**Abstract**

Megalocornea is a defining feature of megalocornea-mental retardation (MMR) syndrome, also called Neuhäuser syndrome, a rare condition of unknown etiology. Here we describe a family with two sons, who were diagnosed with megalocornea, mild mental subnormality and microcephaly, in addition to limb anomalies in the form of clinodactyly in the younger brother, while extradigit and clinodactyly was seen in the older brother. Parents are second degree cousins with no obvious family history of similar problems. Mutations in \( \text{CHRDL1} \) are known to cause X-linked megalocornea (MGC1) and \( \text{FOXC1} \) mutations cause a wide range of syndromic or non-syndromic anterior segment dysgeneses (ASD) phenotypes. Sanger sequencing of \( \text{CHRDL1} \) and \( \text{FOXC1} \) did not identify any potential disease causing variants in this family.

**Conclusions:** Megalocornea-mental retardation (MMR) syndrome is a genetically and phenotypically heterogeneous condition. In this Egyptian family, \( \text{CHRDL1} \) and \( \text{FOXC1} \) have been excluded as the cause. Next generation sequencing is required to identify the genetic cause of the syndrome in this family.
Table 1: Clinical features of MMR syndrome as described in various studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of cases</th>
<th>Mental and motor retardation</th>
<th>Megalocornea</th>
<th>Hypotonia</th>
<th>Craniofacial Abnormalities</th>
<th>Epilepsy/EEG</th>
<th>Neuroimaging Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frank et al. 1973 [15]</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neuhouser et al. 1975 [16]</td>
<td>7</td>
<td>7</td>
<td>4</td>
<td>5</td>
<td>7</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Schmidt R, Rapin, 1981 [18]</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Del Giudice et al. 1987 [5]</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Raas-Rothshild et al. 1988 [19]</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Granbech-Jensen 1989 [20]</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Frydman et al. 1990 [21]</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Kimura et al.1991 [22]</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Tometny et al. 1991 [23]</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Santolaya et al. 1992 [24]</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>4</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Verloes et al. 1993 [25]</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Antinolo et al. 1994 [26]</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Gibbs et al., 1994 [27]</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Barisic et al. 1996 [28]</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Naritomi et al. 1997 [29]</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>Not specified</td>
<td>Not specified</td>
<td>Not specified</td>
</tr>
<tr>
<td>Tominaga et al. 1999 [30]</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>Not specified</td>
<td>Not specified</td>
<td>Not specified</td>
</tr>
<tr>
<td>Sarkozy et al. 2002 [31]</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Balci et al. 2002 [32]</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>Not specified</td>
<td>Not specified</td>
<td>Not specified</td>
</tr>
<tr>
<td>Derbet et al. 2004 [33]</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

including Axenfeld–Rieger syndrome (ARS), Rieger anomaly, Peters anomaly, primary congenital glaucoma (PCG), iris hypoplasia, aniridia, with or without extracocular features such as heart defects, craniofacial abnormalities and pituitary abnormalities [8–11]. Variable expressivity and incomplete penetrance for the associated phenotypes have also been observed [12–14].

**Study Subjects and Clinical Description**

All studies were conducted in accordance with the principles of the Declaration of Helsinki. The study was approved by the local ethics committees. Informed written consent, including permission to publish photographs, was obtained from all participating individuals or parental guardians on behalf of the minors enrolled in this study. Blood samples were donated participating individuals or parental guardians on behalf of the minors enrolled in this study. Blood samples were donated

He is the product of normal pregnancy with no complications, born by normal vaginal delivery, birth weight was 3.000 kg with no neonatal unit admission needed. The mother had taken folate acid supplement in the 1st trimester and inconsistent iron and calcium supplements. Foetal movements were felt by 16th week gestation with normal frequency and normal pregnancy scans. He is currently (2 years of age) suffering delayed walking (walking with support) and speech is developing more or less appropriately (about 10 words).

Hypertelorism, megalocornea, long philtrum, broad nasal root, recession of chin and forehead, fusiform fingers of hands, clinodactyly 2nd–3rd fingers (Lt hand) are evident (Figure 2). Complete simian crease in the left hand and low set prominent ears are present. Mouth examination showed normal palate, uvula and teeth. He has evidence of scoliosis with normal abdomen and chest.

