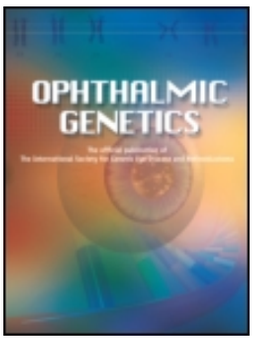

Ophthalmic Genetics

ISSN: 1381-6810 (Print) 1744-5094 (Online) Journal homepage: https://www.tandfonline.com/loi/iopg20

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To cite this article: Khaled K. Abu-Amero, Altaf A. Kondkar, Mustafa A. Salih, Muneera Al-Husain, Muneera Al Shammari, Ghassan Zeidan, Darren T. Oystreck, Ali M. Hellani, Amal Y. Kentab & Thomas M. Bosley (2013) Ophthalmologic Observations in a Patient with Partial Mosaic Trisomy 8, Ophthalmic Genetics, 34:4, 249-253, DOI: 10.3109/13816810.2012.762933

To link to this article: https://doi.org/10.3109/13816810.2012.762933

Published online: 13 Feb 2013.

Ophthalmic Genetics, 2013; 34(4): 249–253

ISSN: 1381-6810 print / 1744-5094 online
DOI: 10.3109/13816810.2012.762933

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CASE REPORT

Ophthalmologic Observations in a Patient with Partial Mosaic Trisomy 8

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ABSTRACT

Background: To carefully assess the phenotype and genotype of a patient with partial mosaic trisomy 8 with particular attention to ophthalmologic features.

Methods: Ophthalmologic and neuro-ophthalmologic examination; neuroimaging; conventional karyotyping; and array comparative genomic hybridization (CGH).

Results: The proband was the only affected child of a non-consanguineous family. At birth she was noted to have facial dysmorphism including telecanthus, low set ears, prominent nares, and an everted lower lip. She had an accommodative esotropia with otherwise normal globes, optic nerves, retinae, and orbits. She also had delayed motor milestones and mild mental retardation associated with agenesis of the corpus callosum. Both karyotyping and array CGH documented mosaic partial trisomy of chromosome 8 that included all of the "q" arm and part of the proximal "p" arm.

Conclusions: This girl had a number of the classic features of mosaic trisomy 8, including an accommodative esotropia with none of the other ocular and orbital anomalies described in patients with mosaic trisomy 8. This report constitutes an initial effort to create a virtual database of patients with mosaic chromosome 8 in which careful phenotype-genotype correlation employing high resolution array CGH may help identify clues regarding the genetic etiology of ophthalmologic features of this syndrome.

Keywords: Accommodative esotropia, agenesis of corpus callosum, dysmorphism, mosaic trisomy 8

INTRODUCTION

Complete trisomy 8 is usually an early lethal condition. Trisomy 8 mosaicism is a less severe disorder with a distinct phenotypic presentation including retarded psychomotor development; moderate to severe mental retardation sometimes associated with corpus callosum agenesis; limb and skeletal anomalies including deep palmar and longitudinal plantar furrows, clinodactyly, and limitation of joint motion; facial dysmorphism with hypertelorism, broad nasal root, and eye abnormalities; and congenital heart defects.[1,2]

Mosaic trisomy 8 has not been reported in Saudi Arabia previously, and the incidence of the disorder is not known in the region. We describe a Saudi child with a rare cytogenetic presentation of mosaic trisomy 8 involving the entire "q" arm and part of the "p" arm[3] who survived past the neonatal period with a number of developmental and dysmorphic features including an esotropia.

Received 14 November 2012; accepted 13 December 2012; published online 13 February 2013

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MATERIALS AND METHODS

Conventional cytogenetic analysis on G-banded chromosomes was performed according to the standard technique on cultured lymphocytes from the father and mother, the proband, and two unaffected siblings (Figure 1A, II:4 and II:5) after obtaining informed consent. Array comparative genomic hybridization (array CGH) was performed using the Affymetrix Cytogenetics Whole-Genome 2.7M array (Affymetrix Inc., Santa Clara, CA, USA) to detect known and novel chromosomal aberrations across the entire genome. The array provides high density coverage of over 400,000 SNP markers and 2.3 million non-polymorphic markers with high density coverage across cytogenetically significant regions. The assay was performed according to the manufacturer's instructions using the reagents provided with the kit.

