Novel disease-causing variants and phenotypic features of X-linked megalocornea

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ABSTRACT

Purpose: The aim of the study is to describe the phenotype and molecular genetic causes of X-linked megalocornea (MGC1). We recruited four British, one New Zealander, one Vietnamese and four Czech families.

Methods: All probands and three female carriers underwent ocular examination and Sanger sequencing of the *CHRDL1* gene. Two of the probands also had magnetic resonance imaging (MRI) of the brain.

Results: We identified nine pathogenic or likely pathogenic and one variant of uncertain significance in *CHRDL1*, of which eight are novel. Three probands had ocular findings that have not previously been associated with MGC1, namely pigmentary glaucoma, unilateral posterior corneal vesicles, unilateral keratoconus, and unilateral Fuchs heterochromic iridocyclitis. The corneal diameters of the three heterozygous carriers were normal, but two had abnormally thin corneas, and one of these was also diagnosed with unilateral keratoconus. Brain MRI identified arachnoid cysts in both probands, one also had a neuroepithelial cyst, while the second had a midsagittal neurodevelopmental abnormality (cavum septum pellucidum et vergae).

Conclusion: The study expands the spectrum of pathogenic variants and the ocular and brain abnormalities that have been identified in individuals with MGC1. Reduced corneal thickness may represent a mild phenotypic feature in some heterozygous female carriers of *CHRDL1* pathogenic variants.

KEY WORDS: *CHRDL1*, brain MRI, megalocornea, heterozygous carriers, keratoconus, posterior corneal vesicles

Introduction

X-linked megalocornea (MGC1; OMIM # 309300) is characterised by congenital bilateral enlargement of the anterior segment of the eye with a horizontal corneal diameter of ≥13 mm after the age of two years, with reduced corneal thickness, an abnormally deep anterior chamber, and normal intraocular pressure (IOP). Other features that develop with age include corneal arcus, mosaic stromal corneal degeneration (shagreen), iris changes and cataract (Meire et al. 1991; Meire 1994; Roche et at. 2002; Webb et al. 2012). These features have not been reported in female carriers although detailed corneal imaging has not been presented (Mackey et al. 1991; Davidson et al. 2014). MGC1 is not associated with systemic disease, although magnetic resonance imaging (MRI) has identified structural brain abnormalities, with the focal loss of myelin in the white matter of two patients (Webb et al. 2012).

MGC1 is caused by hemizygous pathogenic variants in *CHRDL1* (Webb et al. 2012). This gene encodes chordin-like protein 1, an antagonist of bone morphogenetic protein 4 (BMP4), which has a role in embryonic bone formation, regulation of retinal angiogenesis, neuronal differentiation and development of the anterior segment of the eye (Nakayama et al. 2001; Sakuta et al. 2001; Webb et al. 2012; Liu et al. 2019). To date, 21 different *CHRDL1* disease-causing variants have been identified, predicted to result in loss-of-function (Davidson et al. 2014; Pfirrmann et al. 2015). In this study we report seven novel *CHRDL1* pathogenic/likely pathogenic variants and describe ocular features that have not previously been observed in individuals with MGC1. Importantly, we suggest that some heterozygous female carriers can have mild corneal thinning.

Materials and Methods

The study was approved by institutional review boards of the General University Hospital in Prague (964/15 S-IV), the NHS Health Research Authority (17/LO/167) and the Ministry of

