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A case of recombinant chromosome 4: further delineation of the clinical features

Bir rekombinant kromozom 4 olgusunun klinik özelliklerinin ayrıntılı tanımlanması

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Abstract

Recombinant chromosome 4 is a very rare chromosomal aberration with eighteen cases reported in the literature up to date. Here we report a five years old male patient with de novo rec(4) dup(4p) del(4q). The physical examination findings were as follows: caput quadratum, flat occiput, low frontal hairline, hypertelorism, ptosis, blepharophimosis, high arched eyebrows, flat nasal root with anteverted nostrils and short nose, long and smooth philtrum, thin upper lip with triangular mouth, microretrognathia, high arched palate, dental anomalies, large low-set ears, short neck, broad chest with widely spaced nipples, micropenis, cryptorchidism. Conventional cytogenetic analysis revealed the karyotype as 46,XY,rec(4)dup(4p14p16.3)del(4q34.3q35). Flourescence in-situ hybridization (FISH) analysis with sub-telomeric probes for 4p and 4q showed duplication of 4p and deletion of 4q in recombinant chromosome 4. His parents' chromosomal analysis and sub-telomeric FISH analysis were both normal. The patient's final karyotype was reported as 46,XY,rec(4)dup(4p16.3p14)del(4q34.4q35).arr[hg19]4p16.3p14(68,345-36,018)x3,4q34.3q35(177,676,319-190,957,460)x1 detected by Microarray. According the literature all cases with recombinant chromosome 4 have similar clinical findings. Except for our case only one case in the literature has been reported to be de novo. In conclusion, we reported a very rare case of recombinant chromosome 4, which has the largest deletion and duplication in the literature. Further cases with similar findings would help the delineation of the findings associated with this chromosomal abnormality.

Key words: Recombinant chromosome 4,de novo, microarray.

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Özet

Rekombinant kromozom 4, literatürde bugüne kadar bildirilen 18 vakayla birlikte ender görülen bir kromozomal anormalidir. Bu yazıda de novo rec (4)dup(4p)del(4q) karyotipine sahip 5 yaşında bir erkek hastayı bildirdik. Hastanın fizik muayenesinde kaput kuadratum, yassı oksiput, düşük frontal saç çizgisi, hipertelorizm, pitozis, blefarofimozis, yüksek kemerli kaşlar, antevert burun delikleri ile düz burun kökü, kısa burun, uzun ve pürüzsüz filtrum, üçgen ince üst dudak, mikroretrognati, yüksek kemerli damak, diş anomalileri, geniş, düşük kulaklar, kısa boyun, geniş aralıklı meme uçları, mikropenis, kriptorşidizm saptanmıştır. Konvansiyonel sitogenetik analiz sonucunda karyotipin 46,XY,rec(4)dup(4p14p16.3)del(4q34.3q35) karyotipi saptanmıştır. 4p ve 4q için subtelomerik problarla yapılan floresan in-situ hibridizasyon (FISH) analizi, rekombinant kromozom 4'te 4p'nin duplikasyonunu ve 4q'nun delesyonunu göstermiştir. Yapılan microarray analizi sonrası hastanın son karyotipi 46,XY, rec (4) dup (4p16.3p14) del (4q34.4q35) .arr [hg19] 4p16.3p14 (68.345-36.018) x3,4q34.3q35 (177,676,319-190,957,460) olarak rapor edilmiştir. Literatüre göre rekombinant kromozom 4 olan tüm olgular benzer klinik bulgulara sahiptir. Bizim olgumuz dışında literatürde sadece bir olgunun de novo olduğu bildirilmiştir. Sonuç olarak, bu yazıda nadir bir rekombinant kromozom 4 olgusu bildirilmiştir. Benzer bulgulara sahip bildirilecek diğer vakalar, nadir görülen bu rekombinasyonun daha iyi tanımlanmasına yardımcı olacaktır.

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Anahtar kelimeler: Rekombinant kromozom 4, de novo, mikroarray.

