Interstitial Deletion 4q due to a Complex Rearrangement Involving Chromosomes 1, 2, 4, 8, 14 and 16

Kromozom 1, 2, 4, 8, 14 ve 16'yı Içeren Kompleks Kromozom Anomalisinin Yol Açtığı Inserstisyal 4q Delesyonu

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ABSTRACT

Complex chromosome rearrangements (CCR's) involving multiple breaks in two or more chromosomes are rare. The precise characterization of a CCR is difficult and may be inaccurate even by using molecular cytogenetic techniques. Various new molecular techniques such as MLPA, array techniques (CGH, BAC, oligo, SNP, etc.) have proved to be powerful tools for the characterization of CCR's. We present here a patient with a de novo CCR involving chromosomes 1, 2, 4, 8, 14, 16. He was investigated cytogenetically because of multiple congenital anomalies such as macrocephaly with a prominent forehead, epicanthus, ptosis, micrognathia, low set ears, short neck, pectus excavatum, adducted right foot, cryptorchidism, hypotonia and neurodevelopmental delay. Cytogenetic analysis revealed an abnormal karyotype (46,XY,der(1),der(2),der(4),t(8;14),der(16)), while the parents had a normal chromosome count. After FISH investigations using different commercially available probes the karyotype was interpreted as ish t(1:16),ins(4;2),t(8;14). The rearrangements were apparently balanced at a 500-550 band level and revealed no obvious explanation for the phenotype of the index patient. Therefore, an array-CGH analysis (NimbleGen) was initiated and a 14,7 Mb gross deletion was found in chromosome 4q(del(4)(q21.23q23)) including approximately 50 genes.

Key Words: CCR, Interstitial deletion 4qchromosomal abnormalities

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ÖZET

İki ya da daha fazla kromozom kırıklarının yol açtığı, kompleks kromozomal yeniden düzenlenmeleri (KKY) oldukça nadir gözlenmektedir. KKY lerin kesin olarak aydınlatılması moleküler tekniklerle dahi zorluklar içermektedir. Bu anomalilerin sitogenetik ve moleküler detaylarının açıklığa kavuşturulmasında MLPA, dizin teknolojileri (CGH, BAC, oligo, SNP, vd.) etkili olarak kullanılmaktadır. Bu çalışmada makrosefali, öne çıkık belirgin alın, epikantus, pitoz, mikrognati, düşük kulaklar kısa boyun, pectus ekskavatum, içe dönük sağ ayak, kriptoorşidi, hipotoni ve nörogelişimsel gerilik bulguları olan multipl konjenital anomalili olguda yapılan kromozom analizinde kromozom 1, 2, 4, 8, 14 ve 16 nın katıldığı KKY saptanan olgu sunuldu. Sitogenetik çalışma sonrası anormal karyotip (46,XY,der(1),der(2),der(4),t(8;14),der(16)) olarak saptandı. Ticari problarla metafaz FISH çalışması karyotip ish t(1:16),ins(4;2),t(8;14) detaylandırıldı. 500-550 bant düzeyinde yapılan kromozom analizinde görünüşte dengeli kromozom anomalisi ve klinik bulguların açıklanamaması nedeni ile yapılan dizin çalışmasında (array-CGH:NimbleGen), kromozom 4q(del(4)(q21.23q23) bölgesini kapsayan 14.7 MBb büyüklüğünde yaklaşık 50 genin bulunduğu büyük delesyon gösterildi.

Anahtar Sözcükler: Kompleks kromozomal yeniden düzenlenmesi, intersisyal 4q delesyonu, kromozom anomalisi

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INTRODUCTION

The incidence of unbalanced structural chromosomal abnormalities has been estimated to be about 0.73/1000 in live borns(1) and CCR's are seen rarer. Kausch (1988) recognized three major categories of CCR's(2). The first one is three way exchanges, which is the most common category and includes three segments from three different chromosomes. The second category is more complex and involves more than one breakpoint per chromosome, and the third one is characterized by two or more independent simple translocations. Koussef categorized CCR's by the number of break points. Category I includes four and fewer breaks, and category II has more than four break points (3). Although apparently balanced, all types of CCR's are frequently associated with phenotypic abnormalities as compared to simple translocations (2,3,4,5). Imbalances may be hard to detect in the presence of numerous breakpoints and complex rearrangements.

