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A Novel KIF11 Mutation in a Turkish Patient with Microcephaly, Lymphedema, and Chorioretinal Dysplasia from a consanguineous family

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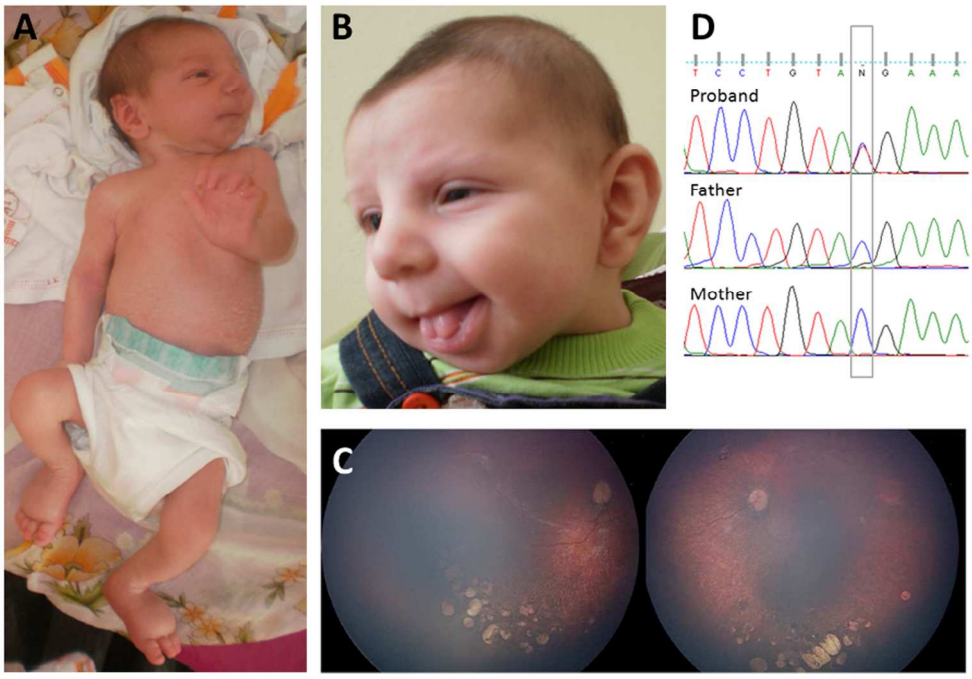

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Clinical Report

A Novel *KIF11* Mutation in a Turkish Patient with Microcephaly, Lymphedema, and Chorioretinal Dysplasia from a consanguineous family

Abstract

Microcephaly-lymphedema-chorioretinal dysplasia syndrome is a rare syndrome that was first described in 1992. Characteristic craniofacial features include severe microcephaly, upslanting palpebral fissures, prominent ears, a broad nose and a long philtrum with a pointed chin. Recently, mutations in *KIF11* have been demonstrated to cause dominantly inherited Microcephaly-lymphedema-chorioretinal dysplasia syndrome. Herein, we present a patient with Microcephaly-lymphedema-chorioretinal dysplasia syndrome whose parents are first cousins. The parents are unaffected, so a recessive mode of inheritance for the disorder was considered likely. However, the proband carries a novel, *de novo* nonsense mutation in exon 2 of *KIF11*. The patient also had midline cleft tongue which has not previously been described in this syndrome.

Keywords: Microcephaly lymphedema chorioretinal dysplasia syndrome; *KIF11*; novel mutation; midline cleft tongue

INTRODUCTION

Microcephaly-lymphedema-chorioretinal dysplasia (MLCRD) syndrome is first described by Feingold and Bartoshesky [1992]. These authors reviewed previously reported patients with different variants of microcephaly, lymphedema, chorioretinal dysplasia and suggested these patients might represent one variable expression of a single entity (MLCRD, #MIM 152950).

To date only few patients with microcephaly lymphedema and/or chorioretinal dysplasia have been reported [Leungh et al., 1985; Feingold and Bartoshesky, 1992; Angle et al., 1994; Kozma et al., 1996; Limwongse et al., 1999; Casteels et al., 2001; Vasudevan et al., 2005; Eventov-Friedman et al., 2009; Hatt Brupbacher et al., 2009; Ostergaard et al., 2012]. Vasudevan et al. [2005] reviewed previous patients with MLCRD syndrome and concluded that this syndrome is associated with distinctive facial features including severe microcephaly, upslanting palpebral fissures, prominent ears, a broad nose with rounded nasal tip and a long philtrum with a pointed chin.