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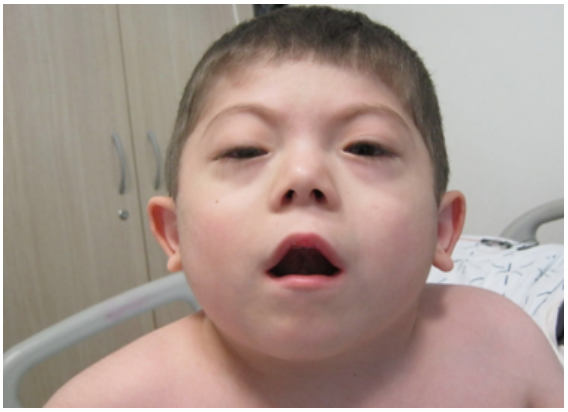
Introduction

Recombinant chromosome 4 is a very rare chromosomal aberration with eighteen cases reported in the literature up to date [1-11]. All of the reported cases are due to parental pericentric inversion of chromosome 4. Here we report a five years old male patient with de novo rec (4) dup (4p) del (4q). This is the second case with de novo rec(4)dup(4p) del(4q).

Clinical summary

The 5 years old patient was the first child of healthy non-consanguineous parents from the second pregnancy. The first pregnancy was a spontaneous abortion at 8th gestational week. He was born at 37th week of an uneventful pregnancy by vaginal delivery. At the time of birth his weight was 2580 gr (3 percentile), length was 49 cm (25 percentile). The patient's head circumference at birth was not available. His mother and father was 26 and 33 years old respectively, at the time of his birth. They also have a healthy boy from a third pregnancy.

The patient's weight was 18 kg (25 percentile), height was 94 cm (<3 percentile) and head circumference was 51 cm (25-50 percentile) at the age of five years. The physical examination findings were as follows: caput quadratum, flat occiput, low frontal hairline, hypertelorism, ptosis, blepharophimosis, high arched eyebrows, flat nasal root with antevert nostrils and short nose, long and smooth philtrum, thin upper lip with triangular mouth, microretrognathia, high arched palate, dental anomalies including malocclusion and microdontia, large low-set ears, short neck, broad chest with widely spaced nipples, micropenis, bilateral cryptorchidism which required orchiopexia (Figure 1a, 1b). He also had bilateral hearing impairment which required bilateral cochlear implant, immune deficiency with low level of IgE and IgG with recurrent airway infections, laryngomalacia, congenital heart malformations (patent ductus arteriosus, ventricular septal defect, dextraposition of aorta, right bundle branch block), multiple hypophyseal hormone deficiency with low levels of parathormone, luteinizing hormone, follicule stimulating hormone. He also had growth and psychomotor retardation. However developmental test could not be performed to the patient. Conventional cytogenetic analysis with standard G-banding revealed the karyotype as 46,XY,rec(4)dup(4p14p16.3)del(4q34.3q35) (Figure 2a).



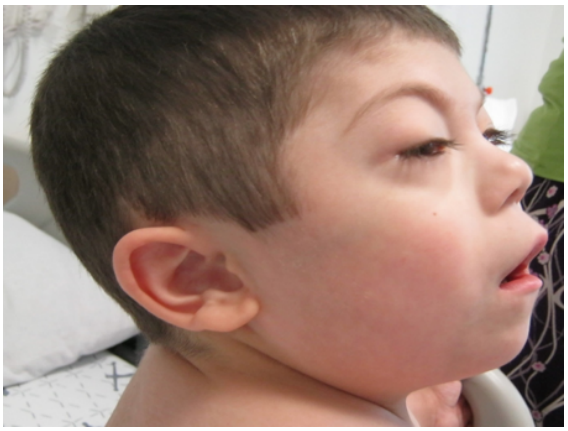


Figure 1 a, b. Facial dysmorphic features of patient (5 years old). Note the low frontal hairline, high arched eyebrows, ptosis, antevert nares, long philtrum, thin upper lip.