New array-based techniques promise to be more efficient tools for the characterization of CCR's as compared to conventional cytogenetics (4,5,6,7).

We present here a patient with interstitial deletion 4q due to a complex rearrangement involving chromosomes 1, 2, 4, 8, 14, 16 and eight breakpoints.

CASE REPORT

The male proband was delivered at term after an uncomplicated gestation by cesarean section. The mother (22y) and the father (28y) were from different villages in Turkey and had no other children. The birth weight was 3630gr (50 percentile) and length 50 cm (50P). He was macrocephalic with a prominent forehead and a large anterior fontanel. He had thin eyelashes and eyebrows, a depressed nasal bridge, epicanthal folds, thin lips, micrognathia, a high and narrow palate, short neck, and bilateral cryptorchidism. He was hypotonic.

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At 1, 5 years cryptorchidism was corrected surgically. Until the age of 3,5 years he had been frequently been hospitalized because of respiratory infections. He had neurodevelopmental delay and did not speek.

At the age of 3,5 years he weighed 11800 gr(3-10P), measured 95 cm (25P) and had an occipito-frontal circumference of 53cm (97P).He had thin hair, arched and laterally wide eyebrows. His eyes were deep-set with epicanthal folds and ptosis. He had a wide depressed nasal bridge, hypoplastic maxilla, micrognathia, a high, narrow palate with regular dentition and thin lips. His ears were low-set. His neck was short and he had a relative shortness of the upper limbs. His thorax was narrow with pectus excavatum. His right foot had a lateral skeletal position anomaly. His hands and feet nails were short and wide. He was hypotonic (figure 1). Echocardiography, abdominal ultrasonography, audiologic tests and eye examinations were normal. Cranial magnetic resonance imaging showed hydrocephaly in the neonatal period. Radiographs showed hyper intensity of cranial bones.