Chorioretinal dysplasia, microcephaly, mental retardation syndrome (CDMMR MIM# 156590) and MLCRD syndrome have some overlapping phenotypic features [Fryns et al., 1995; Ostergaard et al., 2012]. Microcephaly is the essential component of both syndromes. Mild and severe mental retardation has been reported in both MLCRD and CDMMR syndromes [Vasudevan et al., 2005; Ostergaard et al., 2012]. The presence of lymphedema is the diagnostic feature of MLCRD syndrome. Until 2012, molecular defects causing these syndromes were not known and the inheritance patterns were uncertain. Recently, Ostergaard et al. [2012] have revealed that heterozygous mutations in *KIF11* are responsible for both MLCRD and CDMMR syndromes.

Herein, we report a further MLCRD patient with a novel nonsense mutation in *KIF11*.

CLINICAL REPORT

Patient

The male patient was the third child of consanguineous Turkish parents (first cousins). He had two healthy sisters. Prenatal ultrasonography (USG) at 26 weeks gestation showed polyhydramnios and cardiac hypertrophy. Fetal karyotype analysis was recommended, but it was refused by the parents. Thereafter, the mother did not partake in regular prenatal visits. The patient was born at term by spontaneous vaginal delivery. His birth weight was 3250 g (~ 50th centile), height 50 cm (50th centile) and head circumference 31.5 cm (<3rd centile). The following were detected on physical examination: a sloping forehead; upslanting palpebral fissures; large posteriorly rotated ears with large ear lobes; bulbous nose; anteverted nares; full cheeks; long philtrum; thin upper lip; thick lower lip and a midline cleft tongue and he had edema on the dorsum of the feet (Fig.1A, B). Neurological assessment was normal. Fundoscopic examination revealed bilateral optic atrophy and bilateral chorioretinopathy on the 7th postpartum day. Laboratory tests including complete blood count, electrolytes, liver enzymes, urea, creatinine, thyroid hormones, TORCH (Toxoplasmosis, Rubella, Cytomegalovirus, and Herpes simplex virus) screening, urine and blood amino acid chromatography were normal. Abdominal, cranial USG and cranial magnetic resonance imaging (MRI) were normal. Postnatal echocardiography revealed a patent foramen ovale. His karyotype was normal.

The patient was re-examined at 1st, 3rd and 6th months of age. Head circumference was 33 cm at the 1st month (-1.98SD), 34.5 cm at the 3 months (-3.4SD) and 37 cm at 6 months (-4.5SD). All other growth parameters were normal. Edema on the dorsum of the feet was present at every subsequent follow-up examination. Motor development was consistent

with his age. He could appropriately follow objects at 6 months. Visual acuity evaluated by preferential looking test using Teller acuity cards, was 20/360 in the right eye and 20/670 in the left eye. Orthoptic assessment with Hirschberg and alternate cover test was normal. Anterior segment examination was unremarkable while fundoscopy revealed bilateral optic atrophy with paucity of retinal vessels and bilateral chorioretinopathy (Fig. 1C). Mild myopia was detected on cycloplegic retinoscopy. When the patient was 9 months of age, bilateral subnormal scotopic and photopic responses with delayed flicker timing were detected by electroretinogram. Head circumferences and ophthalmological assessments of parents and two siblings were normal. There were no other family members with similar features to the patient.

Mutational Analysis

Direct gene sequencing of all 22 exons and their flanking introns of *KIF11* was performed using methods described previously [Ostergaard et al., 2012]. A heterozygous c.139C>T mutation in exon 2 was identified in the proband, but both parents were mutation negative (Fig. 1D). The observed base change at this position leads to a nonsense mutation (p.Arg47*) and will lead to premature termination of the KIF11 protein product. The variant was not present in dbSNP and it was not observed in a cohort of >600 control samples primarily of European origin.

