be carried out. One of the patients suffered from nystagmus until the age of 3 years. Electoretinograms (ERGs) could be recorded from three of the patients at their initial examination, but they were extinguished. One of the two patients who could not be recorded (patient 1) showed extinguished ERGs 4 years later using the Retival®System (LKC technologies Inc, Gaithersburg, Maryland, USA). Two patients had retinoschisis and one, the oldest, a cataract, which had developed at the age of 25 years. None suffered from microcornea or microphthalmia, a condition where the eyes are small with anatomic malformations. It was not possible to perform visual field examinations or fundus and autofluorescence imaging with these patients, due to the mental retardation and corresponding difficulty in cooperation.

Patients 1 was treated for oedema and cystoid lesions with topical anhydrodrase inhibitor for 12 months, and patient 3 with systemic carbonic anhydrodrase also for 12 months, without any improvement.

All patients suffered from mental retardation, two from microcephaly and one from autism. They all had a short body stature with muscular hypotonia. Three patients were obese, and two patients had scoliosis. Tapered fingers with elongated arms were also present in all patients. Typical facial features were mandibular retrognathia, a high/narrow palate, a short philtrum and a prominent nasal root and middle face.

Discussion
The visual problems in Cohen syndrome are of early onset (Chandler et al. 2002). In our cohort of five patients aged between 9 and 38 years, the ophthalmological examination revealed that all have myopia, astigmatism, fundus pigmentary changes, bull’s eye maculopathy, narrow vessels, hemeralopia, night blindness and photophobia. There was pullor of the optic disc, and the ERG was extinguished in four patients. These ophthalmic features are in line with those previously reported in Cohen syndrome patients (Kivitie-Kallio et al. 2000; Chandler et al. 2002; Taban et al. 2007). Only one of the five patients had a subcortical cataract although lens opacities have been reported in more than half of the Finnish patients with the c.3348_3349delCT deletion (Kivitie-Kallio et al. 2000) and in 86% of the Greek/Mediterranean patients with the c.11564delA deletion (Bugiani et al. 2008; Douzgou & Petersen 2011). One of the five patients had had nystagmus at birth until 3 years of age, and two patients showed a retinoschisis. None
| Patient number | 1  | 2  | 3  | 4  | 5  |
|----------------|----|----|----|----|----|
| **Age at last examination (years)** | 9  | 38 | 19 | 20 | 14 |
| **Sex** | f  | f  | m  | f  | f  |
| **Ophthalmic findings** | | | | | |
| **Visual acuity** | OD | 20/80 | 20/200 | 20/80 | 20/320 | 20/320 |
| | OS | 20/80 | 20/400 | 20/100 | 20/640 | 20/640 |
| **Spherical correction** | OD | −10.0 D | −10.0 D | −14.5 D | −3.25 D | −6.25 D |
| | OS | −10.0 D | −10.0 D | −14.5 D | −3.5 D | −6.25 D |
| **Cylindrical correction** | OD | −5.0 D, 20° | −1.0 D, 180° | −2.5 D, 170° | −2.5 D, 170° | −4.0 D, 8° |
| | OS | −5.0 D, 160° | −1.0 D, 170° | −2.5 D, 170° | −1.75 D, 175° | −4.0 D, 178° |
| **Colour vision** | ND | Few tritan errors | Diffuse error (Lea PV16 test, BIN) | ND | ND |
| **Visual field** | NR | NR | NR | NR | NR |