Health, Northern A Health and Disability Ethics Committee, Auckland (NTX/06/12/161) and we adhered to the principles of the Declaration of Helsinki. Ten probands and all affected and unaffected first-degree relatives that agreed to participate were included into the study. Each participant, or their legal guardian, provided informed consent prior to enrolment. Clinical examination included Snellen best corrected visual acuity (BCVA) converted to decimal values, slit lamp biomicroscopy and IOP measured by applanation tonometry. Corneal tomography was assessed by Scheimpflug imaging (Pentacam, Oculus, Wetzlar, Germany) and/or spectral domain optical coherence tomography (SD-OCT) (Spectralis, Heidelberg Engineering GmbH, Heidelberg, Germany), which was also used for measurement of the retinal nerve fibre layer (RNFL). Corneal ectasia was detected by the Pentacam build-in software utilizing Topographic Keratoconus Classification (TKC) with following grading TKC: 1 early disease, TKC: 1–2, 2, moderate, TKC: 2-3, 3, 3-4, 4, severe) (Wahba et al. 2016; Goebels et al. 2017). Horizontal white-to-white (WTW) corneal diameter, axial length (AL) and anterior chamber depth (ACD) were recorded (IOL-Master V.5, Carl Zeiss Meditec AG, Jena, Germany). Endothelial cell density was assessed by specular microscopy (Topcon SP-3000P, Topcon Corp, Tokyo, Japan, or Noncon ROBO Pachy SP-9000, Konan Medical Inc, Irvine, CA, USA).

MRI was performed on two probands. The first was examined with a 3 Tesla (T) MRI scanner (MAGNETOM Skyra, Siemens Healthcare, Erlangen, Germany). The protocol comprised 3D T1 magnetization-prepared rapid acquisition with gradient echo (MPRAGE), 3D fluid attenuated inversion recovery (FLAIR), 2D T2 weighted images (T2WI) and diffusion weighted images (DWI). Whole brain volume and regional brain volumes were measured. The second proband was examined on a 1.5T MRI scanner (Achieva, Philips Healthcare, Best, the Netherlands) with a protocol that comprised 2D FLAIR, 2D T2WI and DWI.

We performed Sanger sequencing of the entire coding region of *CHRDL1* gene (reference sequence NM_001143981.2) in all probands (Webb et al. 2012). Direct sequencing was then

used to confirm the identified pathogenic/likely pathogenic variant in available relatives. Evaluation of variant pathogenicity was based on evidence categories outlined by the American College of Medical Genetics and Genomics (ACMG) (Richards et al. 2015). Briefly, because the disease-causing mechanism for MGC1 is known (loss-of-function), frameshifting variants and variants located in canonical splice sites, conserved essential cysteine residues, and nonsense variants were considered pathogenic unless located in the last coding exon. For the missense variants that does not alter a cysteine residue, *in silico* analysis was performed using a range of tools including assessment of the possible effect on pre-mRNA splicing. General population frequency of the detected sequence changes was mined from gnomAD v.2.1.1. (Karczewski et al. 2020). Given that MGC1 is a very rare disease (Webb et al. 2012; Davidson et al. 2014; Mackey et al. 1991), only variants with minor allele frequency ≤ 0.0005 were evaluated for possible pathogenicity.

Results

CHRDL1 variants

We detected ten rare variants in *CHRDL1*, all absent from gnomAD v.2.1.1. Two of the sequence changes have been described previously as a cause of MGC1, eight were novel (Table 1, Fig. 1). Three novel missense changes were identified, c.207G>C; p.(Glu69Asp) in proband 5, c.436T>G; p.(Cys146Gly) in family 7 and c.968G>T; p.(Cys323Phe), that were predicted to be pathogenic by the majority of the algorithms used (Supplementary Table 1 and 2). The cysteine residues within the highly conserved cysteine-rich von Willebrand factor type C domains are hot-spots for pathogenic variants in X-linked megalocornea (Davidson et al. 2014). The substitution c.207G>C; p.(Glu69Asp) was located at the intron/exon boundary so we hypothesized that it may affect pre-mRNA splicing rather than exerting a pathogenic effect through changing the amino acid at position 69. Of the four algorithms used for assessing splicing, two predicted that the variant abolishes the splice donor site (Supplementary Table 2). According to the ACMG standards the p.(Glu69Asp) was classified

as a variant of uncertain significance (Richards et al. 2015). The remaining variants were frameshift (x1), nonsense (x3) or affecting the canonical splice site positions +1 and +2 (Table 1) and are predicted to lead to loss-of-function.