Array CGH data were analyzed using the Affymetrix® Chromosome Analysis Suite v1.2 (ChAS) software (Affymetrix Inc. CA, USA). In the absence of internationally recognized criteria for analysis of high resolution array CGH results, we devised new, preliminary criteria to ensure accuracy and to avoid analysis of copy number variations that are probably not pathologic. To be considered potentially pathologic, a copy number variation had to satisfy all the following criteria: (1) it was not reported in the Database of Genomic Variants (DGV; http://projects.tcag.ca/variation/) among normal controls; (2) it was not present in at least 50 healthy controls of similar ethnicity; (3) it segregated with the phenotype and was not present in unaffected family members; and (4) it included an area of the genome encompassing one or more functional genes. The threshold for gain or loss was adjusted to 10 kb.

CASE REPORT

The parents of the proband were not related, and she was the seventh child in a family with six other unaffected children (Figure 1A). After delivery she was noted to have dysmorphic facial features with telecanthus and low set ears. On examination at age 10 months, she had a prominent forehead, hypertelorism with a broad nasal root (Figure 2A), prominent nares, low-set, cupped ears with malformed helices (Figure 2B and 2C), and full lips with an everted lower lip (Figure 2D). She had clinodactyly (Figure 3A), prominent creases of the palms and soles (Figure 3B and 3C), and hypoplastic nails of the fingers and toes (Figure 3D and 3E).

