Phenotypic correlation and molecular cytogenomic study of a patient with 9p duplication and 14q terminal deletion

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Received 24-Oct-2019
Revised 14-Apr-2020
Accepted 14-May-2020
Published 11-Jul-2020

Middle East Journal of Medical Genetics
2019,8:150–157

Background
Partial trisomy of the short arm of chromosome 9 is among the most common autosomal anomalies, leading to specific clinical characteristics including intellectual disability, short stature, craniofacial dysmorphism, and digital anomalies. Typical clinical features of 14q terminal deletion syndrome include intellectual disability, microcephaly, postnatal growth retardation, muscular hypotonia, and dysmorphic features.

Patient and aim
In this study, we report on a 7.5-year-old female patient with de novo trisomy 9p and deletion of 14q32.3 presented with delayed motor and mental milestones, dysmorphic features, microcephaly, short stature, and hypotonia. The aim of this study was to delineate breakpoints and identify the genotype/phenotype correlations.

Methods and results
The chromosomal abnormalities in the patient were characterized by G-banding, fluorescent in-situ hybridization (FISH), multiple ligation probe amplification, and array CGH. Karyotype showed 46, XX, add (14)(q32.3). FISH revealed deletion of 14q subtelomere and duplication of 9p subtelomere. Multiple ligation probe amplification detected 9p subtelomere trisomy. Array CGH identified 34 Mb duplication of chromosome 9p and 378 kb deletion of chromosome 14q32.3.

Conclusion
Different cytogenomic tools are crucial to delineate breakpoints and the involved genes. FISH technique allows the proper characterization of suspected chromosomal abnormalities on its chromosome site, whereas array CGH identifies the exact copy number changes with the involved genes, which facilitate genotype/phenotype correlation.

Keywords:
Array CGH, deletion 14q, fluorescent in-situ hybridization, genotype-phenotype correlation, multiple ligation probe amplification, trisomy 9p

Middle East J Med Genet 8:150–157

2090-8571

Introduction

Trisomy 9p is considered the fourth most frequent autosome anomaly in a live born infant after trisomy 21, 18, and 13, with the first described case being in 1970 (Rethoré *et al.*, 1970), as the short arm of chromosome 9 is relatively poor in genes and therefore is compatible with survival (Venter *et al.*, 2001; Littooij *et al.*, 2002). Characteristic clinical features include various degrees of intellectual disability, short stature, craniofacial abnormalities, microcephaly, cleft lip and palate, hypertelorism, prominent nose, short philtrum, downturned corner of the mouth, malformed ears, and short wide neck; however, skeletal, cardiac, and genital anomalies have been observed (Fryns *et al.*, 1979; Wilson *et al.*, 1985; Concolino *et al.*, 1998; Tsezou *et al.*, 2000; Akalin *et al.*,2014).

Phenotype-genotype correlation studies suggested that a critical region of classical 9p trisomy is located within 9p22→p23 (Fujimoto *et al.*, 1998; Haddad *et al.*, 1996), whereas Christ *et al.* (1999) proposed a shorter critical region 9p22.1→p23, and also DeRavel *et al.* (2004) proposed an even shorter critical region located within 9p22.1→p22.2.

In most cases, partial 9p trisomy results from parental reciprocal translocations between chromosome 9 and another autosome (Littooij *et al.*, 2002); however, direct 9p duplication was reported only in a few cases (Guanciali Franchi *et al.*, 2000). In most cases, phenotypic heterogeneity occurs due to the variable size of the duplicated segment and the frequent concomitant monosomy of another chromosome segment (Littooij *et al.*, 2002). Prenatal diagnosis of partial trisomy 9 is feasible upon sonographic suspicion,

using amniocentesis or chorionic villus sample analysis by aCGH (Lopez-Felix *et al.*, 2017).

