TWO CASE STUDY:

Miller-Dieker-syndrome without lissencephaly and 7q11.23-duplication syndrome

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Authors: Ruszova E., Havlikova P., Jiraskova L., Skutilova V., Senkerikova M.
Department of Clinical Genetics, University Hospital Hradec Kralove

Introduction

This study presents two CGHarray results that were not easy to interpret. In case of our first patient E.Z. (born in 2014) microdeletion (≈2,45 Mbp) in the region 17p13.3, which overlaps a minimal critical Miller-Dieker syndrome (MDS) region, was revealed. PAFAH1B1(LIS1) gene, as a candidate gene for lissencephaly was placed outside of the CNV variant. In our second case of patient J. P. (born in 2012), CGHarray identified CNV variant (duplication, ≈1,3 Mbp) in the region 7q11. 23. The aim of the study was to decide between Williams-Beuren syndrome (WBS) via interruption of *GTF2IRD1* gene and 7q11.23- duplication syndrome.

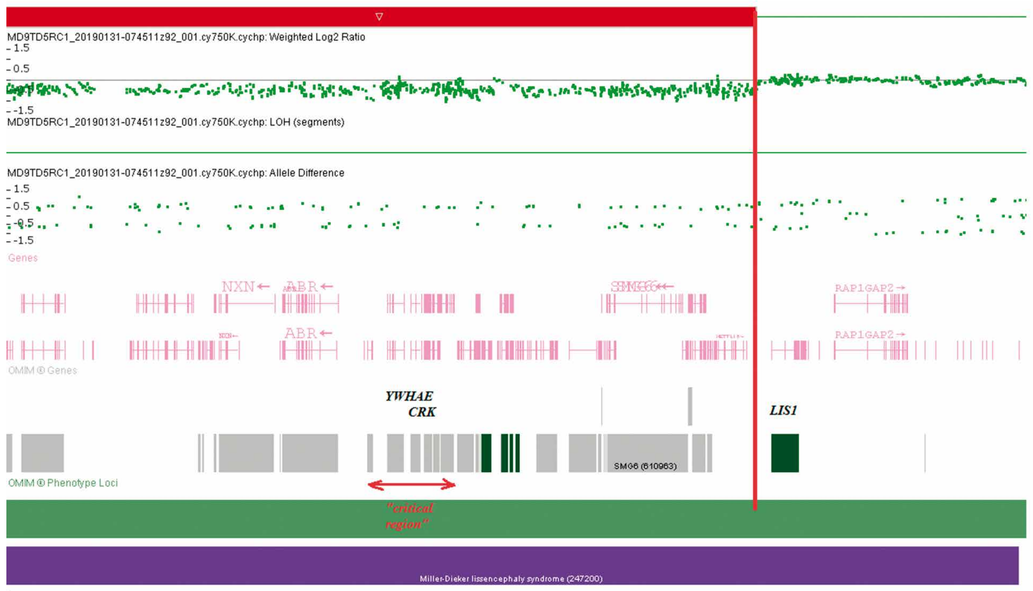
Materials and mothodology

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of University Hospital Hradec Kralove. Patient's DNA was isolated from the whole blood according to the standard procedures (DNA 101 MagCore Genomic DNA Whole Blood Kit, RBC Bioscience, Taiwan). 300 ng of DNA was digested, labeled and hybridized according to the manufacturer's instructions (Cytoscan assay protocols, Affymetrix, ThermoFisher, USA). Cytoscan human oligonucleotide microarrays, platform 750 K were used to analyze the genome. The respective theoretical resolution levels of the microarrays were 100 kbp. The arrays were scanned using the GeneChip microarray scanner 3000 7G (Affymetix, ThermoFisher, USA). Data were analyzed using the AMDS v.1 software and CNVs were detected in the Chromosome Analysis Suite (CHAS) v.4 software (Affymetrix, ThermoFisher, USA).

