Array CGH identified rare chromosomal micro-imbalance
tin three patients with congenital malformations and
ternal retardation

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Introduction

In Bulgaria, about 3,100 children are born with congenital malformations annually. Most malformations are present at delivery and are due to genetic and non-genetic factors. Submicroscopic chromosome aberrations can cause mental retardation (MR), congenital malformations and miscarriages. The etiology of intellectual and developmental impairment remains unidentified in about 50% of the patients despite extensive clinical examinations and laboratory investigations.

Case 1: Clinical summary

We report the details of a 15 months old boy. The patient was born from fourth uneventful pregnancy. He was referred for genetic diagnosis, because of developmental delay and dysmorphic features. His facial features were distinct with hypertelorism, depressed nasal bridge, epicanthic facial asymmetry with right facial hypertrophy, malformed auricles and bilateral simian creases.

Case 2: Clinical summary

We present here details of a six months old boy who was referred for genetic evaluation due to the developmental delay and dysmorphic features (Fig. 1-4): - Facial dysmorphism: delticophatophy, metopic suture synostosis, upslanting palpebral fissures, short nose with anteverted nares, long philtrum, micrognathia, thin upper lip; - Low-set malformed auricles with prominent helix; - Proximal placement of thumbs, incomplete simian creases; - Hammer thumbs, pes equinovarus; - Hypoplasia, scapula hypoplasia, cryptorchidism; - Omphalocele, cardiac defect, moderate hypertonia.

Case 3: Clinical summary

We describe a 14 months old girl referred to our genetic center because of severe developmental delay, mental retardation (IQ 48) and dysmorphic features. The patient was born from second uneventful pregnancy. Her facial features were distinct with low set ears, short philtrum, upslanting palpebral fissures, frontal bossing, microcephaly, tapering fingers.

Materials and methods:

Eleven patients with DDI/CM of unknown etiology were selected for high-resolution array-CGH screening for genomic imbalances. We found chromosome micro-imbalance in 3 patients from the study group.

1. Karyotype analysis - peripheral blood lymphocytes culture, conventional cytogenetic analysis, 450 band level
2. Array CGH analysis: We have used genomic array CytoChip (BlueGnome, Cambridge, UK), covering the entire genome at a median 550Kb. It investigates sub-telomeres at a median 250Kb resolution, reliably detect mosaicism and examine 90 known genetic conditions at a median 100Kb resolution. This resulted in an average density of 1 clone/0.5Mb by 4400 clones. Text and sex-matched reference genomic DNA was labeled by random-priming, using BlueGnome Fluorescent Labeling System.

Microarray validation:

Array CGH analysis: FISH study of the patient chromosomes with locus specific bladFISH probe confirmed the deletion in 9p23 region on metaphases and interphases from peripheral blood lymphocytes. FISH analysis of the parents proved a de novo deletion in the boy.

Discussion and conclusion

- show that array CGH could improve the prenatal diagnosis for carriers of chromosomal rearrangements.
- illustrate the ability of this methodology to interpret many regions in one assay is valuable when studying patients with non-specific clinical findings.

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