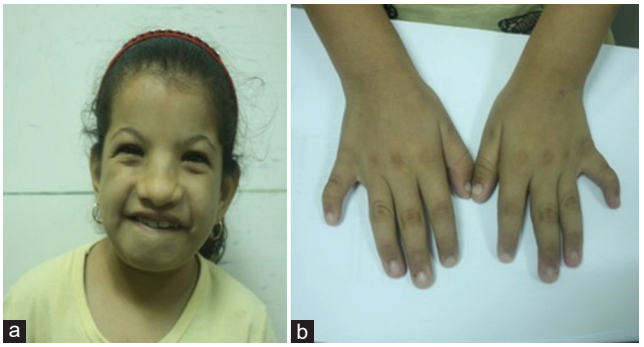
Deletions of chromosome 14 is relatively rare, and when detected, it can be an interstitial deletion with variable breakpoints (Turleau *et al.*, 1948; Elliott *et al.*, 1993) or an apparently terminal deletion of variable size (Yen *et al.*, 1989; Miller *et al.*, 1992) or as a ring chromosome (Howard *et al.*, 1988).

Phenotypes associated with linear 14q terminal deletions are neurologic deficits (mental retardation and hypotonia), specific dysmorphic face (microcephaly, high and prominent forehead, blepharophimosis, epicanthi, broad and flat nasal bridge, short bulbous nose, a broad philtrum, thin upper lip, small and carp-shaped mouth, highly arched palate, abnormal dentition, low-set ears with malformed helices, and micrognathia), and a single palmar flexion crease. Major congenital malformations are relatively uncommon in terminal 14q deletion patients, except for congenital heart defects (CHD) (Karnitis *et al.*, 1992; Wintle *et al.*, 1995; Ortigas *et al.*, 1997; Van Karnebeek *et al.*, 2002; Maurin *et al.*, 2006; Engels *et al.*, 2012). Retinitis pigmentosa and seizures were observed in patients with ring 14q23.3 deletion (Meschede *et al.*, 1998). The aim of this study was to delineate breakpoints and identify the genotype/phenotype correlations.

Case report

A 7.5-year-old female child was referred from the Multiple Congenital Anomalies Clinic (Center of Scientific Excellence) of the National Research Center, complaining of delayed motor and mental milestones, short stature, and seizures. Birth history was uneventful, with a normal vaginal delivery with a birth weight of 2.750 kg, and the age of the father and mother at the time of birth of their child was 28 and 19 years, respectively. Our patient is the oldest child of three normal female siblings. Parents gave a history of delayed milestones, manifested as delayed sitting until the age of 1 year and delayed walking until the age of 2.5 years. They have also described tonic-clonic seizures (four times) started at the age of 3 years and extended over a period of 2 years. Pedigree analysis showed no paternal consanguinity, with no history of similarly affected other family members. Clinical examination revealed that the proband had dysmorphic features in the form of arched scanty eyebrows, bilateral epicanthic folds, hypertelorism, broad nasal bridge and bulbous nose, short philtrum, thick lips, downturned corner of mouth, macrostomia, broad chin, low-set ears, short neck (Fig. 1a), bilateral clinodactyly of little fingers (Fig. 1b), right simian crease, and bilateral broad big toes. Anthropometric measurements showed she had normal weight of 19 kg (–0.8SD), had microcephaly [head circumference was 48.5 cm (–2.3SD)], and had short stature [height 106 cm (–2.7SD)].

Figure 1



(a) Patient showing dysmorphic features in the form of arched scanty eyebrows, bilateral epicanthic folds, hypertelorism, broad nasal bridge, bulbous nose, short philtrum, thick lips, downturned corner of mouth, macrostomia, broad chin, low-set ears, and short neck. (b) Hands of the patient showing bilateral clinodactyly of little fingers.

Neurological examination showed mild hypotonia with normal reflexes. EEG revealed right frontocentral epileptogenic activity, whereas computed tomography brain finding was normal. Evaluation of psychomotor development using Arabic version of Portage program showed that the patient had profound developmental delay (Portage, Wisconsin, USA). Echocardiography and pelviabdominal ultrasonography findings both were normal.