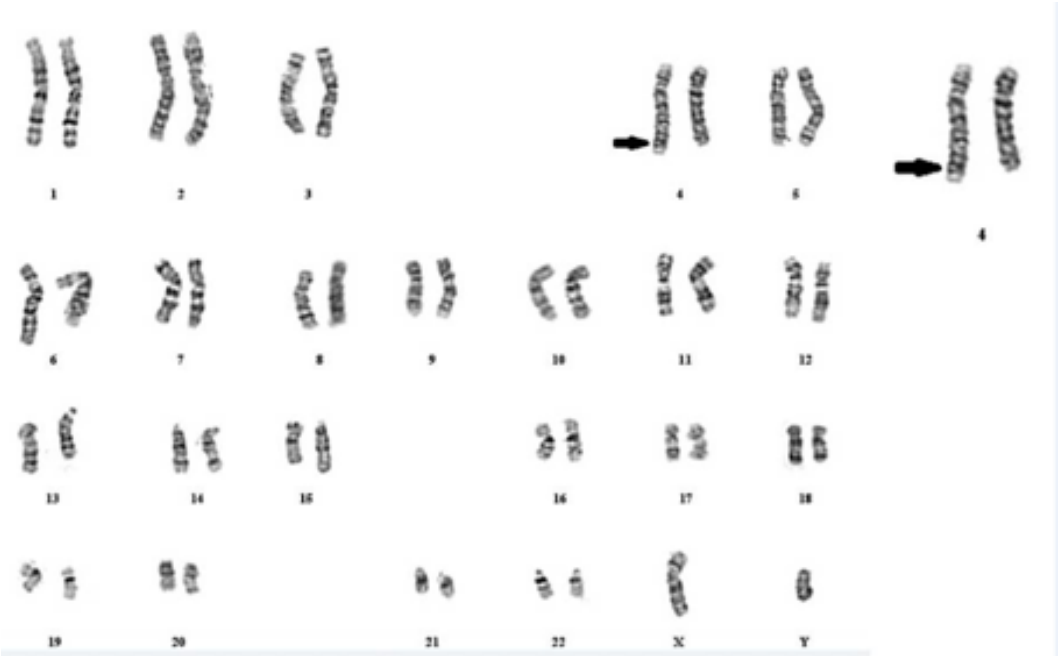


Figure 2a. Karyotype of the patient with standart G-banding. Note the additional 4p terminal bands on 4q (arrow).

Flourescence in-situ hybridization (FISH) analysis with sub-telomeric probes for 4p and 4q showed duplication of 4p and deletion of 4q in recombinant chromosome 4. His parents' chromosomal analysis and sub-telomeric FISH analysis were both normal.

Results

Conventional cytogenetics

Chromosome analysis of the patient and his parents were performed from cultured peripheral lymphocytes using standard G-banding and revealed 46,XY,rec(4)dup(4p14p16.3) del(4q34.3q35) for the proband (Figure 2a) while the parents had normal constitutional karyotypes.

Flourescence in-situ hybridization

Duplication of 4p and deletion of 4q in the recombinant chromosome 4 were confirmed by 4p and 4q specific sub-telomeric probes. On the recombinant chromosome 4, double and symmetrical signals of the 4p sub-telomeric probe were detected, however, no signal for 4q was observed (Figure 2b).