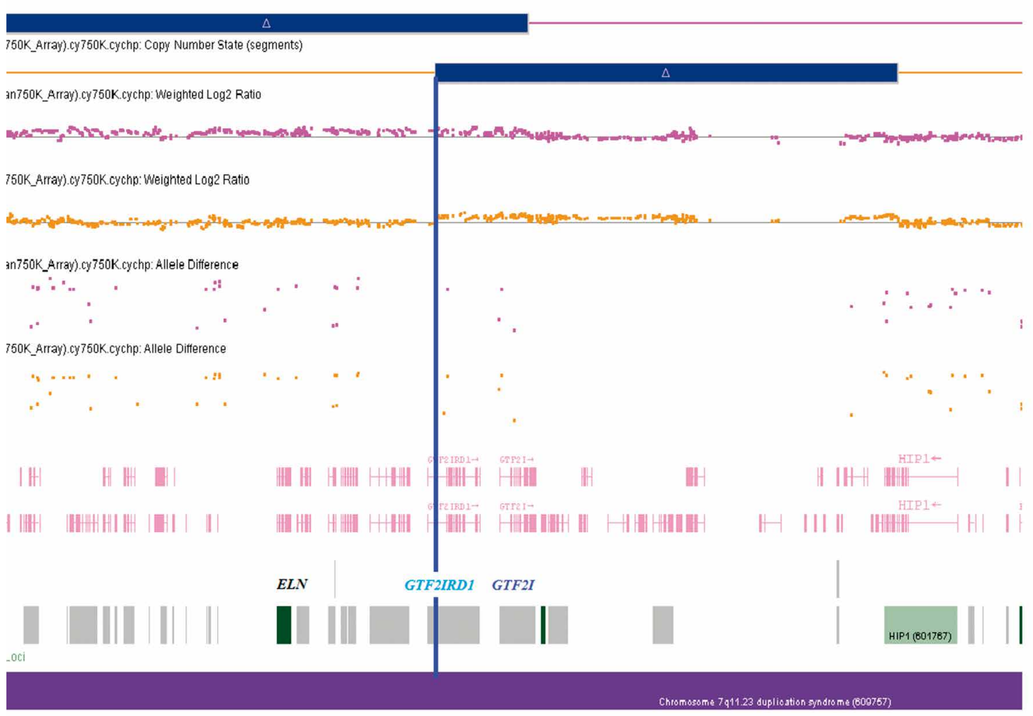
Results

Ad1) Assessed genotype pathological, *de novo* CNV variant was observed: arr[hg19] 17p13.3(525_2446505)x1 involving the „MDS telomeric critical region" with *TUSC5, YWHAE, CRK, MYO1C, SKIP* genes and exons 1 to 4 of the *PITPNA* gene. The minimal MDS critical region spans only about 258 bp[1] (**Picture n. 1**, *patient E.Z.*).

Ad2) Assessed genotype pathological, arr[hg19] 7q11.23(73891944_75197788)x3 was detected. Gene elastin (*ELN*) answerable for congenital heart disease (CHD) lied outside the WBS typical region (**Picture n. 2**, *patient J.P.*). This duplication of 1,3Mbp in size interferes with *GTF2IRD1* gene, therefore integrity interruption of the gene cannot be excluded. The same CNV variant was determined in mother.



Picture n. 1: Array comparative genomic hybridisation (aCGH) ratio plot showing loss in the region 17p13.3 (patient E.Z.).



Picture n. 2: Array comparative genomic hybridisation (aCGH) ratio plot showing gain in the region 7q11.23 (patient J.P. - orange sample in comparison to the "typical" 7q11.23 microduplication - purple EQA sample).

Discussion

Review of all published cases[2] indicates that deletion of *YWHAE* gene, not *LIS1* gene, results in cognitive impairment, structural abnormalities of the brain (neuroradiologic changes) and facial dysmorphism. Gene *CRK* seems to be a candidate gene for growth restriction[2].

Gtf2I transcription factor family is the main candidate sensitive to dosage in WBS region[3]. According to Schneider et al. (2012)[4], *GTF2IRD1* tr. factor contributes to the neurologic deficits, craniofacial abnormalities, motor coordination and anxiety, decreased spontaneous and diminished motor coordination and strength. Even though a perturbation of *GTF2IRD1* gene cannot be omitted, presence of the same CNV variant in mother and patient's phenotype accompanied with mild developmental delay, severe speech and language delay, hyperactivity disorder, normal locomotor activity, normal social interaction in small groups, normal hearing, normal response to loud noises, no ocular problems, normal iris, normal malar area, short philtrum and thin lips more likely points to the 7q11.23-duplication syndrome.

Conclusion

Analyses suggest that additional genes distal to *LIS1* may be responsible for the variable phenotype consisting of developmental delay, facial dysmorphology, growth retardation and other abnormalities seen in MDS but not in isolated lissencephaly patients (ILS). Large deletions toward 17p telomere, including *YWHAE* gene result in more severe phenotype as observed in MDS.

Our first laboratory experience with the 7q11.23-duplication case, a new emerging syndrome (associated with severe delay in expressive language-that is distinct from any other typical clinical features seen in WBS), is connected with patient's „normal" face finding and inheritance of duplication from a parent (normal/or very mildly affected).

References

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[4] Schneider et al. 2012, *J Autism Dev Disord.* 42(7): 1459-69. doi: 10.1007/s10803-011-1389-4