

## **Congenital Hypothyroidism in Two Infants with "De Novo" Translocated Down Syndrome: A Case Report**

### **“De Novo” Translokasyonlu İki Down Sendromlu Bebeğe Konjenital Hipotiroidizm: Vaka Sunumu**

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#### **Özet:**

Down Sendromu en yaygın kromozomal anöploididir ve zeka geriliğinin en yaygın genetik nedenidir. Genellikle, fazla bir kromozom 21 ile karakterizedir. Görülme sıklığı 1:100'dir. Down sendromunun bir formu da kromozomun uzun kolunun 21q [dup(21q)] "de novo" çoğalmasına bağlı gelişir. Down sendromlu bebekler konjenital hipotiroidizm açısından yüksek risk taşımaktadır (1). 'De Novo' prezentasyonlar 25000 canlı doğumda 1 oranında nadir görülür. Bu nedenle Down sendromlu bebeklerde dup (21q) sıklığı %2 iken 'de novo' translokasyonlu hastalarda konjenital hipotiroidizm saptanması ilgi çekicidir. Down Sendromunun klinik özelliklerini gösteren iki hastaya konvensiyonel sitogenetik teknikler uygulanmış ve karyotipleri 46,XX, rob (21) (q10q10) ve 46, XY, rob (21) (q10q10) bulunmuştur. Ailelerin karyotipleri normaldir. Bebeklerde ayrıca konjenital hipotiroidizm de saptanmıştır. 'De novo' Down sendromu ve konjenital hipotiroidizm birlikteliği nadir bulunduğundan bu iki vaka bildirmeye değer bulunmuştur.

**Anahtar sözcükler:** Down Sendromu, de novo, translokasyon 21/21

#### **Summary:**

Down Syndrome (DS) is the most common chromosomal aneuploidy and also the most common genetic reason of mental retardation. It is generally characterized by an extra chromosome 21. The incidence is 1:1000. One form of Down syndrome is due to "de novo" duplication of chromosome 21q [dup(21q)]. Infants with Down syndrome are at high risk for congenital hypothyroidism (1). Since 'de novo' presentations are rare as 1 over 25000 live births and the frequency of dup (21q) is 2% of Down patients the presence of congenital hypothyroidism in 'de novo' Down patients is intriguing. Here; conventional cytogenetic analysis was carried out for two cases with clinical features of Down syndrome and the karyotypes were found as 46, XX, rob (21) (q10q10) and 46, XY, rob (21) (q10q10). Both of the babies had congenital hypothyroidism and were under treatment. Since the association of 'de novo' Down syndrome and congenital hypothyroidism is rarely reported in literature; it was found these cases worthreporting.

**Key words:** Down Syndrome, de novo, translocation 21/21

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#### **Introduction**

Down syndrome (DS) is the most common chromosomal aneuploidy syndrome which was first clinically described at 1866 by J. Langdon Down and named after him. Furtherly the syndrome was identified as a chromosome 21 trisomy by Dr. Jérôme Lejeune in 1959 (3). The incidence is about one of every 800-1000 babies born all over the world each year. It is generally characterized with the presence of all or part of a third copy of chromosome 21. In addition to most common physical characteristics like interior epicanthic folds, small mouth and teeth, flat nasal bridge, the babies are generally motor/mentally retarded.

Congenital heart disease, hypotonia, short neck, shortened hands and clinodactyly are also common (4).

Trisomy 21 (47,XX,+21) is caused by a meiotic nondisjunction event during gametogenesis and results with the production of an extra copy of chromosome 21 leading to structural and functional abnormalities (5). In general, 90% of cases with DS are due to pure trisomy 21 which is called the classical type, 6-7% are of mosaic type (the presence of normal and abnormal cell types) and 3-4% are due to Robertsonian location (6,7).