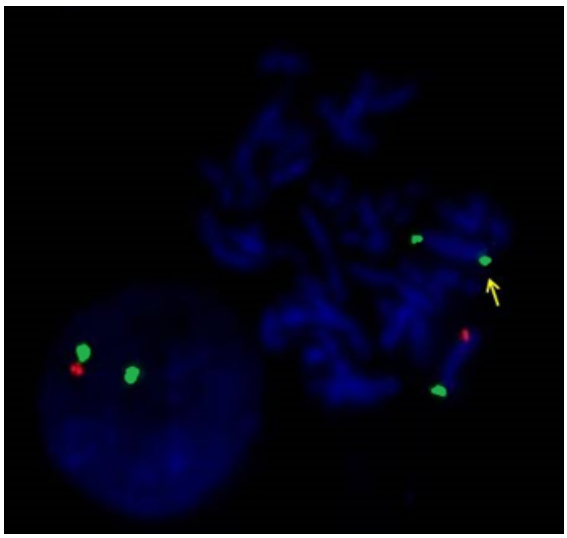


Figure 2b. Duplication 4p, deletion 4q detected on recombinant chromosome 4 by sub-telomeric FISH probe (Chromoprobe Multiprobe- T System, Cytocell Ltd., Cambridge, UK). Arrows indicate the duplicated 4p material on both ends of the choromosome (green signals).

Array CGH

We detected 35949,8 Kb duplication on 4p and 13281,1 Kb deletion on 4q by using Affymetrix CytoScan® 750K SNP array (Affymetrix Inc., California, USA) (Figure 3). There are 104 and 24 OMIM (Online Mendelian Inheritance in Man) listed genes in the duplicated and deleted regions respectively. Thirty of the duplicated and 10 of the deleted genes were associated with clinical phenotypes. The patient's final karyotype was reported as 46,XY,rec(4)dup(4p16.3p14)del(4q34.4q35).arr[hg19]4p16.3p14(68,345-36,018)x3,4q34.3q35(177,676,319-190,957,460)x1.

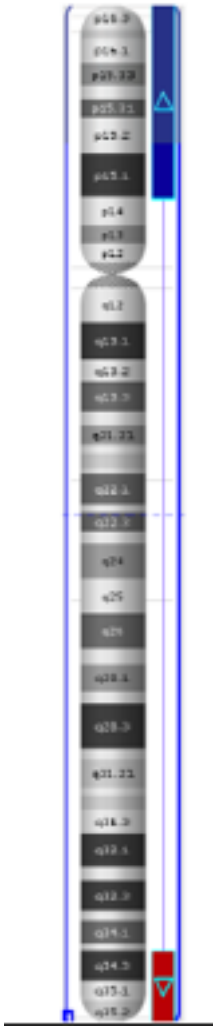


Figure 3. Gene view output from Chromosome Analysis Suite (ChAS) software (Affymetrix, Inc., Santa Clara, CA, USA). The top line shows the segmental copy number state where the blue bar indicates gains and the red bar indicates the losses, consistent with the following graphics located below. The bottom graph shows the Log2 ratio data for two which is plotted by position along chromosome. Approximately 36 Mb duplication and 13.3 Mb deletion at chromosome 4 was determined. Individual probes are represented as dots according to their position in the genome. Vertical bars indicate individual genes, their position in the genome, and size.

Discussion

We reported a case with de novo recombinant chromosome 4 which had the largest deletion and duplication in the literature, to the best of our knowledge, in this clinical report. Recombination of chromosome 4 is a very rare event with eighteen reported cases in the literature up to date [1-10]. Ten of them were because of parental pericentric inversions of chromosome 4 (6 paternal/ 4 maternal). Except for our case only one case in the literature has been reported to be de novo [4]. FISH was only performed to four of all reported cases [8-10] and only two of them were confirmed with array CGH [9-10]. According the literature, all cases have the same or very close breakpoints, within sub-bands p13~p15 and q35 (Table 1).

As shown in table 1, all cases with recombinant chromosome 4 have similar clinical findings. Due to little changes in breakpoints, there are some differences between clinical findings. Our patient had laryngomalacia, similar to the patient reported by Battaglia et al., and multiple hypophyseal hormone deficiency reported to be the first case in the literature. Loss of several genes including DCTD, ING2, and MLF1IP located on 4qter may be responsible for this entity since these genes are predominantly expressed in thyroid (DCTD), testis and adrenal gland (ING2), and testis (MLF1IP).