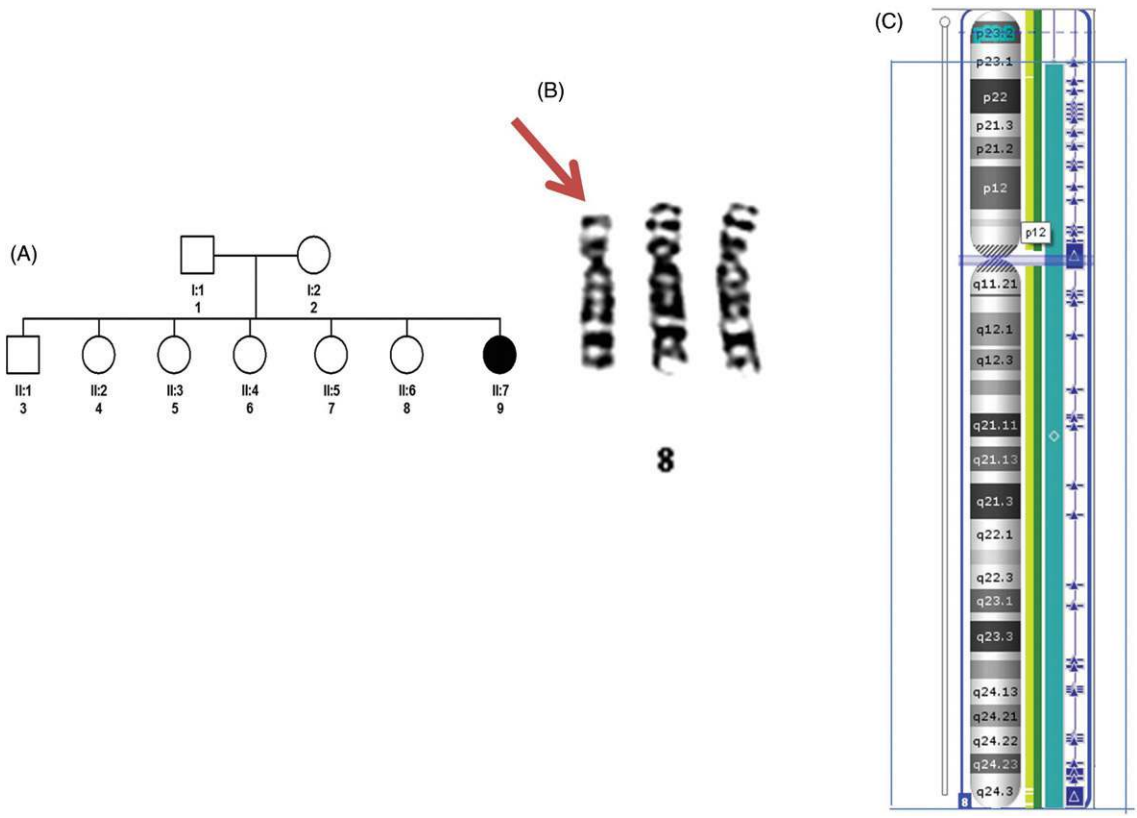

FIGURE 1. Pedigree and chromosomal studies. (A) Family pedigree; (B) traditional karyotyping showing partial trisomy of chromosome 8; (C) array comparative genomic hybridization detailing quantification of the duplicated area of chromosome 8 involving the entire long arm and a portion of the proximal short arm.

Elbow joint extension and supination was limited. Hair appeared normal and had no pili bifurcati (Figure 3F).

She developed generalized seizures during the neonatal period that were controlled with carbamazepine.

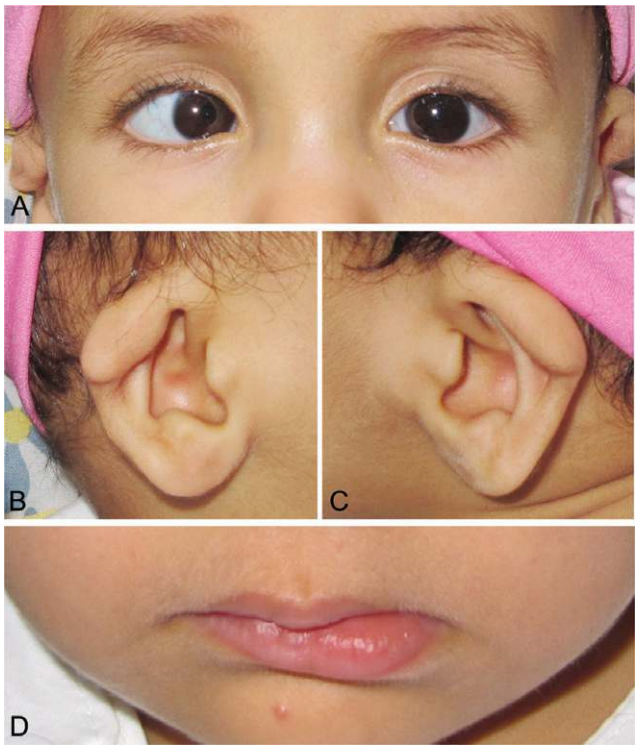

FIGURE 2. Facial features. External photos taken at age 18 months documenting (A) a broad nasal root, lids with a slight anti-mongoloid slant, and a moderate comitant esotropia; (B and C) low-set, cupped ears with malformed helices; and (D) full lips with an everted lower lip.

She had delayed developmental milestones so that at age 19 months she was sitting, standing with some support, turning over, and crawling, although she was not yet walking or talking. Brain MRI showed agenesis of corpus callosum (Figure 4) with no other major anomalies.

Her parents first noted that her eyes appeared crossed at approximately 9 months of age. Neuro-ophthalmologic examinations at ages 16 and 19 months were significant for a small, playful, visually observant baby girl with a mild anti-mongoloid slant to the lids OU (Figure 2A). Afferent visual functioning

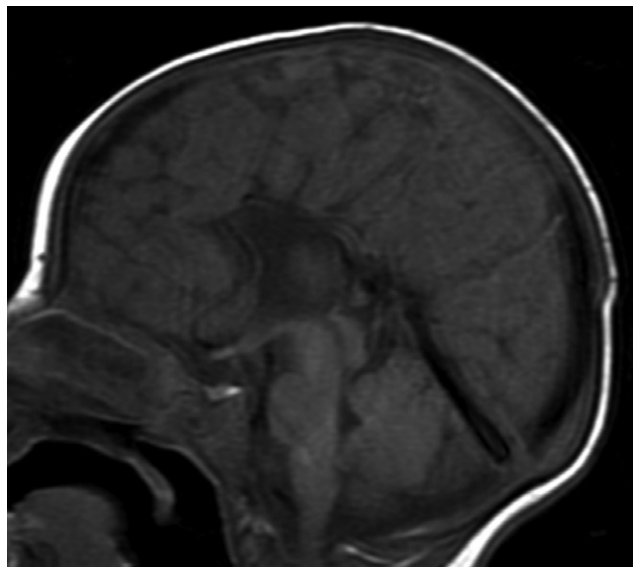

FIGURE 4. Neuroimaging. Sagittal T1-weighted MR image of the brain showing agenesis of the corpus callosum.

