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Partial Duplication of Chromosome 8p: Report of 5 Patients and Review of Literature

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ABSTRACT

The partial chromosome 8p duplication is a rare syndrome and is associated with a characteristic phenotype, including multiple congenital anomalies and mental retardation of various degrees. However, different outcomes depend on the size and location of the duplicated area. We present clinical and cytogenetic data of 5 Arab patients with de novo inversion duplication of 8p. This report provides additional cases to the growing literature.

Key Words:

Chromosome duplication, multiple congenital anomalies, mental retardation, phenotype

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INTRODUCTION

Partial duplication of short arm of chromosome 8 has been described in a considerable number of patients. The majority of these duplications had resulted from an unbalanced segregation of parental balanced translocations involving chromosome 8.[1-9] Carriers for this type of partial duplication are thus monosomic for other chromosomal material involved in the translocation. The phenotypic outcome depends on the amount of duplicated/deleted genetic material. Also, a considerable number of chromosome 8p rearrangements have resulted from *de novo* events; such as tandem duplications of 8p, deletions of 8p23, pericentric inversions 8 (p23 q22), and isolated duplications of 8p23.[10-15] However, some of these aberrations showed no clinical manifestation.[11,12-16,17] In human genome large obvious paracentric inversions are frequent at a rate of 1-5/10000 individuals.[18] A common long human paracentric inversion polymorphism spanned>2.5Mb, was identified on chromosome 8p23.1-22. The estimated allele frequency was 21% in 50 unrelated individuals of European ancestry.[19] There is a common agreement that inversion duplication of 8p is a chromosomal abnormality of maternal origin that causes multiple abnormalities[3-5,20-21],including developmental delay, mental retardation of various degrees with speech involvement and different craniofacial abnormalities, microcephaly and agenesis of the corpus callosum. Additional symptoms like

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orthopaedic abnormalities, scoliosis and/or kyphosis, hypotonia and congenital heart defect have also been observed.

At Kuwait Medical Genetics Centre (KMGC), five patients karyotyped for multiple congenital anomalies were found to be carriers for de novo inversion duplication of 8p. The rearrangements were subsequently characterized by Fluorescent in situ hybridization (FISH) analyses. Their clinical findings and related cytogenetic results are discussed.

Case report:

Patient 1:

The proband was a Kuwaiti girl, the third born child to healthy, distally related parents, father being 31 years old and mother 29 years old at delivery. She had two more healthy sibs, a boy and a girl. Her mother's first pregnancy ended as abortion in the first trimester. She was delivered at 36 weeks of gestation by normal vaginal delivery due to premature rupture of membranes. She weighed 2150g and developed severe neonatal jaundice for which she was incubated for a period of 11 days and extensive blood transfusion was provided. She presented with bossing of fore head, wide anterior fontanel, micro retrognathia, high arched narrow palate, bulbous nose, everted lower lip, large ears and mega cornea. She had wide gap between first and second toes with deep planter creases. Brain CT showed partial agenesis of head of caudate nucleus. Karyotype revealed 46, XX with a *de novo* inv dup 8p (p21-p ter). Her sister's and parent's karyotypes were normal.

Patient 2:

This Proband was a Kuwaiti male, the fifth born child of healthy first cousin parents, father being 39 years old, and mother 36 years old at delivery. Mother had two previous first trimester abortions for unknown causes, and one neonatal death of a girl due to pulmonary hypoplasia. He also had two normal sisters and a younger brother. He was born at term by spontaneous vaginal delivery, however, the pregnancy was complicated in its second trimester by vaginal bleeding and maternal diabetes, for which the mother was hospitalized for about one month. All birth measurements were not available. In his first year, he had mild psychomotor delay for which he received physiotherapy. At 8 years of age, he was referred to KMGC in order to evaluate his phenotypic features. His height was 122cm (<10 centile), weight 25kg (<50 centile) and OFC was 51cm (<50 centile). He presented with high forehead, brachycephaly, full cheeks, bulbous nasal tip, macrostomia with thick lower lips, down turned angles of mouth, gum hyperplasia, large fissured tongue, high arched narrow palate, large ears with flattened helix and prominent tragus. Additionally, there was pectus excavatum, generalized hypotonia, tapering fingers with atrophy of thenar and hypothenar muscles and laxity of interphalangeal joints, contracture of knee joints, bilateral talepus equino varus, undescended testis and severe mental retardation. Karyotype was 46, XY, der (8), inv dup (8p 12-22) with deletion of 8p 23p ter. Brain CT revealed agenesis of corpus callosum. Skeletal survey showed generalised osteopenia. Abdominal ultrasound was normal. Parental karyotypes were normal.