Ocular phenotype of affected males

Males with hemizygous *CHRDL1* pathogenic variants displayed the characteristic phenotype of MGC1 with an increased horizontal corneal diameter (range 13.5-16.0 mm), a reduced central corneal thickness (CCT) (range 354-456 µm), and an abnormally deep anterior chamber (range 4.66-6.31 mm) (Fig. 2A, D, E). Iris atrophy was documented in 7 of 10 patients. Other phenotypic features such as arcus, cataract and shagreen varied according to the age of the proband (Fig. 2B, C).

Of note were the additional clinical findings in four probands. The proband from family 5 developed visual field defects at age 39 years from bilateral secondary glaucoma. Optic disc cupping and RNFL loss from advanced glaucoma was present in the left eye (Table 2). Gonioscopy showed pigment deposition in the angle and fine vessels crossing the trabecular meshwork. In addition to medical therapy, selective laser trabeculectomy was required to control the IOP in the left eye.

Patient II:1 from family 7 (Fig. 1) was noted at birth to have enlarged corneas and was managed as a glaucoma suspect until the age of 6 years, when he was discharged. He was referred again at the age of 39 years because of raised IOP in the right eye. At examination the best corrected visual acuity BCVA was 1.0 bilaterally and the IOP was 22 mmHg in the right eye and 13 mmHg in the left eye. There were two bands at the level of Descemet membrane in the right cornea, initially considered to be Haab striae secondary to arrested congenital glaucoma, but more likely to be linear posterior corneal vesicles (PCVs) (Fig. 2F). He had bilateral iris transillumination defects with pigment dispersion, and left Fuchs heterochromic iridocyclitis manifesting as stellate keratic precipitates and pigment dispersion,

which we thought was unrelated to the MGC1 phenotype. With gonioscopy, both anterior chamber angles were noted to be underdeveloped with fine vessels crossing the trabecular meshwork (Fig. 2G). The optic discs were mildly asymmetric (cup disc ratio 0.2 right eye, 0.3 left eye) but the visual fields were normal. He had an uneventful bilateral phacoemulsification with intraocular lens insertion at age 43 and 47 years, respectively. He is currently managed as a glaucoma suspect on treatment with timolol 1mg/g gel once daily to both eyes.

The proband from family 8, who had no family history for MGC1 or keratoconus, was noted to have abnormal eyes from birth and was diagnosed with MGC1 at age 21 years, when he was also noted to have advanced keratoconus in the left eye with typical inferotemporal corneal steepening and thinning (TKC grade 3-4). The keratoconus did not progress over the subsequent 10 years and he has not developed ectasia of the right cornea. The most recent central corneal thickness (CCT) measurements were 418 μm in the right eye and 411 μm in the left eye taken when the proband was aged 31 years (Fig. 2H, I). At this examination, the BCVA with scleral contact lenses was 1.0 bilaterally, but he had developed a left exotropia with diplopia.

The proband from family 9 was aware that he had abnormal eyes but the diagnosis of MGC1 was not made until he was referred with cataract at age 52 years. He had an uncomplicated left phacoemulsification with intraocular lens implantation, but subsequently there was partial zonular dehiscence with phacodonesis that caused uveitis, intraocular bleeding and secondary glaucoma [Uveitis-Glaucoma-Hyphaema (UGH) syndrome]. This could not be controlled with medical therapy and glaucoma tube drainage surgery was performed at age 56 years, with a vitrectomy and removal of the intraocular lens at age 57 years.
Ocular findings in the affected males including additional, and possibly related but previously unreported features in MGC1, are summarized in Table 2.