Tables 1 and 2 identify the clinical presentations of chromosome 9p trisomy and 14q deletion that were reported by some authors in comparison to our patient, whereas Table 3 represents the clinical markers of both trisomy 9p and 14q32.3 in comparison with our patient.

A signed consent form was obtained from the father of the patient for participation in the study. The Medical Ethical Committee of the National Research Centre approved this study.

Cytogenomic studies

Chromosomal analysis of peripheral blood lymphocytes was performed for the patient and both parents (Verma and Babu, 1995). Metaphases were analyzed and karyotyped according to ISCN (2016). Karyotype of the patient was 46, XX, add (14)(q32.3) (Fig. 2), whereas parental karyotypes were normal 46, XY for the father and 46, XX for the mother.

Fluorescence in-situ hybridization (FISH) studies were performed according to Pinkel *et al.* (1986) and manufacturer instructions using whole chromosome

Table 1 Main clinical features of 9p duplication described by some authors in comparison with our patient

Authors	1	2	3	4 P1→P4	Our patient
9p duplication	P12→p24 10 months, Boy	P13.1→p24.3 13 years, Girl	P11.2→p24.3 14 years, Boy	P11→p24.3 4 10/12 years 1 7/12 y	P11→p24.3 7 6/12 years, Girl
Microcephaly	+	+	+	+	+
Brachycephaly	+			+	
Epicanthal folds	+	+			+
Micrognathia	+				
Down slantingpalpebral fissures			+	+	
Prominent/largenose			+		+
Bulbous nasal tip	+	+	+	+	+
Deep set eyes	+		+	+	
Hypertelorism	+			+	+
Low-set ears		+		+ +	+
Malformed ears					+
Downturnedcorners of the mouth	+	+		+ +	+
Thin upper lip	+				
Short neck	+			++	+
Fifth finger short				+	
Nail hypoplasia	+		+	+ +	
Clinodactyly			+	+ +	+
Brachydactyly		+			
Neuro- psychomotor development delay	+	+	+	++	+
Hypotonia			+		+
Growth delay			+		+
Genital abnormalities			+		
Speech delay		+			+
Mental retardation				Severe profound	Profound

Authors: (1) Tsezou *et al.* (2000); (2) Chen *et al.* (2011); (3) Guilherme *et al.* (2014); (4) Temtamy *et al.* (2007).

Table 2 Clinical features of studies with a 14q32.3 deletion syndrome in comparison with our patient

	1	2	3	4	5	Our patient
Age	12 years	2 2/12 years	3 3/12 years	2 years	3 9/12 years	7 6/12 years
Development	Mild intellectual impairment	Moderate deficit	Slow language development	Moderate global developmental delay	Moderate global developmental delay	Profound developmental delay
High forehead	+	+	+	?(-)	+	_
Broad nasal bridge	+	+	+	?(-)	+	+
High arched palate	+	+	+	+	+	_
Epicanthic folds	?	+	+	Blepharophimosis and ptosis	+	+
Single palmar crease	_	?	+	+	+	+
hypotonia	_	+	_	+	_	+
Clinodactyly	_	_	+	_	_	+
eye anomalies	_	Ptosis	Left optic nerve coloboma	Ptosis	Left esotropia	_
Congenital heart disease	+	_	_	_	_	_
Seizures	_	_	_	_	_	+
Chromosome breakpoint	14q32.3	14q32.2	14q32.2	14q32.3	14q32.31	14q32.3

(1) Hreidarsson and Stamberg (1983); (2) Telford *et al.* (1990); (3) Wang and Allanson (1992); (4) Wintle *et al.* (1995) (case 3); (5) Ortigas *et al.* (1997).