Patient 3:

The proband was a Syrian girl, the sixth born child to healthy, unrelated parents, mother being 32 years old and father 43 years at time of delivery. Mother had two first trimester abortions. Patient had five sisters and one elder brother. She had one uncle who died at age of 8 years due to unclarified renal disorder, and one first cousin male who had dextrocardia with VSD. She was delivered at term by spontaneous vaginal delivery and weighed 3200g. She was incubated for one week because of cyanosis, hypothermia and a small ASD which was later closed spontaneously. At 8 months, she was hospitalized because of recurrent tonic clonic seizures. Patient was referred to KMGC at age of 5 years and 3 months for assessment of her dysmorphic features, developmental delay and seizures. She weighed 18kg (50th centile), with an OFC of 46cm (98th centile). She had brachycephaly, broad forehead, bitemporal depression, hypertelorism, down slanting of palpebral fissures, low set ears, broad nasal tip, down turned thin lips, high arched palate, and short webbed neck. The hands displayed fixed flexion deformity of fifth fingers and deep palmer creases. His feet showed overriding of third and fourth toes, and deep planter creases. Other abnormalities observed were hypotonia, cutis marmurata of skin and scoliosis of spine. Psychomotor development has been severely delayed. She was on Depakine for the last six months for treatment of epilepsy. Chromosomal analysis revealed a *de novo* 46,XX dup (8) (p22) (Figure 1 and Figure 2). Her parental karyotypes were normal. EEG revealed abnormal records, skeletal survey showed generalized osteopenia with spinal scoliosis. Other investigations were normal such as CBC, LFT, abdominal ultrasound, echocardiography, brain CT scan and MRI.

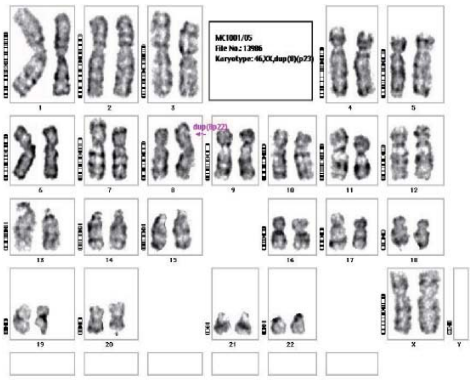

Fig. 1: Conventional karyotype of case 3 showing duplication of chromosome 8p22 region.

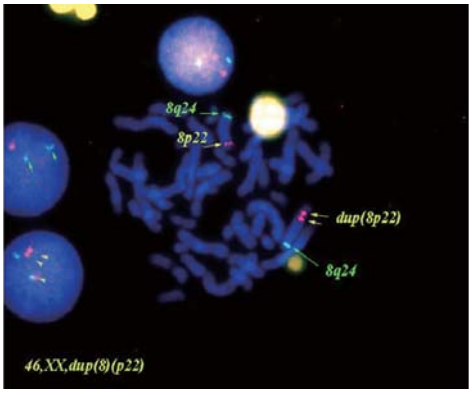

Fig. 2: FISH analysis on metaphase spread and interphase nuclei showed duplication of chromosome 8p22 region.

Patient 4:

The proband was an Egyptian girl, the second born child to healthy, non-consanguineous parents. Family history was irrelevant. She has one normal elder brother. She was delivered at term following uneventful pregnancy, by caesarian section due to foetal distress. She was referred to genetics centre at age of two years for evaluation of her psychomotor retardation and her facial

features. Physical examination showed high forehead with frontal and parietal bossing, prominent eyes, micrognathia, hypertelorism, small feet with planter flexion, muscular hypotonia and delayed psychomotor milestones. Fundal examination, EEG and cardiac ultrasound were normal. However, CT of brain revealed agenesis of corpus callosum. Chromosomal and FISH analyses showed *de novo* 46XX, dup 8 (p22-23). Her parental karotypes were normal.

