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AN 11-YEAR-OLD BOY WITH DOWN SYNDROME PHENOTYPE AND PARTIAL DUPLICATION IN 21Q11.2-Q21 REGION

S t r e s z c z e n i e: Opis przypadku 11-letniego chłopca z zespołem Downa ze stwierdzoną *de novo* częściową duplikacją chromosomu 21. pary. W pracy dokonano prezentacji algorytmu diagnostycznego, jak również skrótowego przeglądu literaturowego.

A b s t r a c t: We report a clinical case of an 11-year-old boy with *de novo* partial duplication of chromosome 21st pair and some clinical features of Down syndrome. Using hr – CGH method (high resolution Comparative Genomic Hybridization) we detected a quantitative change (a duplication) in 21q21 – q11.2 region. To confirmed the results of hr-CGH analysis we used Quantitative Fluorescent Real Time PCR method with four primers for two different genes located in duplication region.

K e y w o r d s: Down syndrome, hr-CGH, partial duplication, Quantitative Fluorescent Real Time PCR.

I n t r o d u c t i o n: Down syndrome (DS) is a chromosomal disorder caused by the presence of all or part of an additional 21st chromosome [3], [4], [5]. Investigations made during the last 20 years showed that partial trisomy of 21q22 regions is a sufficient determinant of clinical symptoms DS. Down syndrome is always associated with some intellectual and cognitive ability impairment, physical growth retardation and a particular set of dysmorphic facial features.

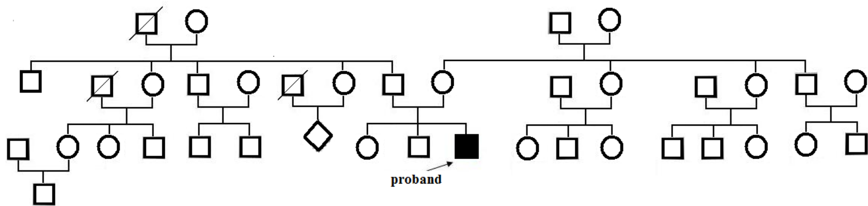
Individuals with Down syndrome tend to have a lower than average cognitive ability, often ranging from mild to moderate developmental disabilities. A small number have severe to profound mental disability. Health concerns for individuals with Down syndrome include a higher risk for congenital heart defects and thyroid dysfunctions.

M a t e r i a l s: We present a boy with some dysmorphic features typical for Down syndrome with a duplication in 21q11.2-q21 region. A proband was born to a G3, P3 (third pregnancy) healthy mother at 40 weeks of gestation. The parameters at birth were: weight 3420 g, length 56 cm, head circumference 34 cm, Apgar score 9 points. A psychomotoric development was normal at first, nevertheless a speech delay was observed. According to a consulting psychologists his cognitive ability is lower than average. That is why, a boy was sent to school with a one-year delay. Although he follows an individual syllabus. The child showed difficulty in knowledge acquisition. No congenital defects were detected.

Clinical evaluation of the child revealed hypotrophy, mild muscle hypotonia and a variety of dysmorphic features, including high forehead, hypertelorism, upslanting palpebral fissures, epicanthal folds of the eyelids, long and flattened philtrum, thin lips, brachydaktyly and short, broad hands.

Both parents and siblings of patient were healthy. Genealogy was not charged in the direction of genetically determined diseases. On figure bellow (Figure 1) we present the proband's pedigree.

Figure 1. The proband's pedigree



M e t h o d o l o g y: Classical cytogenetic analysis chromosomes in T-cells from peripheral blood – 550 GTG banding method – revealed a normal male karyotype 46, XY. Hr – CGH analysis, which is used for detection of small unbalanced chromosomal translocations [2], showed duplication on long arm chromosome 21th pair (Figure 2) in region of q21-q11.2 band. Twenty metaphases target slides were analyzed what resulted in average value from 35 chromosomes 21th pair – five chromosomes were throwed aside become of chromosomal collisions. To eliminate the possible mistakes and the false positive results

the molecular analyses were conducted. Two randomly chosen genes located in duplication region – *JAM2 (junctional adhesion molecule 2)* and *TMPRSS15 (transmembrane protease, serine 15)* were analysed. *B-actin* gene with a locus on chromosome number 7 was used as a control. In Table 1 we present additional information for both genes.