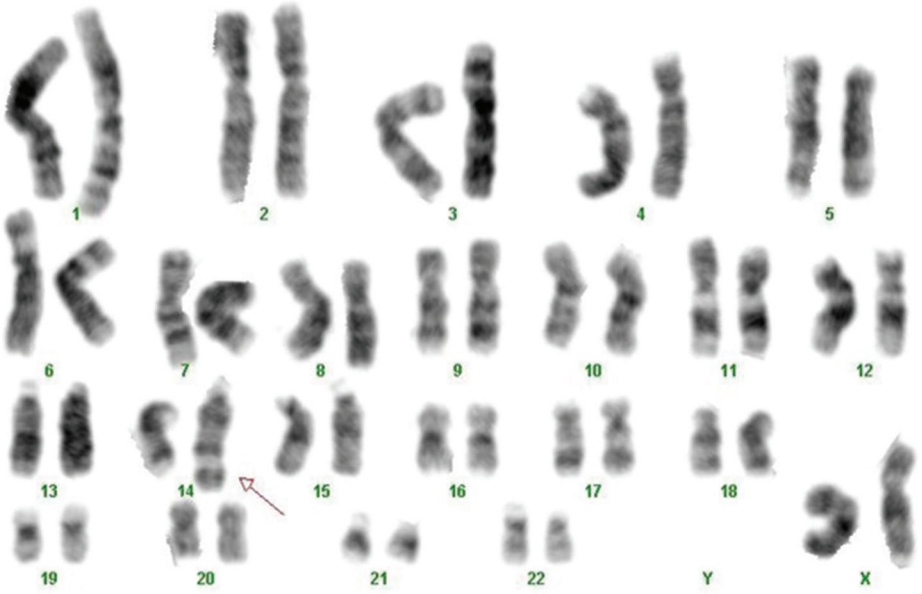
paint probe for chromosome 14 (Cytocell, Cambridge, UK) spectrum red demonstrated that the origin of added material was not from chromosome 14 (Fig. 3a). ToTel Vysis probe mixtures (Abbot Laboratories, Illinois, USA) using mix. 7 (7p spectrum green, 7q spectrum orange and 14q spectrum orange and spectrum green) showed only one signal of 14q (Fig. 3b), denoting 14q subtelomere deletion, whereas using mix. 9 probe (9p spectrum green, 9q spectrum orange and 17q spectrum orange and spectrum green) showed 3 green signals of 9p (Fig. 4a). Application of locus specific identifier probe for chromosome 9 (Abbot Laboratories) (nine CEP spectrum green and nine p21 spectrum orange) demonstrated three signals, indicating that the added segment to chromosome 14 was owing to trisomy of chromosome 9 p (Fig. 4b). FISH revealed 46, XX.ish t(9;14)(Tel 9p+, locus specific identifier 9p21+, CEP 9+, Tel 14q-).

Table 3 The clinical presentation of 9p trisomy, 14q32.33 deletions and our patient

Clinical presentation	9p trisomy	14q32.33 deletion	Our patient
ID	+	+	+
Development	Delayed		Delayed
Stature	Short stature790		Short stature
Tone		Hypotonia	Hypotonia
Seizures		+	+
Skull	Microcephaly and brachycephaly	Microcephaly	Microcephaly
Eyes	Enophthalmos, small eyes, antimongoloid, and hypertelorism	Blepharophimosis, epicanthal fold, and retinitis pigmentosa	Arched, scattered eyebrows, epicanthal fold, and hypertelorism
Ears	Low-set ears	Low-set ears	Low-set ears
Nose	Broad nose, bulbous nose tip	Broad flat nasal bridge short bulbous nose	Broad nose and bulbous tip
Mouth	Downward slanting, cleft lip and palate, small jaw	Small, carp shaped High arched palate	Downward slanting, short philtrum, thick lips, macrostomia, and broad chin
Neck	Short		Short
Hand and Feet	Hypoplastic of phalanges	Simian crease	Bilateral clinodactyly, bilateral broad big toe, and simian crease
CHD		CHD	Normal heart

CHD, congenital heart defects.