In the Robertsonian case, the long arm of chromosome 21 is attached to another chromosome, often chromosome 14 [45, XX, der (14;21) (q10;q10)] yet it may be with any other acrocentric chromosome. A person with such a translocation is phenotypically normal. The presenting karyotype will be 45, XX, t(14;21) but 14th chromosome will have an extra translocated chromosome 21. This may also occur with translocation of two chromosome 21s as 45, XX, t(21q;21q). Although the rearrangements between Rob (14q21q) and (21q21q) take place at equal frequencies, nearly half of rob (14q21q)s come from one of the carrier parents while most (95%) of rearrangement (21q21q)s occur as de novo (8,9) in which there is an aberrant chromosome consisting of two long arms of human chromosome 21.

The prevalence of hypothyroidism is 3%, in cases of DS which is higher than the normal population. Since ‘de novo’ translocations are 2-3% of cases of DS, the association of ‘de novo’ translocations and congenital hypothyroidism is expected to be rare (10). We couldn’t find enough information on this association in the relevant literature and therefore found these cases worth reporting.

### Case Reports

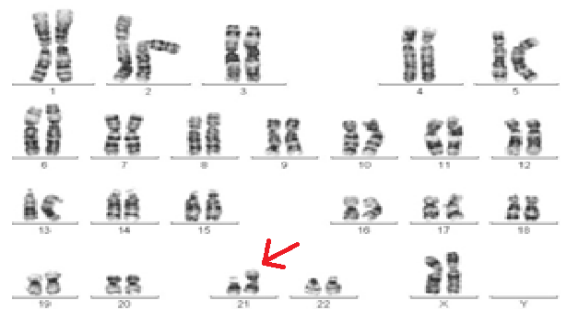
Two patients aged 4 and 9 months with classical findings of DS (hypertelorism, flat nasal bridge, mongoloid facial appearance, palmar simian lines) were sent for genetic analysis from outpatient clinic of Family Medicine of Istanbul Medeniyet University, Goztepe Training and Research Hospital in 2011. Chromosomal analysis of peripheral blood lymphocytes was performed according to standard protocols (11). Peripheral blood was drawn and mononuclear cells isolated from the buffy coat by centrifugation were suspended in RPMI 1640 medium supplemented with 10% (v/v) heat-inactivated fetal calf serum and 2% phytohemagglutinin (PHA) for 72 hours at 37°C. Chromosome preparations were obtained from lymphocyte cultures and analyzed after Giemsa-Trypsin-Giemsa (GTG)-banding (12). 30-50

metaphases of each individual were analyzed for karyotypes of suspected structural and numerical anomalies. The karyotypes were interpreted using the recommendation of the International System for Human Cytogenetic Nomenclature 2005 (ISCN) (9).

### Findings

Cytogenetic analysis showed karyotypes 46, XX, rob (21) (q10q10) (figure 1) and 46, XY, rob (21) (q10q10) (figure 2). The first case had interatrial septum secundum defect. Her sibling did not have similar karyotypes. Both cases were under treatment for congenital hypothyroidism. The parental age was 28 and 29 respectively and had normal karyotypes.

**Figure 1.** Karyotypes 46, XX, rob (21) (q10q10)



**Figure 2.** Karyotypes 46, XY, rob (21) (q10q10)



## Discussion

The prevalence of thyroid diseases in Down syndrome which is characterized by typical phenotype, dysmorphic facial characteristics and mental retardation is 3% which is higher than normal population (13). In a study with infants having Down syndrome, the risk of congenital hypothyroidism is found to be 35 times higher than the normal population (14). Since hypothyroidism may be congenital or acquired, these patients should be followed up periodically for thyroid functions. Many studies failed to demonstrate the reason for the common association of non-otoimmune subclinical hypothyroidism and TSHr and Gs (alpha) genes (15).

We could not do a statistical comparison due to the small number of our cases. Nevertheless, we believe that this presentation will create a data for further studies. More comprehensive functional and molecular research is necessary for further significant interpretations.

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