Ocular phenotype of carrier females

We were also able to examine three females confirmed to be heterozygous carriers of *CHRDL1* pathogenic variants. Individual II:4 from family 4 (Fig. 1), was noted to have keratoconus pattern on corneal topography in the right eye at the age of 26 years during an assessment for laser refractive surgery. She had no known allergies. At age 36 years her BCVA was 1.0 bilaterally. In addition to mild right keratoconus on corneal topography with an asymmetric bowtie and inferior steepening (TKC grade 1-2) (Rabinowitz et al. 1996) both corneas were abnormally thin (thinnest pachymetry 428 μm in the right and 434 μm left eye) (Table 3, Fig. 3A, B). Her sister (individual II:2), who was confirmed to be a heterozygous carrier for the same *CHRDL1* variant, also had reduced corneal thickness with a thinnest pachymetry of 466 μm in the right eye and 465 μm in the left eye (Fig. 3C, D). However, all other parameters were normal (Table 3). There was no family history for keratoconus in family 4. A third female carrier (individual I:1 from family 3) had bilaterally normal corneal thickness (Table 3) with no evidence of keratoconus.

Assessment of structural brain changes in affected males

The MRI of the proband from family 2 demonstrated an arachnoid cyst in the right temporal region and mid-sagittal malformations (cavum septum pellucidum et vergae) (Fig. 4A-C). There was also a small T2 hypersignal lesion in the white matter of the left frontal lobe (Fig. 4D). The MRI of the proband from family 5 showed small arachnoid cysts in the infratentorial and left temporal regions, and a neuroepithelial cyst in the right ventricle (Fig. 4E-G). There were also three nonspecific small T2 hyperintensity lesions in the white matter of the frontal lobes (Fig. 4H). Total brain volume and regional volumes showed no significant atrophy.

Discussion

We report twelve individuals with MGC1 from ten families and identify eight novel *CHRDL1* variants. Four of the probands had phenotypic features that have not previously been associated with MGC1. The c.207G>C p.(Glu69Asp) was considered as either a missense or splicing variant, however, in silico analysis precluded unequivocal support of this change as pathogenic, and the change is therefore listed as variant of uncertain significance. The remaining six novel pathogenic variants either lead to a frameshift, predicted to disrupt splicing or introduce a premature stop codon. Two variants were missense affecting a conserved functional cysteine residue, consistent with previous reports (Webb et al. 2012; Davidson et al. 2014).

Although subjects with MGC1 have an abnormal anterior segment and trabecular meshwork they are not considered to be at increased risk of developing glaucoma (Mackey et al. 1991; Meire et al. 1991; Webb et al. 2012; Davidson et al. 2014). However, two individuals in this series developed secondary raised IOP in their third or fourth decade, one with advanced visual field loss and one managed with topical medications as a glaucoma suspect. The mechanism is uncertain, but pigment deposition onto the trabecular meshwork may predispose the eye to aqueous outflow obstruction and secondary glaucoma (Scuderi et al. 2019). As standard IOP measurements may not be accurate due to corneal thinning and maldevelopment, regular RNFL measurement as a non-invasive examination might be of benefit to the MGC1 patients. One of the individuals reported in the current study had Fuchs heterochromic iridocyclitis, which is also a risk for secondary glaucoma and may share other overlapping features with MGC1 such as early-onset cataract (Mohamed et al. 2005). A third individual developed glaucoma secondary to a dislocated intraocular lens implant, which was probably the result of chronic intraocular lens induced inflammation.

Unilateral keratoconus was identified in one of the twelve MGC1 individuals; although the diffusely thinned cornea in MGC1 may be a risk factor for corneal ectasia, keratoconus has

not previously been associated with MGC1 (Webb et al. 2012; Davidson et al. 2014).

We also examined three female heterozygous carriers of pathogenic MGC1 variants. Two of them, who were sisters (II:2 and II:4) from family 4, had abnormally thin corneas, and individual II:4 also had mild unilateral keratoconus. However, the female carrier I:2 from family 3 had a normal corneal thickness bilaterally.