Neurological examination revealed decreased motor power in both upper and lower limbs (grade II to grade IV) with moderate hypotonia, and normal deep reflexes. No obvious abnormalities in external genitalia were seen.

Ophthalmological examination revealed a corneal diameter of 14mm in Rt eye and 15 mm in left eye, moderate myopia, hypotrichosis, normal ocular reflexes with normal fundus and intraocular pressure. Head circumference was 43.5 cm (far < 5th), Height was 82 cm (0.4th) and weight was 8.5 kg (<0.4th).

The older brother has better developmental history with mild delay compared to the younger brother. He has 5 years, increased corneal diameter (13mm bilaterally), normal fundus, myopia with right convergent squint, hypertelorism, long philtrum, and mild hypotonia with normal reflexes (Figure 3).

Broad nasal root was evident, with history of an extra finger beside the little finger on the left hand, which was removed at the age of 6 months. There were variable toe insertion levels.

in both feet. Chest, abdomen, genitalia, skin, and back were normal. His head circumference was 49 cm (far < 5th centile), height was 98 cm (about 25th centile) and his weight was 15 kg (25th-50th centile) at birth. He started walking at 1 2/12, had head support at the age of 7 months, and was sitting by 9 months of age. He had 4 words of speech at the age of 1 year.

He is the product of normal pregnancy with normal scans and foetal movements, and normal vaginal delivery. Birth weight was 3.100 kg. He had mild neonatal jaundice and was incubated for 3 days for phototherapy.

Molecular genetic analysis

All CHRDL1 and FOXC1 exons and intron-exon boundaries were directly Sanger sequenced from PCR amplimers as previously described [1,34]. No mutation was identified in CHRDL1 or FOXC1 in the two affected brothers.

Discussion and Conclusion

MMR syndrome is a phenotypically heterogeneous condition, with megalocornea and ID as pathognomonic features. Other clinical manifestations include neurological, craniofacial, digital anomalies and so forth. The genetic cause of MMR is yet to be fully elucidated. The similar ratio of reported male to female patients indicates no sex bias and therefore suggests an autosomal recessive or a de novo inheritance mode [16, 5, 21, 24, 25]. Interestingly, a recent study identified a missense mutation, p.(Cys155Tyr) in the CHRDL1 gene in a male patient with a diagnosis of MMR syndrome [3]. However, extraocular phenotypes have not been observed in any previously reported MGC1 patients with confirmed CHRDL1 mutations. This finding suggests that in this patient, MMR may be a digenic condition, where CHRDL1 mutation accounts for the ocular phenotype, and the genetic cause of the extraocular phenotypes remains unexplained. FOXC1 is a ubiquitously expressed transcription factor, which regulates cell viability and resistance to oxidative stress in the eye [35,36]. FOXC1 mutations have been associated with a wide range of ASD, such as ARS, a genetically diverse group of developmental disorders, including peters anomaly, aniridia, and PCG, which affect several anterior segment structures of the eye, with a high risk of blindness due to glaucoma [37]. In addition to ocular findings, systemic anomalies such as ID, hypotonia, facial dysmorphism, and bilateral sensorineural deafness have been described in patients with 6p25 microdeletion, which encompassed the FOXC1 gene [38]. These mutations were encountered to be associated with carcinogenesis mainly breast cancer and melanoma by activating MST1R/P13K/AKT [39-40]. Follow up of affected brothers is done regularly by systemic clinical examination and some laboratory tests including full blood count and occult blood in stools.

In this study, two brothers diagnosed with MMR syndrome were recruited suggesting X-linked or recessive inheritance of the condition. No mutation was identified in the CHRDL1 or FOXC1 genes by Sanger sequencing of the coding regions, however the genes cannot be fully excluded as copy number variations or mutations in non-coding regions were not tested using this approach. Due to the rarity of this condition, next generation sequencing (NGS) in a cohort of MMR patients is essential to identify the underlying genetic cause(s) of this poorly understood syndrome.

Funding

This work was funded by UCL Ophthalmology institute, London and National Research centre, Egypt.
References