DISCUSSION

MLCRD syndrome is an autosomal dominant hereditary disease, which shares many clinical features with CDMMR syndrome [Ostergaard et al., 2012]. These authors first identified heterozygous mutations in *KIF11* in three unrelated patients with MLCRD syndrome using whole exome sequencing. Subsequently, they found additional patients with MLCRD syndrome and CDMMR syndrome having different heterozygous mutations in *KIF11* using Sanger sequencing. In their study, fourteen heterozygous mutations (two nonsense, two splice site, four missense, and six indels causing frameshifts) in *KIF11* were reported [Ostergaard et al., 2012]. Two of them were *de novo*. The MLCRD patient in the present study was from a consanguineous marriage and there would have been an initial supposition that this was most likely to be a recessively inherited condition. In fact, the proband has a novel, nonsense mutation which was not detected in either parent, and is a *de novo,* dominantly acting change in *KIF11*.

MLCRD syndrome and CDMMR syndrome are allelic disorders. The distinctive feature of MLCRD syndrome is the presence of lymphedema. The lymphedema presents at birth and is commonly seen in lower limbs, particularly on the dorsum of the feet. The lymphedema is usually persistent, but responds well to compression garments in affected patients [Ostergaard et al., 2012]. Our patient had also lympedema on the dorsum of the feet which presented at birth. We recommended compression garments to treat lymphedema.

The ocular findings of MLCRD syndrome are peripheral retinal pigmentation, retinal folds, chorioretinopathy, optic atrophy and macular degeneration. There have been a few reports of patients with vision problems [Limwongse et al., 1999; Casteels et al., 2001 Eventov-Friedman et al., 2009; Hatt Brupbacher et al., 2009]. Normal vision in the presence of peripheral retinal pigmentation has been reported in some patients [Limwongse et al., 1999;

Eventov-Friedman et al., 2009]. Chorioretinopathy was described as the most common and highly specific finding in patients with *KIF11* mutations [Ostergaard et al., 2012]. Retinal folds, microphthalmia and optic atrophy were not detected in 19 patients with MLCRD syndrome and 8 patients with CDMMR syndrome described previously [Ostergaard et al., 2012]. In our patient, both bilateral optic atrophy and bilateral chorioretinopathy were observed on fundoscopic examination but he could follow objects with his eyes. The nonsense mutation, p.Arg47*, detected in the patient may be associated with bilateral optic atrophy, or this could be a chance association.

Normal to mild and severe mental retardation has been reported in MLCRD patiens [Vasudevan et al., 2005, Ostergaard et al., 2012]. However, it was not possible for us to evaluate precisely this aspect of development in our patient because of his young age. Most of the patients with MLCRD syndrome are generally characterized by normal growth [Eventov-Friedman et al., 2009]. Our patient's early motor development was normal.

Prenatal ultrasonographic findings have not been reported in the majority of patients with MLCRD syndrome. However, nuchal thickness, microcephaly, intrauterine growth retardation have been detected in a number of fetuses [Fryns et al., 1995; Casteels et al., 2001; Eventov-Friedman et al., 2009; Vasudevan et al., 2005]. Additionaly, congenital heart defects including atrial septal defect, ventricular septal defect and right aortic arch have been reported in four patients to date [Limwongse et al., 1999; Casteels et al., 2001; Strauss et al., 2005; Eventov-Friedman et al., 2009]. One of these four patients has been described by Strauss et al. [2005] and reviewed by Vasudevan at al. [2005]. In our patient, polyhydramnios and cardiac hypertrophy were detected by prenatal USG. However, postnatal USG revealed a patent ductus arteriosus but cardiac hypertrophy was excluded.

Vasudevan et al. [2005] reviewed previous patients with different combinations of microcephaly, chorioretinal dysplasia and lymphedema and concluded that MLCRD syndrome is associated with distinctive facial features including severe microcephaly, upslanting palpebral fissures, prominent ears, a broad nose with rounded nasal tip and a long philtrum with a pointed chin. All these characteristic facial features were present in our patient. Additionally he had a midline cleft tongue not previously described in this syndrome.

Study of additional MLCRD and CDMMR syndrome patients with mutations in *KIF11* may help to establish phenotype-genotype correlation.

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Fig. 1. Clinical features of the proband and sequencing chromatogram. **A:** The patient at the age of seven days. Note sloping forehead, posteriorly rotated ears, large ear lobes, and edema over the dorsum of the feet. **B:** The patient at the age of six months. Note a midline cleft tongue. **C:** Clinical fundoscopic photographs representing bilateral optic atrophy with paucity of retinal vessels and bilateral chorioretinopathy. **D:** Chromatogram of the heterozygous change, c.139C>T, in the proband (upper trace). Both parents (middle and bottom trace) are wild type at this position.