Patient 5:

The proband was a Kuwaiti girl, the only born child to healthy, non-consanguineous parents, mother being 23 and father 28 years old. Family history revealed presence of a maternal brother, sister and an uncle with a congenital eye disorder of an unclarified type. She was delivered following an uneventful pregnancy at full term, by caesarian section because of prolonged labour and foetal distress. She weighed 2750g. She was referred to the genetics clinic at age of 15 months for assessment of her developmental delay She had a length of 69cm (<5th centile), a weight of 8kg (<5th centile), and OFC of 45cm (<5th centile). On physical examination dysmorphia was noted. It included hypertelorism, downward slanting of palpebral fissures, broad nasal bridge, strabismus, curved eye brows, thin lips with flat philtrum, high arched palate, a small benign haemangioma behind right ear lobe and short neck (Figure 3A and Figure 3B). She also showed mild muscular hypotonia, umbilical hernia and deep planter creases.

Fig. 3a: Characteristic facial features of inversion duplication of chromosome 8p as shown in patient 5.

Fig. 3b: lateral view of the face in patient 5 showing a small haemangioma under right ear

Chromosomal and FISH analyses revealed a *de novo* 46,XX, inv dup (8p23) as her parents karyotype were normal. CT of brain showed defect in the shape of skull vault with no evidence of craniostenosis. Other investigations were normal such as CBC, LFT, abdominal ultrasound, echocardiography and EEG. I.Q assessment at age of 30 months showed mild mental retardation with speech delay.

DISCUSSION

We have described the clinical and cytogenetic findings of 5 patients carrying *de novo* direct/or inversion tandum duplication of chromosome 8p with breakages at different segments and normal homologues. Initially, conventional chromosomal analyses with GTG banded metaphase were performed according to the standard procedure. To determine the chromosomal breakpoints more precisely, FISH technique was applied on metaphase spread and interphase nuclei using whole chromosome painting (WCP 8) and c-myc oncogene probe for locus (8q24.12-q24.13) [VYSIS]. Chromosomal analysis of all parents revealed normal karyotypes.

To date, more than 50 cases with direct or inv dup (8p), which can be either di or monocentric has been published.[3-7,11,13-16,20,22] The prevalence of both types is estimated to be 1/22 000-30 000 of the white western population. The majority of described cases were associated with facial dysmorphism, mental retardation, brain defects and/or developmental delay. The variability of phenotypic features associated with 8p duplication can be attributed to differences in chromosomal imbalances.

As with the previously published cases, clinical findings of our 5 patients included multiple congenital anomalies, developmental delay or mental retardation (Table 1).

A spectrum of cardiac dysfunction and serious cardiac malformations were the second most prominent feature found in some cases with 8p23.1 duplication.[13,23-29]

A number of authors suggested that a candidate gene/or a cluster of genes located in 8p23 region behaves as a dominant mutation that interferes with normal cardiac morphogenesis leading to a wide spectrum of congenital heart defects, including conotruncal lesions, atrial septal defects, atrioventricular canal defects, and pulmonary valve stenosis.[23-25] An 8p heart defect critical region was delineated, and the zinc finger transcription factor GATA4 was considered a likely candidate for these defects.[26] This finding was later supported by Pehlivan et al. who identified haploinsufficiency of GATA4 in several patients with interstitial deletion of 8p23.1 and congenital heart disease.[27] Where as Giglio and coworkers. excluded a major role of GATA4 in these congenital heart defects[28], as molecular investigations of 8p deletion in their cohort of patients have narrowed the critical region for a single candidate gene associated with heart defect, to the 5-cM interval between D8S1825 and WI-8327 at chromosome 8p23. Only one of our patients (Case 3), a carrier of 46, XX, dup (8) (p22), presented with congenital hear defect (ASD) with no obvious deletion involving the critical 8p region. Some cases with inv dup of 8p may be associated with undetectable small deletions[21], therefore, further molecular characterization of this region would clarify it. Follow up of other patients would identify or exclude any cardiac complications in the future.