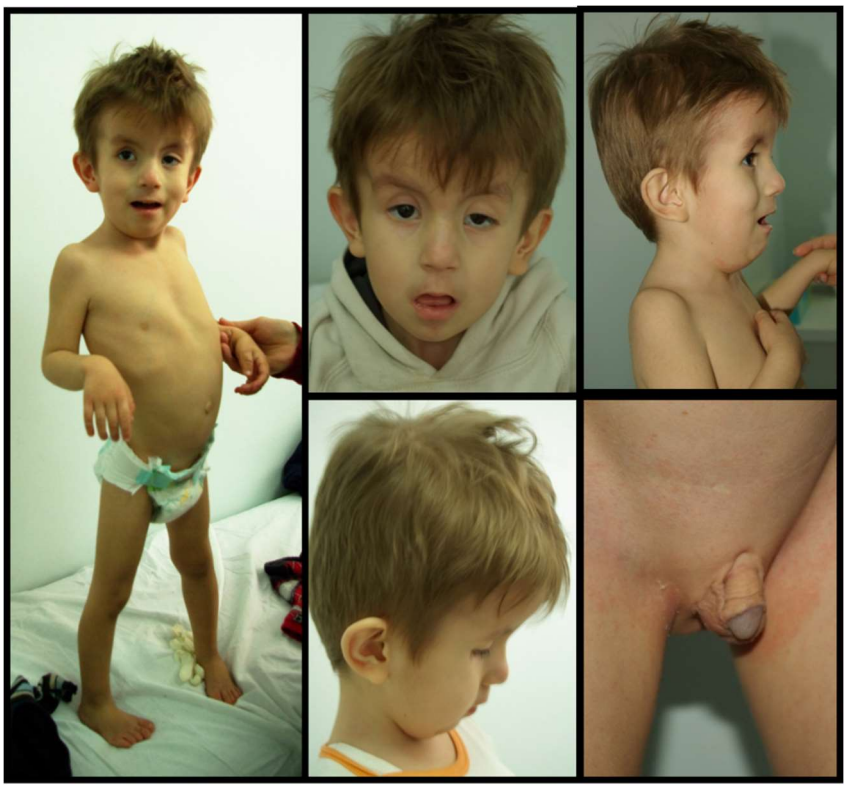

Figure1: Index

Cytogenetic analysis

Conventional chromosome analyses revealed CCR's involving the long arms of chromosomes 1, 2, 4, 8, 14 and 16 (figure 2). Karyotype was then defined as 46,XY,der(1),der(2),der(4),t(8;14)(q13;q13),der(16) (figure 2a). The rearrangements were apparently balanced at a 500-550 band level and revealed no obvious explanation for the phenotype. Parental chromosome analyses were both normal.

FISH

FISH results suggested that the CCR's were formed by two different translocations and one insertion (figure 2c-i). The karyotype was defined as follows :46, XY,der(1),der(2),der(4),t(8;14)(q13;q13),der(16).ish t(1:16)(q42;q13),ins(4;2)(q21;q33q37)?,t(8;14)(q13;q13)dn

There was no indication of a chromosomal imbalance.