Individuals with MGC1 have been reported to have a normal corneal endothelial cell morphology and density, consistent with an excessive growth of the cornea, rather than the reduced endothelial cell density that follows the IOP-induced distension associated with congenital glaucoma (Skuta et al. 1983). In individual II:1 from family 7, who was a glaucoma suspect, we identified linear lesions at the level of Descemet membrane with a reduced corneal endothelial cell density, an appearance that we considered was consistent with PCVs (Pardos et a. 1981; Noguchi et al. 2018). However, we recognise that further studies are required to confirm whether these observations represent an expanded phenotype for MGC1 or are chance associations.

The pigment dispersion that is a feature of MGC1 is usually accompanied by iris transillumination defects, which are common in adults with MGC1. It is unclear whether the abnormal appearance of the iris is the result of congenital iris hypoplasia or secondary atrophy. We suspect that the mechanism for the pigment dispersion in MGC1 is distinct from the abnormal iris and zonule contact with the lens that is thought to be the cause for the more common pigment dispersion syndrome (Scuderi et al. 2019). However, although we documented iris abnormalities as early as nine years of age, we are not aware of documented reports of iris abnormalities in infants with MGC1.

Brain MRI has previously been reported in two individuals with MGC1, in which 3T scans and voxel-base morphometry demonstrated a reduction in the white matter volume but with tract

integrity that did not compromise brain function (Webb et al. 2012). In the current study we performed brain MRI on two additional unrelated individuals with MGC1. As well as the previously reported nonspecific changes in the white matter (Webb et al. 2012), we detected arachnoid cysts, a neuroepithelial cyst, and a midsagittal neurodevelopment pathology.

In conclusion, we have expanded the spectrum of pathogenic variants in *CHRDL1* and identified additional phenotypic features in individuals with MGC1. Our study suggests that heterozygous female carriers may show a minimal phenotype represented by corneal thinning possibly, evolving into a keratoconus pattern in some individuals. Brain MRI confirmed the presence of structural abnormalities in MGC1, but our data also show previously unreported findings. The recruitment and assessment of further affected individuals and carriers is required to ascertain the association of these ocular and brain abnormalities in MGC1 cohorts.

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Conflicts of Interest

The authors declare no conflict of interest.

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Fig. 1. Pedigrees and sequence chromatograms of *CHRDL1* variants identified in ten families with X-linked megalocornea. Variant status is shown in all affected individuals as well as family members that were available for genotyping.

Fig. 2. Ocular findings observed in males with X-linked megalocornea. A) Lateral photograph documenting enlarged corneal diameter and deep anterior chamber (left eye), B) slit-lamp photograph showing iris hypoplasia and arcus (arrow) (right eye), and C) mosaic stromal corneal degeneration (shagreen) (right eye); individual IV:1, family 5, age 40 years. D) diffuse reduction in corneal thickness imaged with spectral-domain optical coherence tomography (right eye) and E) deep anterior chamber on Scheimpflug image (right eye); individual II:1, family 2, age 47 years. Photograph showing linear bands at the level of Descemet membrane (white arrows) in direct illumination (right eye) (F), and the anterior chamber angle with pigment deposited on the trabecular meshwork (right eye) (G), of individual II:1, family 7, age 38 years. Front sagittal curvature, pachymetry and posterior elevation maps of the right (H) and left eye (I) of individual II:1, family 8, age 31 years; note inferonasal steepening and thinning in the left eye confirming the presence of keratoconus.

Fig. 3. Corneal tomography of two female heterozygous carriers. Front sagittal curvature, pachymetry and posterior elevation maps of the right (A) and left eye (B) of female II:4 from family 4 and the right (C) and left eye (D) of female II:2 from family 4. Note inferior steepening in A and thinning in A-D.

Fig. 4. Brain magnetic resonance imaging of two individuals with X-linked megalocornea. A) Proband from family 2; an arachnoid cyst in the right temporal region, B) cavum septum pellucidum and C) cavum vergae, D) hyperintensity lesion in the white matter of the left frontal lobe (red arrows). E) Proband from family 5; small left arachnoid cysts in the infratentorial and F) temporal regions, G) neuroepithelial cyst in the right ventricle, H) hyperintensity lesion in white matter of the frontal lobes (red arrows).