Patient 5 showed some features of Kabuki syndrome. A recent report described a duplication of 8p22–p23.1 in multiple patients with Kabuki

Table 1: Clinical features and karyotypes of 5 patients with partial duplication of 8p

	Patient 1 **6211**	**Patient 2** **8579**	**Patient 3** **13986**	**Patient 4** **16237**	**Patient 5** **18341**
Karyotype Proband	46, XX, inv dup (8) (p21-pter)	46,XX, inv dup (8) (p12-22), del p23-pter	46, XX, dup (8) (p22)	46, XX, derv 8 inv dup 8 (p22-p23)	46, XX, dup (8) (p23)
Sibs	Sister normal				
Skull	Frontal Bossing , wide anterior fontanelle	High Forehead, brachycephaly	Microcephaly, broad forehead	High Forehead, frontal and parietal bossing	Microcephaly, broad forehead
Eyes	Megalocornea	Hypertelorism	Hypertelorism, downslanting	Prominent	Arched eyebrows, strabismus, ectropion of lower eyelids,
Ears	Large ear lobes	Large malformed	Low set		Low set, prominent
Nose and nasal bridge	Bulbous nasal tip	Bulbous nasal tip	Broad		Broad
Mouth and palate	high arched narrow palate, everted lower lips	Thick lower lips, fissured tongue, carp mouth, high arched palate, gum hyperplasia	High arched palate, thin lips		High arched palate, thin upper lip
Micrognathia	+	+	-	+	+
Neck and chest	-	Pectus excavatum	Short webbed		Short neck
Hand and foot	Gap between 1st and 2nd Toes, deep planter creases	Hyper-extensible, long tapering fingers TEV	Flexion deformity left hand, bilateral overriding 3rd and 4th toes	Small feet, planter flexion	-
CNS anomalies	Agenesis of head of caudate nucleus	Agenesis of corpus callosum	Epilepsy	Agenesis of corpus callosum	-
Congenital heart anomalies	-	-	ASD	-	-
Musculoskeletal anomalies	Hypotonia	Hypotonia, TEV contracture deformity knee joints, kyphoscoliosis, generalized osteopnia	Hypotonia	Hypotonia	Hypotonia
Skin	-		Cutis marmorata		-
Genitalia	-	Undescended testis		-	-
Growth and development	Mental retardation	Mental retardation	Severe mental retardation	delayed	Mental retardation

syndrome.[30] However, 8p22–p23.1 duplication may not be a common mechanism for Kabuki syndrome as this suggestion was disproved later by other researchers.[31-33] Moreover, we have performed FISH analyses for 6 patients with Kabuki syndrome and excluded chromosomal aberration at this region (Marafie et al. unpublished data). Future molecular investigations should help to achieve a final genetic localization of this syndrome.

In keeping with previously published reports, all our 5 patients had variable degrees of craniofacial manifestations and psychomotor/mental retardation. Three of our patients were found to have agenesis of corpus callosum; patients 4 and 5 carried duplication of p23 region, while patient 2 had inv dup 8p12-22 with deletion of p23 pterminal region. This is the only patient with terminal deletion of 8p in association with the 8p duplication, which is contrary to what was reported by some authors.[4,5,21,34] Patient 1 had agenesis of head of caudate nucleus, she carried inv dup (8) (p21-pter). This region was suggested to be the critical region for 8p duplication syndrome.[35] Also; a gene for brain development might be present at 8p region.[36]

The phenotypic effect of isolated 8p23.1 duplication is a subject of debate. Duplication of 8p23.1-23.3 was considered an irrelevant aberration detected in a phenotypicaly normal male, however its relation to his oligoasthenozoospermia could not be explained.[17] Also, 8p23.1 duplication was reported in a mother and her two daughters with minor clinical manifestations.[8] Whereas other authors emphasized its clinical implication in several patients.[13,29]

Furthermore, a woman carrier for inv dup (8p) with developmental anomaly and cerebral palsy developed breast cancer at age of 36 years. However, an association between breast cancer and inv dup (8) (cent-->p23.1) was excluded. On the contrary, deletion in regions 8p11-p12, 8p21-p22, and duplication of 8p12 are postulated to be associated with breast cancer.[22]

A group of researchers have identified a locus on chromosome 8p23, associated with maturity onset diabetes of the young, which is a subtype of diabetes defined by an autosomal dominant inheritance and a young onset. A gene at that locus may account for 30% of the cases not caused by any of 6 previously discovered genes.[37]

Regular follow up of these patients is recommended to exclude further medical complications. Since the parents have normal karyotype with no evidence for mosaicism, the recurrence risk is very small for these families. In conclusion, molecular cytogenetic diagnosis of structural anomalies enables accurate genetic counselling of such families.

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