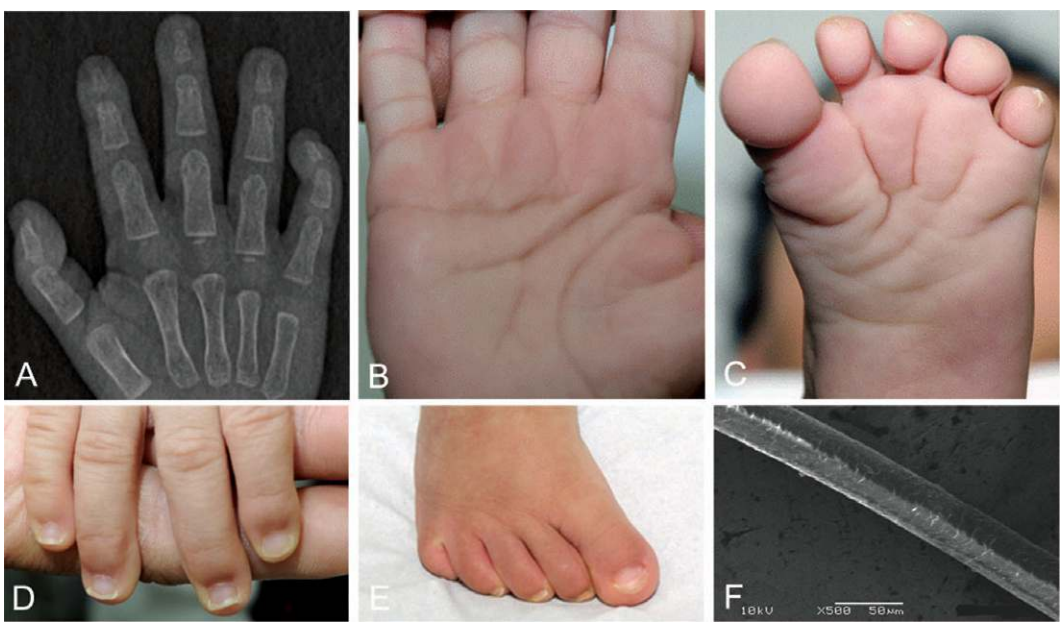

FIGURE 3. Other features. (A) Right hand X-ray showing clinodactyly of the fifth digit; (B) photograph of right hand showing deep palmar crease; (C) photography of left foot showing deep plantar crease; (D and E) photography of the dorsal surface of the right hand and left foot showing hypoplastic nails; and (F) electron microscopic image of a hair showing normal shape without pili bifurcati.

seemed excellent bilaterally; she was particularly clever at mimicking the position and movement of her examiners. Ocular anterior segments were normal bilaterally with a handheld slit lamp, and her refraction was +5.50 OU. Intraocular pressure was normal by finger tension. Optic disks, posterior poles, and retinal peripheries appeared normal on dilated fundoscopic examination. Extraocular motility was full, but she had a variable, 30 diopter comitant esotropia (Figure 2A), easily cross fixating using either eye with no nystagmus.

G-banded metaphase chromosomes revealed the presence of trisomy 8 in the proband but not her parents or unaffected siblings (Figure 1B). The extra chromosome 8 had a missing distal part of the "p" arm, and a mosaicism level of 74% was established after counting 100 cells. Array CGH confirmed partial duplication of chromosome 8 extending from 9,975,813 to 146,292,212 (total size 136,316 kb) that corresponded to duplication of cytogenetic band p23.1 to q24.3 (Figure 1C). The copy number state was equal to 2.5 throughout the duplicated area, indicating that this partial duplication was likely to be mosaic. The confidence value calculated by the ChAS software was 90% with a marker count of 105,725 spanning the duplicated area. This partial mosaic trisomy 8 was *de novo* and segregated with the phenotypic features described here because it was not detected in the proband's parents, two unaffected sisters, and 59 unrelated individuals of similar ethnicity.