Table 1. Characteristic of *JAM2* and *TMPRSS15* genes

	Gene	Primer's sequence (5'→3')	Product's size	Gene's localization
1.	*JAM2*	GAAGGCAAAGACCTAAAATGGCT TTGGCAGTGTTGTAATGCCTATG	*276*	*27,011,584-* *27,089,874*
2.	*TMPRSS15*	GGCTCGTGAAGGTGCTCTCAGC CGGAGTTGCTACTCAGTTTGTGACC	522	*19,641,433-* *19,775,970*

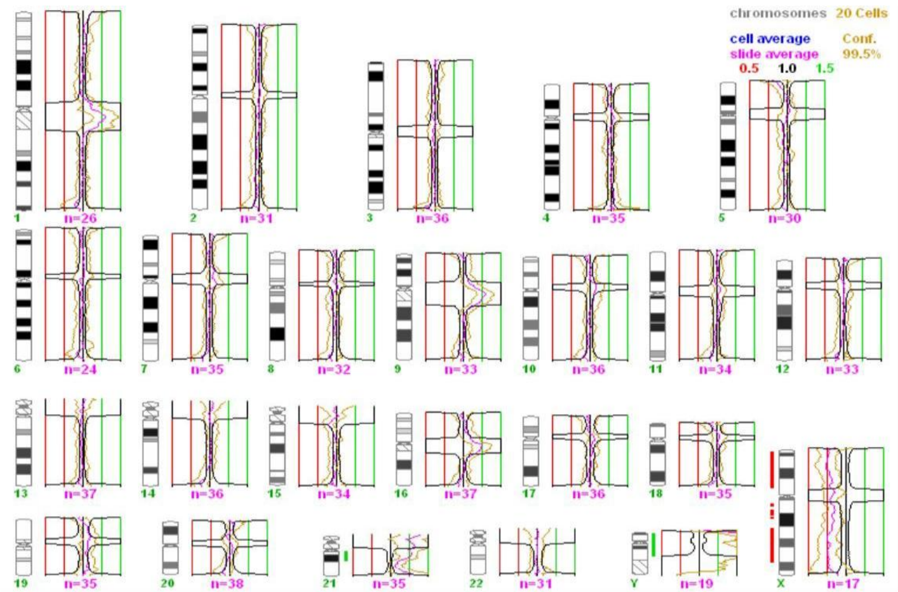
Reference DNA was isolated from 8 healthy people. Results of quantitative real time PCR – Syber® Green analyses showed that both genes (*JAM2, TMPRSS15*) were present in three copies – procedure was repeated twice (see Table 2). Every time we used two different thinning of DNA (100 and 50 ng per probe) [1].

Table 2. Results of Quantitative Fluorescent Real Time PCR

Gene	Value of used DNA	ΔCt (probe)	ΔCt (control sample)	ΔΔCt [%]
JAM2	50ng	4,050	4,704	157,353
	100ng	3,105	3,61	141,912
TMPRSS15	50ng	3,980	4,497	142,109
	100ng	3,035	3,580	145,902
Average value of ΔΔCt from all experiments				146,819

In support of analyses we established the size of change on about 7 Mbp.

Figure 2. Results of hr – CGH analysis. The green colour on ideogram of chromosome 21st pair marks the region of duplication. Sex chromosomes are false, positive control



D i s c u s s i o n a n d c o n c l u s i o n s: Down syndrome due to 21 trisomy is the most common cause of mental retardation and developmental malformation (congenital heart defects) in our population. Investigations made during the last 20 years showed that partial trisomy of 21q22 regions is a sufficient determinant of clinical symptoms DS. This region has been called "Down's syndrome critical region". Our case showed that partial trisomy 21q11.2-q21 region can be the cause of some symptoms of DS what is in agreement with the results of other studies. It is possible that imperfection of hr-CGH method (the lack of possibility of identification the cell mosaics, unbalanced chromosomal changes with the frequency lower than 25% and the size smaller than 2-4 Mbp) influenced on possibility of detection changes in critical for DS region 21q22 in this case, however received diagnostic conduct permits us to suggest about correctness of results [6].

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