Figure 2

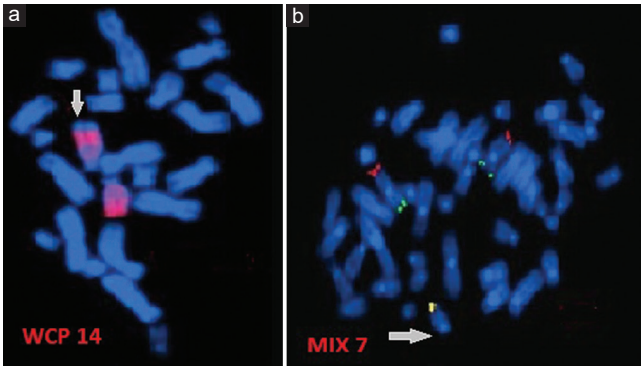


Karyotype of the patient showing 46,XX,add (14)(q32.3).

Multiple ligation probe amplification (MLPA) was done using SALSA MLPA probemix P070-B2 Human Telomere-5. Minimal of three references were used per test. The assay was carried out according to the manufacturer's instruction (MRC-Holland). DNA denaturation and overnight hybridization of the MLPA probemix was done on the first day, whereas probe ligation and amplification were done on the second day. The amplified products were electrophoresed using Genetic Analyzer ABI 3500 (Thermo Fisher Scientific – Waltham, Massachusetts- United States of America). The ABI data were interpreted using the Coffalyser software-MRC Holland, Netherland (www.mlpa.com). MLPA revealed the origin of the added chromosomal material; it only detected 9p subtelomeric duplication, whereas subtelomeric 14q deletion was not detected because 14q MLPA probe was more proximal than the deleted region (Fig. 5).

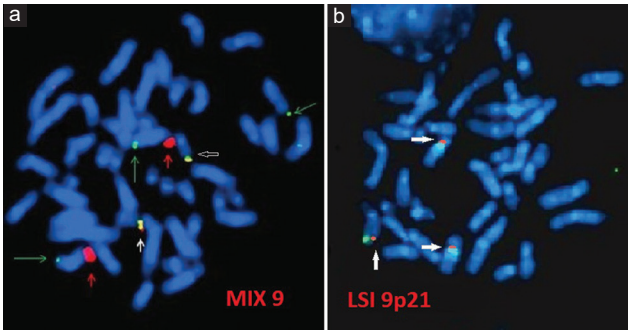
Array CGH was applied according to the manufacturer's manual, and using Cytoscan HD Gene chip (Affymetrix, Santa Clara, California, USA), Gene chip hybridization oven 645, wash using fluidic station 450 (Affymetrix), scanned by Gene chip scanner 3000, using chromosome analysis suit (CHAS) software (Affymetrix, Santa Clara, California, USA). Array CGH demonstrated 43 Mb duplication of chromosome 9 and 378 kb deletion of chromosome 14 (Fig. 6a and

Figure 3



(a) Fluorescent in-situ hybridization using whole chromosome paint 14 demonstrating that the added segment (red arrow) was not a part of chromosome 14. (b) Fluorescent in-situ hybridization using ToTel Probes (mix. 7) showed 2 green signals of chromosome 7p, 2 red signals of 7q, and only one signal of chromosome 14q (red and green); red arrow denoting deletion.

Figure 4



(a) Fluorescent in-situ hybridization using total subtelomeres probes (mi × 9) showed three green signals of chromosome 9p (green arrows), two red signals of 9q (red arrows), and two signals of chromosome 17q (red and green)(arrow head in white). (b) Fluorescent in-situ hybridization using Locus specific identifier of chromosome 9 (CEP 9 spectrum green for control and 9p21 locus spectrum orange) showed 3 signals.

b), arr[GR Ch38]9p24.3p13.3(751084_34431081) x3,14q32.33 (106311528 _ 106689554)x1.

Discussion

Trisomy of the short arm of chromosome 9 is a well-recognized clinical syndrome. Various degrees of intellectual disability, short stature, dysmorphic facial features, and hand-foot abnormalities are the characteristic manifestations (Angle *et al.*, 1999, Temtamy *et al.*, 2007; Al Achkar *et al.*, 2010; Akalin *et al.*, 2014), whereas the terminal deletion of chromosome 14 is associated with neurological deficits, specific dysmorphic facies, and CHD in rare cases (Van Karnebeek *et al.*, 2002; Maurin *et al.*, 2006; Engels *et al.*, 2012).