DISCUSSION

The proband had a typical clinical presentation of mosaic trisomy 8[1,2] resulting in mild dysmorphism with a large forehead, a broad nasal root, low-set ears, and an everted lower lip (Figure 2). She had clinodactyly and mild contractures at both elbows, prominent creases in palms and soles, hypoplastic nails, and no pili bifurcate (Figure 3).[4]

This young girl had partial mosaic trisomy 8 encompassing the entire long arm and part of the short arm documented both by conventional karyotyping and by array CGH. Most reported cases of mosaic trisomy 8 involve the long arm of chromosome 8 and less commonly other parts of chromosome 8 or other chromosomes.[5] Chromosome 8 contains 1476 genes, and the duplicated portion of chromosome 8 in this patient included all but 19 genes located at the distal end of the short arm (8p23.1 – pter). The causative link between the clinical features of this patient and potentially abnormal expression of more than 1400 duplicated genes is currently impossible to assess accurately because relatively little is known about the effect of degree of mosaicism,[6] the phenotypic sequela of individual chromosome 8 gene overexpression,[7] the potential interaction of hundreds of overexpressed genes,[8] or the phenotypic effect of duplicated areas on chromosome 8 that include genetic regulatory elements in intronic regions.[9]

This patient has two unusual genetic features. Mosaic trisomy 8 usually involves the "q" arm and rarely the "p" arm.[5] Since she had a phenotype typical of mosaic trisomy 8, it might be plausible to hypothesize that the genes encompassed by the "p" arm duplicated area do not contribute significantly to her general phenotype. In addition, this is the first mosaic trisomy 8 patient reported with Middle Eastern ethnicity. Studying more patients with mosaic trisomy 8 from this region of the world will reveal if their genotype and phenotype routinely resemble those of other ethnicities. It is possible, for example, that involvement of the "p" arm is a more common feature in this region.

The only ophthalmologic abnormality in our patient was a moderate esotropia that was first noticed at age 9 months in the setting of substantial hyperopia. Strabismus is reported to be common in mosaic trisomy 8 (Supplementary Table 1 – available online), although some reports do not describe ocular motility in enough detail to know whether strabismus was the same as in this patient.[1] The presence of this ocular misalignment may support the concept that an accommodative esotropia is the most common ophthalmological sign of partial mosaic trisomy 8 and that this feature is quite possibly associated with trisomy of the long arm of chromosome 8, the most commonly involved portion of the chromosome.[5]

Of particular note is that the patient did not have any other ophthalmologic abnormality described with mosaic trisomy 8 (Supplementary Table 1). Previous reports most commonly have not detailed what portion of chromosome 8 was affected, leaving open the possibility that the 19 genes not duplicated at the distal end of the short arm of chromosome 8 in our patient might be responsible for the occurrence of some other ophthalmologic abnormalities. Alternative explanations include an effect of degree of chromosome 8 mosaicism (although our patient had a relatively high trisomy 8 percentage)[6] or random variability in expression of certain duplicated genes.[8]

The patient had neonatal seizures, diffuse hypotonia, and a moderate developmental delay associated with agenesis of the corpus callosum, which has been recognized as a characteristic occurrence in mosaic trisomy 8 for almost 40 years.[2] The genetic etiology of this developmental brain anomaly is unknown in trisomy 8 patients,[10] but it may be reasonable to hypothesize that abnormal expression of genes in the most commonly involved long arm of the chromosome is responsible.[6] Applying reasoning inverse

to that above, it seems unlikely that the 19 genes not duplicated in the distal short arm of the chromosome are involved.

Array CGH now offers a high resolution technique for quantification of the degree of mosaicism and accurate identification of the duplicated chromosomal region in patients with partial or complete mosaic trisomy 8. Over time, this information can be correlated with phenotypic features of additional mosaic trisomy 8 patients so that the genetic changes associated with various phenotypic features may be better understood. This report constitutes an initial attempt to create a virtual database of mosaic trisomy 8 patients that catalogues the association between types of ophthalmologic involvement, degree of mosaicism, and affected areas of the chromosome. Eventually, this effort may permit a better understanding of how expression of various genes on chromosome 8 affect development of the globes and ocular motor system, thereby increasing our understanding of the elements crucial for normal human visual and neurologic development.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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