There are some clinical findings reported in the literature due to duplication of the distal 2/3 of p arm of chromosome 4: mental retardation, growth retardation, microcephaly, prominent glabella, small forehead, low hairline, deep-set eyes, downslanted palpebral fissures, broad and flat nasal root with bulbous or pug nose tip, trianguler mouth, high arched palate, large low-set posteriorly rotated ears, short neck, widely spaced nipples, join contractures, malposition of fingers and toes and for male patients, genital anomalies [6-9].

Table 1. Clinical features of the patients with recombinant chromosome 4 and our patient.

	Wilson *et al.* (1970)	Dallapiccola *et al.* (1974)	Rethore *et al.* (1974)	Kleczkowska *et al.* (1992)	Hirsch and Baldinger (1993)	Battaglia *et al.* (2002)	Garcia-Heras and Martin (2002)	Stembalska *et al.* (2007) (older proband)	Stembalska *et al.* (2007) (younger proband)	Maurin *et al.* (2009)	Morteza *et al.* (2013)	Our patient
Sex	M	F	M	F	F	M	F	F	F	F	M	M
Breakpoints	N/A	p13q35	p14q35	p14q35.2	p15.32q35	p14q35	p15q35	p14q35	p14q35	p15.1q35	p15.1q35	p14q34.3
Size of duplication	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	32 Mb	23.81Mb	35.94Mb
Size of deletion	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	4Mb	4.36Mb	13.28Mb
Parental origin	P	P	P	De novo	P	M*	M*	M*	M*	P	P	De novo
Growth retardation	+	+	+	N/A	N/A	+	+	-	-	+	+	+
Psychomotor retardation	+	+	+	+	+	+	+	+	+	+	+	+
Microcephaly	+	+	+	+	N/A	+	+	+	+	-	+	-
Pointed chin	+	+	+	+	N/A	N/A	-	+	+	+	+	+
Thin upper lips	+	+	+	+	N/A	+	-	+	+	+	+	+
Abnormal ears	+	+	+	+	+	+	-	+	+	+	+	+
Short neck	N/A	+	+	+	N/A	+	+	+	+	+	+	+
Broad chest	N/A	+	+	+	N/A	+	+	+	+	N/A	+	+
Dental anomalies	N/A	N/A	N/A	+	N/A	N/A	+	+	+	-	-	+
Congenital heart defects	-	-	+	N/A	N/A	+	+	-	-	+	+	+
Genital Anomalies	+	-	+	N/A	N/A	+	-	-	-	-	+	+
Laryngomalacia	-	-	-	-	-	+	-	-	-	-	-	+
Coloboma	+	-	-	N/A	N/A	+	-	-	-	-	-	-
Wide spaced nipples	N/A	+	+	+	N/A	N/A	+	-	-	+	-	+

F: Female, M: Male, M*: Maternal, P: Paternal, N/A: Non-available

Cardiac defects are rarely seen in pure duplication 4p cases. In recombinant chromosome 4 cases cardiac defects and urogenital malformations are probably due to the deletion of 4q terminal bands [9]. Our patient had three genes deleted in this region which are located to 4q35.1 and highly expressed in cardiac tissues; SLC25A4, SORBS2 and PDLIM3. SORBS2 protein is expressed 50 to 200 fold higher in heart than in other tissues. It is important in signal coordination and cell adhesion [9]. PDLIM3 is also highly expressed in cardiac muscle and important for the development of cardiac muscle [9]. SLC25A4, on the other hand, is a member of the mitochondrial carrier subfamily of solute carrier protein genes. SLC25A4, forms a dimer on the mitochondrial membrane, which carries ADP across the inner membrane into the mitochondrial matrix and ATP from the matrix into the cytoplasm [12]. Deletion of 4q35.1 region causes cardiac defects because of the loss of these genes.

In conclusion, we reported a very rare case of recombinant chromosome 4, which has the largest deletion and duplication in the literature. Further cases with similar findings would help the delineation of the findings associated with this chromosomal abnormality.

Conflict of interest: No conflict of interest was declared by the authors.

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