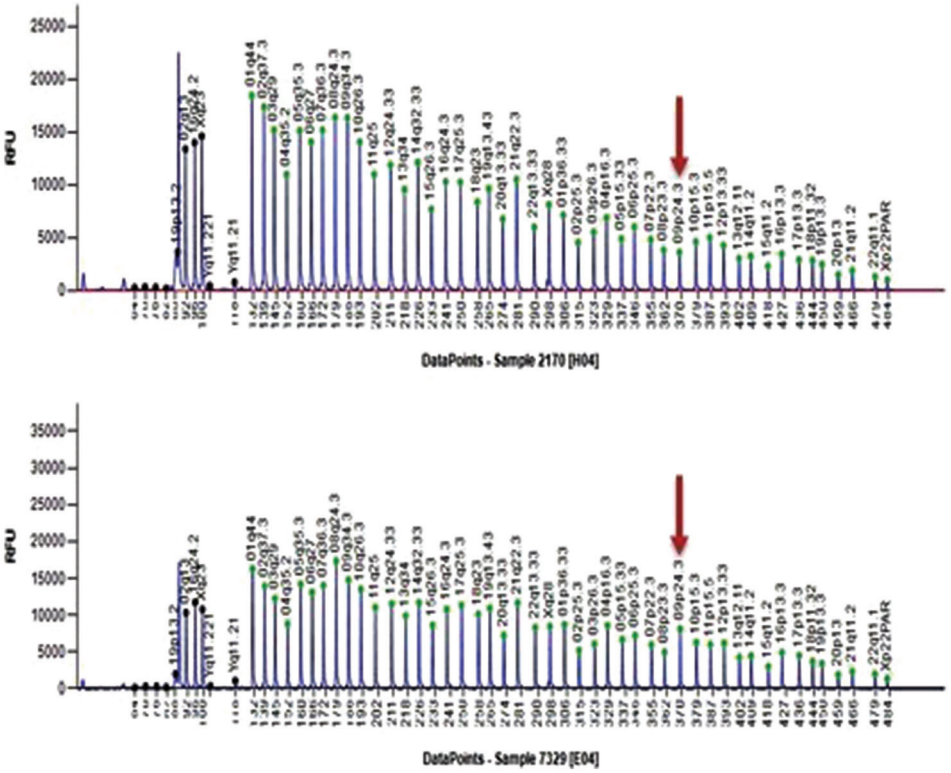
We present a 7.5-year-old female child with trisomy 9p and terminal deletion of 14q32.33. She was complaining of delayed motor and mental milestones, short stature, and seizures.

In most patients, 9p trisomy was derived from a parent carrying a balanced reciprocal translocation and was accompanied with a concurrent deletion of other chromosome, and isolated de novo duplications are infrequent (Abu-Amero *et al.*, 2010; Akalin *et al.*, 2014). Angle *et al.* (1999) reported partial 9p trisomy with partial trisomy of 14q, inherited from a healthy parent. On the contrary, our patient's abnormality was de novo and involved 14q monosomy.

Our patient shares many criteria with trisomy 9p, like profound developmental delay, delayed speech, dysmorphic features (bilateral epicanthic folds, hypertelorism, broad nose, downward corner of the mouth, and low-set ears), short neck, bilateral clinodactyly, hypotonia, and microcephaly (Tsezou *et al.*, 2000; Temtamy *et al.*, 2007; Chen *et al.*, 2011; Guilherme *et al.*, 2014), as shown in Table 1. Compared with other studies of 14q 32.33 deletion (Hreidarsson and Stamberg, 1983; Telford *et al.*,1990; Wang and Allanson, 1992; Wintle *et al.* 1995; Ortigas *et al.* 1997) (Table 2), our patient shares profound developmental delay, seizures, bilateral epicanthic folds, broad nose, downward corner of the mouth, low-set ears, bilateral clinodactyly, right simian crease, hypotonia and microcephaly.