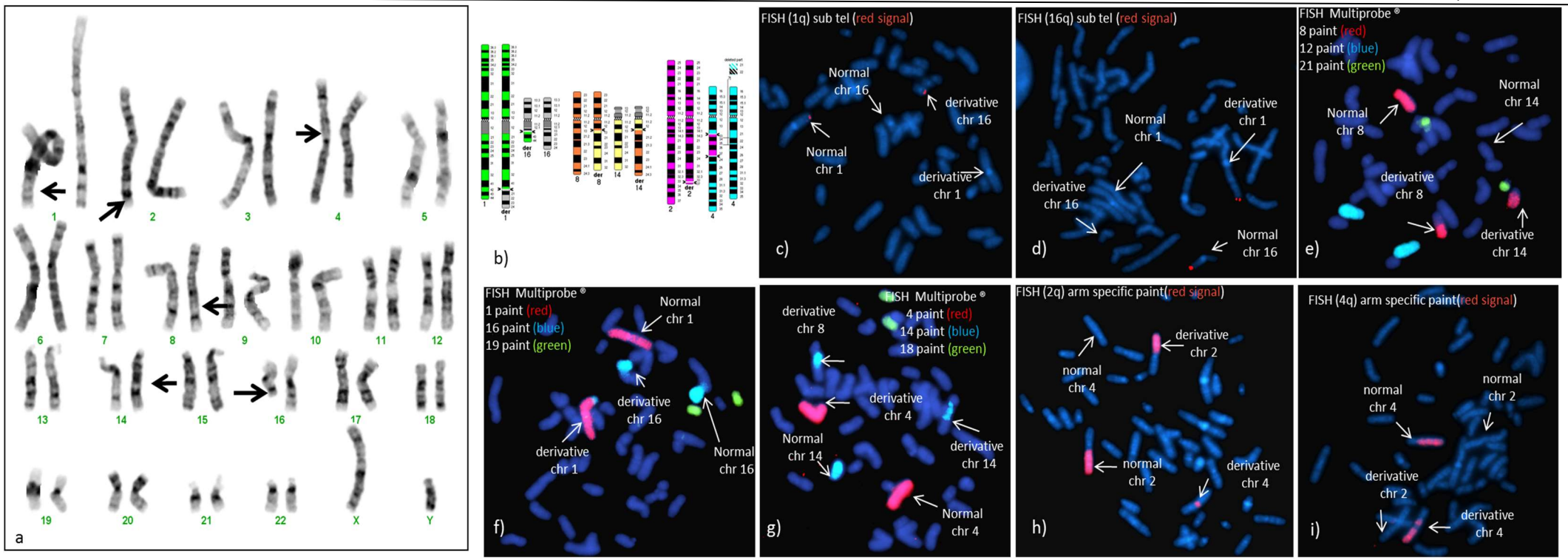

Figure 2: a) GTG banded karyotype, b)Partial derived idiograms, c) FISH with sub telomeric prob (Cytocell®) of 1q, d) FISH with sub telomeric prob (Cytocell®) of 16q, e, f, g) FISH Multiprobe ® Octochrome, h) FISH arm specific painting probe (Metasystem®) of 2q i) FISH arm specific painting probe (Metasystem®) of 4q

Array CGH

An array-CGH analysis (NimbleGen® HG 18 Tiling 385K CGH v2.0) was initiated and a 14,7 Mb gross deletion was found in chromosome 4q (del(4)(q21.23q23)).

The final karyotype designation is 46, XY,der(1),der(2),der(4),t(8;14)(q13;q13),der(16).ish t(1:16)(q42;q13),ins(4;2)(q21;q33q37)?,t(8;14)(q13;q13).arr(GRCh37) 4q21.23q23(85,600,000-100,300,000) x1dn (Figure 2b, figure 3)

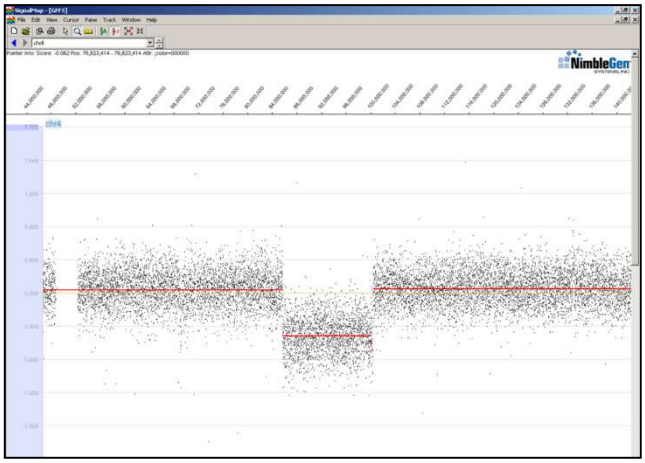

Figure 3: Signal maps picture of array CGH

DISCUSSION

This case nicely illustrates the diagnostic power of the new array technology. There are some 15 reported cases of del(4)(q21.23q23) (8,9,10,11,12,13,14,15,16,18,19,20,21,22,23). Eight of them had a prominent forehead, seven of them had hypotonia, low-set ears, 6 of them had mental retardation, short stature, depressed nasal bridge, 4 of them had micrognathia, 3 of them had high palate, 2 of them had short limbs, macrocephaly, hydrocephaly, delayed closure of fontanelles, speech delay and one had short neck, tapering fingers, cryptorchidism which were all seen in our patient anomaly (Table 1).

Table 1: Comparison of clinical finding of the case with literature

Clinical Findings	This case	*Literature* *(8,9,10,11,12,13,14,15,16,18,19,20,21,22,23)* (16 cases)
prominent forehead	+	8/16
hypotonia	+	7/16
low-set ears	+	7/16
mental retardation	+	6/16
short stature	+	6/16
depressed nasal bridge,	+	6/16
micrognathia	+	4/16
high palate	+	3/16
short limbs,	+	2/16
macrocephaly,	+	2/16
hydrocephaly,	+	2/16
delayed closure of fontanelle,	+	2/16
speech delay	+	2/16
short neck	+	1/16
tapering fingers	+	1/16
cryptorchidism	+	1/16
epicantus	+	-/16
ptotic eyelids	+	-/16
hypoplastic nails	+	-/16
right foot skeletal anomaly	+	-/16

In our case, array CGH studies led to the clear identification of del(4)(q21.23q23) which includes approximately 80 genes. 19 of them are marked as cDNA clone or putative protein on USCS database. Only 13 known genes are related with various diseases (Table 2).