| **Autofluorescence** | NR | NR | NR | NR | NR |
| **Fundus** | Pigmentary changes (bone spicules), bull’s eye maculopathy, narrowing of the retinal vasculature | Pigmentary changes (bone spicules), bull’s eye maculopathy, narrowing of the retinal vasculature | Pigmentary changes (bone spicules), bull’s eye maculopathy, narrowing of the retinal vasculature | Pigmentary changes (bone spicules), bull’s eye maculopathy, narrowing of the retinal vasculature | Pigmentary changes (bone spicules), bull’s eye maculopathy, narrowing of the retinal vasculature |
| **Optic nerve** | Pallor | Pallor | No pallor | Pallor | Pallor |
| **OCT** | Oedema | Small cysts | Extinguished | Oedema | Oedema |
| **ERG** | OD | Extinguished | Extinguished | Extinguished | Extinguished |
| | OS | Extinguished | Extinguished | Extinguished | Extinguished |
| **Strabismus** | No | No | No | No | No |
| **Iris coloboma** | No | No | No | No | No |
| **Cataract** | No | No | No | No | No |
| **Hemeralopia** | Yes | Yes | Yes | Yes | Yes |
| **Retinoschisis** | Yes | No | No | No | No |
| **Microcornea** | No | No | No | No | No |
| **Microphthalmia** | No | No | No | No | No |
| **Nystagmus** | Yes | Yes | Yes | Yes | Yes |
| **Age of night blindness (years)** | 3 | 6 | 8 | 3 | 3 |
| **Age of photophobia (years)** | 1 | 6 | 8 | 3 | 3 |
| **Neurocognitive findings** | Yes | Yes | Yes | Yes | Yes |
| **Mental retardation** | Yes | Yes | Yes | Yes | Yes |
| **Autism** | No | No | No | No | No |
| **Microcephaly** | Yes | Yes | Yes | Yes | Yes |
| **Body features** | Yes | Yes | Yes | Yes | Yes |
| **Short stature** | Yes | Yes | Yes | Yes | Yes |
| **Joint hypermobility** | Yes | Yes | Yes | Yes | Yes |
| **Muscular hypotonia** | Yes | Yes | Yes | Yes | Yes |
| **Scoliosis** | Yes | Yes | Yes | Yes | Yes |
| **Hemeralopia** | Yes | Yes | Yes | Yes | Yes |
| **Retinoschisis** | Yes | Yes | Yes | Yes | Yes |
| **Microcornea** | No | No | No | No | No |
| **Microphthalmia** | No | No | No | No | No |
| **Nystagmus** | Yes | Yes | Yes | Yes | Yes |
had iris coloboma, microcornea or microphthalmia, as found in some Cohen patients (Resnick et al. 1986; Kivitie-Kallio et al. 2000; Chandler & Manson 2009). We also examined the OCT images (Fig. 1, right) of this Cohen syndrome cohort. All patients showed a cystoid macular oedema (CME) or cysts, as in retinitis pigmentosa, as also reported by Beck et al. (2018), which can cause a reduction of central vision (Strong et al. 2017). The SD-OCT horizontal cross sections also demonstrate atrophy of the outer retinal layers. The SD-OCT horizontal cross sections also demonstrate atrophy of the outer retinal layers. In patient 1, the SD-OCT images show a preserved island of outer nuclear layers and ellipsoid zone within the fovea, complicated by CME. Patient 2 has few cystic changes (the photographs were of low quality because of the cataract), and the images from patient 3 show an oedema from the outer nuclear layer up to inner nuclear layers. In the OCT images of patient 4, an oedema in the inner nuclear layers is found in both eyes, with subretinal fluid on the nasal side of the left eye (OS). In patient 5, the ellipsoid zone is interrupted and outer retinal layers are atrophic complicated by CME.