The pericentromeric region of chromosome 9 is rich in segmental duplication or low copy repeats that predispose it to nonallelic homologous recombination resulting in a high frequency of polymorphic variants located adjacent to the centromere (Willatt *et al.*, 2007). Duplications are either transchromosomal or chromosome-specific duplications (Eichler, 2001). Our patient's unequal recombination between nonhomologous chromosomes would have probably originated the duplication in 9p that rearranged with chromosome 14q by nonhomologous end-joining mechanism. In our case, the whole 9p is duplicated encompassing the critical region responsible for the characteristic phenotype (9p22→p23) (Fujimoto *et al.*, 1998; Haddad *et al.*, 1996; Christ *et al.*, 1999; De Ravel *et al.*, 2004). In our patient, the duplication on of chromosome 9 was 34 Mb, arr[GRCh38]9p 24.3p13.3(751084_34431081) x3. This region encompass 125 OMIM genes. These genes are responsible for impaired intellectual development; neurodevelopmental disorder with progressive microcephaly; spasticity; brain anomalies; variation in skin, hair, and eye pigmentation; trigonocephaly; 46, XY sex reversal; mental retardation; chromosome 9p deletion syndrome; and cerebellar hypoplasia. Based by the UCSC Genome Browser database (http://

Figure 5



Electrogram of a normal control person (Top) and electrogram of our patient (bottom). The longitudinal axis represents the multiple ligation probe amplification peak heights, and transverse axis represents the chromosome bands covered by the P070 kit. The arrows indicate the location of the 9p subtelomeric area. The patient's electrogram shows about 50% increase of the height of the multiple ligation probe amplification peak at 9p, indicating 9p subtelomeric duplication.

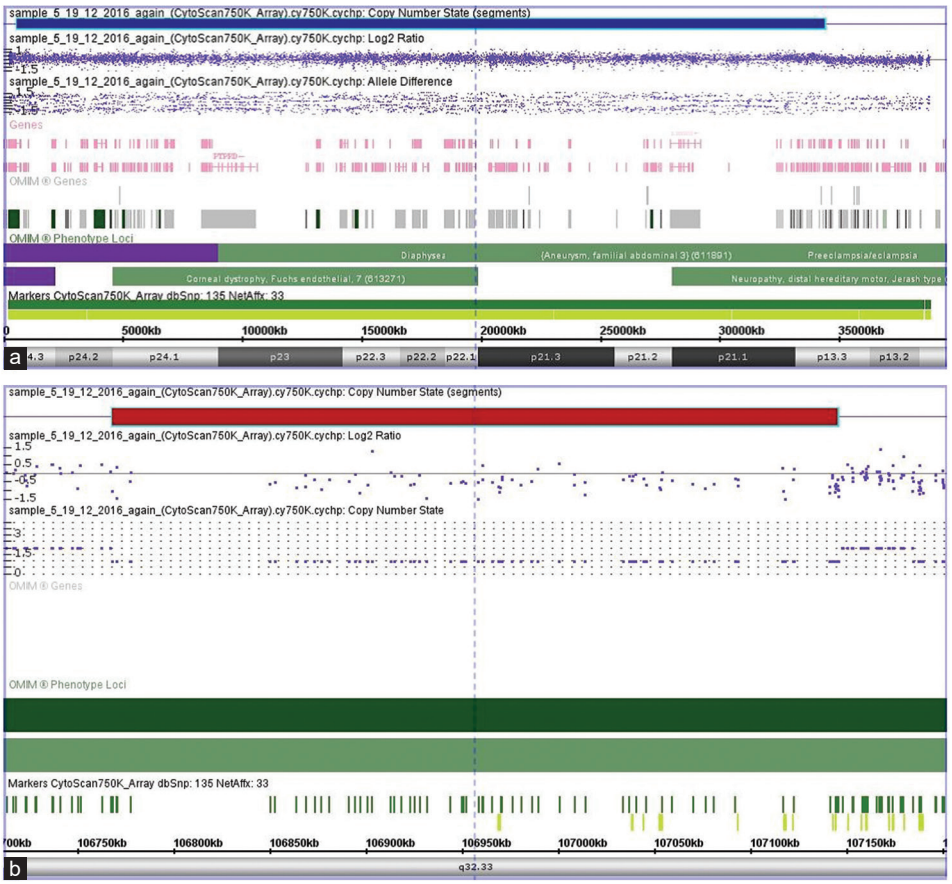
genome.ucsc.edu), the duplicated region contains several genes; *DMRT1*, *DMRT3*, and *DMRT2* are related to gonadal development causing abnormal external genitalia, hypospadias, or gonadal dysgenesis in 46, XY infants (Muroya *et al.*, 2000; Shan *et al.*, 2000; Livadas *et al.*, 2003). *FREM 1* gene encodes a basement membrane protein that may play a role in craniofacial and renal development, which was presented in our patient (dysmorphic features and microcephaly but without renal affection). Genes involved in the development of the central nervous system are *PSIP1*, *SIGMAR1*, *PAX5*, and *CNTNAP3*. In the present study, our patient complained of profound developmental delay, seizures, and hypotonia. *FOXD4* gene is associated with speech and language delay (Hauge *et al.*, 2008), which manifested in our patient. All described genes are dose sensitive and cause abnormalities when deleted or mutated, but our patient represented an overexpression (triplication), probably causing functional impairment (Guilherme *et al.*, 2014).