Table 2: Known disease related genes in the deleted chromosome 4q

Gene symbol	Gene name	Ralated disease
MAPK10	mitogen-activated protein kinase 10	Epileptic encephalopathy, Lennox-Gastaut type, (autosomal dominant)
DSPP	dentin sialophosphoprotein preproprotein	Disorder: Deafness, autosomal dominant 36, with dentinogenesis, 605594 , Dentin dysplasia, type II, 125420, Dentinogenesis imperfecta, Shields type II, 125490, Dentinogenesis imperfecta, Shields type III, 125500, (autosomal dominant)
ABCG2	ATP-binding cassette, sub-family G, member 2	Disease Class: CANCER, PHARMACOGENOMIC Positive Disease Associations: cancer , irinotecan pharmacokinetics, irinotecan toxicity lung cancer, kidney cancer,lymphoma, rosuvastatin pharmacokinetics, (unknown inheritence)
PKD2	polycystin 2	Disorder: Polycystic kidney disease, adult, type II (autosomal dominant)
DMP1	dentin matrix acidic phosphoprotein isoform 1	Disorder: Hypophosphatemic rickets, 241520,(autosomal recessive)
SPP1	secreted phosphoprotein 1 isoform a	Disease Class: CANCER, CARDIOVASCULAR, IMMUNE, METABOLIC, OTHER Positive Disease Associations: asthma IgE, hepatitis B liver, cancer, intima media-thickness, nephrolithiasis ,pseudoxanthoma elasticum, rheumatoid arthritis, systemic lupus, (unknown inheritence)
SNCA	alpha-synuclein isoform NACP112	Disease Class: CHEMDEPENDENCY, NEUROLOGICAL, PSYCH Positive Disease Associations: alcohol abuse, Alzhemer's Disease, Parkinson's Disease, pyschoses ;methamphetamine depence Dementia, Lewy body, 127750, (autosomal dominant)
PGDS	prostaglandin-D synthase	Disease Class: IMMUNE Positive Disease Associations: Asthma, (unknown inheritence)
PDLIM5	PDZ and LIM domain 5 isoform e	Disease Class: PSYCH Positive Disease Associations: schizophrenia, (unknown inheritence)
BMPR1B	bone morphogenetic protein receptor, type IB	Disease Class: REPRODUCTION Positive Disease Associations: increased ovulation rate Disorder: Brachydactyly, type A1, D, type A2, 112600 , (autosomal dominant) Chrondrodysplasia, acromesomelic, with genital anomalies, 603248, (autosomal recessive)
RAP1GDS1	RAP1, GTP-GDP dissociation stimulator 1 isoform	Disorder: Lymphocytic leukemia, acute T-cell , (unknown inheritence)
ADH4	class II alcohol dehydrogenase 4 pi subunit	Disease Class: CHEMDEPENDENCY, NEUROLOGICAL, (unknown inheritence)
HNRNPDL	HNRPDL HNRPD-like protein au-rich element rna-binding factor JKTBP	Muscular dystrophy, limb-girdle, type 1G, (autosomal dominant)

Autosomal dominant limb-girdle muscular dystrophy (LGMD) type1G related *HNRNPDL* gene placed on the deleted region (17). The autosomal dominant PKD2 gene related to polycystic kidney disease, adult, type II and the DSPP gene related to deafness with dentinogenesis both map in this region. We will further evaluate our patient for possible symptoms. The differences of the clinical findings between our patient and the literature may be related to the break point disruptions and the size of the loss region.

Conflict of interest

No conflict of interest was declared by the authors.

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