Based on the ophthalmological results on a retinal level, a diagnosis of retinitis pigmentosa can be made for all subjects on the appearance of the fundus, vessels, the optic nerve head and the presence of pigmentation. Concerning the syndromic symptoms, the differential diagnoses of inherited syndromes, where retinopathy is associated with mental retardation, include Bardet–Biedl and Alstrom syndromes. However, the phenotype of Alstrom includes deafness, diabetes mellitus and cardiomyopathy, which are not present in our patients, and Bardet–Biedl patients normally have polydactyly and renal problems. Further possible diagnoses are Prader–Willi syndrome, with an autosomal dominant mode of inheritance and no retinal dystrophy, or Angelman syndrome, where microencephaly and seizures are common (Chandler et al. 2002; Puech 2014; Wang et al. 2016). The diagnosis of Cohen syndrome is based on the clinical features listed in Table 1 and is confirmed genetically for all patients.

All 5 patients have the typical clinical features of Cohen syndrome: mental retardation, short stature, muscular

| Patient number | Obesity | Hands | Small and narrow with clinodactyly | Hands/elongated arms | Femur | Hirschsprung’s disease | Mandibular retrognathia | Short phalanges | Prominent middle face | Haplodiploid arm | Prominent nasal root | Genotype |
|----------------|---------|-------|-----------------------------------|---------------------|-------|-----------------------|-----------------------|---------------|---------------------|--------------|---------------------|----------|
| 1              | No      | Yes   | No                                | ND                  | ND    | No                    | No                    | Yes           | Yes                 | Yes          | No                  | ND       |
| 2              | Yes     | Yes   | Yes                               | ND                  | ND    | No                    | Yes                   | Yes           | Yes                 | Yes          | No                  | ND       |
| 3              | ND      | Yes   | Yes                               | ND                  | ND    | Yes                   | Yes                   | Yes           | No                  | ND          | No                  | ND       |
| 4              | Yes     | Yes   | Yes                               | ND                  | ND    | Yes                   | Yes                   | Yes           | Yes                 | Yes          | Yes                 | ND       |
| 5              | Yes     | Yes   | Yes                               | ND                  | ND    | Yes                   | Yes                   | Yes           | Yes                 | Yes          | Yes                 | ND       |

Table 1. (Continued)

| Patient number | Hands | Hands/elongated arms | Femur | Hirschsprung’s disease | Mandibular retrognathia | Short phalanges | Prominent middle face | Genotype |
|----------------|-------|----------------------|-------|-----------------------|-----------------------|---------------|---------------------|----------|
| 1              | ND    | ND                   | ND    | ND                    | ND                    | ND            | ND                  | ND       |
| 2              | ND    | ND                   | ND    | ND                    | ND                    | ND            | ND                  | ND       |
| 3              | ND    | ND                   | ND    | ND                    | ND                    | ND            | ND                  | ND       |
| 4              | ND    | ND                   | ND    | ND                    | ND                    | ND            | ND                  | ND       |
| 5              | ND    | ND                   | ND    | ND                    | ND                    | ND            | ND                  | ND       |

Genotype

- **VPS13B:** Deletion Exons 18–19 Deletion Exons 46–50 compound heterozygous
- **VPS13B:** c.1563G>A; p.Tyr2704* homozygous
- **VPS13B:** c.8112C>G; p.Tyr2704* homozygous
- **VPS13B:** c.6055_6056delGA; p.Asp2019Glnfs*15 homozygous
- **VPS13B:** c.6055_6056delGA; p.Asp2019Glnfs*15 homozygous

F = female; M = male; ND = no data; NR = not recordable; OD = right eye; OS = left eye.

* Electroretinograms (ERGs) recorded at age 13.
Five different mutations were observed in our cohort. These included two large deletions covering exons 18–19, and the other exons 46–50. Comparable deletions of this size have been previously reported (Katzaki et al. 2007; Balikova et al. 2009; Parri et al. 2010). As the latter was observed in two unrelated patients in our cohort, this might either point to a common founder of this variant, or a mutation hotspot.

The heterozygous splice site mutation c.1563G>A;p.= affecting the splice donor of intron 11 was found in patient 2, this mutation has also previously been reported in a 5 year old German/British Cohen patient (Seifert et al., 2008), and the authors confirmed that it is a true splice site mutation by RT-PCR on RNA extracted out of peripheral blood samples resulting in aberrant spliced VPS13B transcripts. The nonsense mutation found in patient 3, c.8112C>G p.Tyr2704* has not been previously reported. The same holds true for the 2 bp deletion found in the sibling patients 4 and 5, VPS13B c.6055_6056delGA; p.As2019Glnfs*15. This was a family with roots in Syria but living in Germany.

According to Wang et al. (2016), correlations between genotype and phenotype have not been identified. Our cohort is too small to speak on specific corrections.

In conclusion, our study shows phenotypic variability and heterogeneity in the extremely rare Cohen syndrome and adds two new mutations to the long list of variants causing this rare syndrome. Ophthalmological symptoms such as night blindness and photophobia at a young age, with high myopia, early cystoid oedema in the OCT and a bull’s eye macula in funduscopy, indicate, in combination with particular facial features and tapered fingers, a suspected Cohen syndrome. Progression should be routinely monitored and the patient’s visual aid requirements regularly considered (Garcia-Ballesta et al. 2004; Chandler & Clayton-Smith 2010; Wang et al. 2016).

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