Patients with 14q32.33 deletion syndrome present with intellectual disability, developmental delay, characteristic facial abnormalities, and CHD.

The 14 q32.33 region deleted in our patient encompassed 15 OMIM genes, the most important of them are responsible for hemifacial microsomia, coronary heart disease, and microphthalmia.

Bonaglia *et al.* (2018) reported 52 patients who had de novo unbalanced translocations which involved terminal deletion associated with partial duplication of another chromosome or inversion duplication deletion (inv-dup del) of one chromosome to which a terminal segment of another chromosome or the same chromosome is added. They postulated that several mechanisms may be the cause of these unbalanced translocations; one is the meiotic nondisjunction followed by postzygotic partial trisomy rescue of the supernumerary chromosome with terminal deletion of the recipient chromosome. Another mechanism is meiotic or postzygotic asymmetric break of a dicentric chromosome which produces two chromosomes, one with deletion and the other with inv-dup del. The repair occurs by telomere capture from another chromosome or the same chromosome to ensure chromosome stability. The first mechanism may be the cause of unbalanced translocation in our patient. Unfortunately, the DNA of the parents was not available to predict the origin of this unbalanced

Figure 6



(a) Partial molecular karyotype of chromosome 9; the blue bar indicates 9p duplication, the log 2 ratio at 0.3, and the allele difference is 4. (b) Partial molecular karyotype of chromosome 14, the red bar indicates 14q deletion, the log 2 ratio at – 0.45, CN state at 1.

translocation. We recommend performing different cytogenetic approaches for these types of chromosomal anomalies, as the FISH technique characterizes the exact type of chromosomal rearrangement in its site, and the array CGH precisely identifies copy number changes and the involved genes, which facilitate genotype/phenotype correlation.

Acknowledgements

The authors acknowledge the Science and Technology Development Fund (STDF grant 5253) for supporting this work.

Centre of Excellence for Human Genetics, Science and Technology Development Fund (STDF), Academy of Science Research and Technology, Egypt (Grant number: 5253).

Elgerzawy A.M.S. (MD) (professor) literature research, data acquisition, manuscript preparation, and manuscript editing; El Ruby M.O. (PhD) (professor) clinical evaluation and genetic counseling; Hammad S.A. (PhD) (professor) experimental studies; Kamel A.K. (PhD) (professor) experimental studies, data acquisition, and data analysis; Hussein S.H. (MSc) (Research Assistant) experimental studies; Abd Allah S.G. (PhD) (Researcher) experimental studies; Mohamed A.M. (PhD) (professor) design, experimental studies, data analysis, manuscript preparation, and manuscript editing.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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