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## Tzu Chi Medical Journal

journal homepage: [www.tzuchimedjnl.com](http://www.tzuchimedjnl.com)

## Clinical Practice and Therapeutics

## Dup(3) (p23p25) syndrome and array-based comparative genomic hybridization

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## ARTICLE INFO

## Article history:

Received 1 August 2011

Received in revised form

20 September 2011

Accepted 3 October 2011

A high resolution peripheral blood G-banded chromosome study was arranged for a 3-month-old female infant due to the presence of multiple congenital anomalies (MCA), including: flat face, flat occiput, flat nasal bridge, retrognathia, fish mouth, low set and dysplastic ears, temporal narrowing, short neck and prominent nuchal fold, and clinodactyly and hypoplastic toe nails (Fig. 1). Soon after birth, the infant was found to have mild whole body edema with hypoalbuminemia of an unknown cause and congenital heart disease, which included patent ductus arteriosus (PDA) and tricuspid regurgitation. No evidence of congestive heart failure or PDA persisted after two doses of oral indomethacin. Preterm labor had not occurred and the infant's birth weight was 3.2 kg. During follow-up at an outpatient clinic, weak crying, extended daytime sleeping, and delayed developmental milestones were noted by the early infant developmental screening program.

Karyotyping revealed 46,XX, dup(3) (p23p25) (20 cells); a surprising *de novo* chromosomal aberration due to the fact that parental peripheral blood chromosome studies were normal. No similar chromosomal anomaly has been identified in Taiwan or in the scientific literature. Chromosomal microarray (CMA) by array-based comparative genomic hybridization (aCGH) was carried out in order to determine copy number of the chromosomal aberration and revealed: arr 3p26.3p24.2 (RP11-6301 → RP11-1149N13) ×3 (Fig. 2).

In 2010, consensus was that CMA is a first-tier clinical diagnosis method for patients affected by multiple congenital anomalies,

autism spectrum disorder, unexplained developmental delay, or intellectual disability because CMA has greater sensitivity when detecting submicroscopic deletions or duplications. The density of aCGH is sufficient to allow detection of copy number changes around 1 Mega base-pair (Mbp). This should be compared to G-banded karyotyping which detects genomic imbalances in the range of 5–10 Mbp on occasion. CMA represents a greater than 10-fold improvement in resolution and narrows down potential indications from G-banded karyotyping to obvious chromosomal diseases, e.g. Down syndrome, especially when there is a family history of chromosomal rearrangement or a history of multiple miscarriages.

As part of the patient's clinical care and with the parents' informed consent, there were clear indications that supported carrying out aCGH, making it possible to pinpoint the more precise genomic variations. Nonetheless, issues associated with chromosomal variations of uncertain clinical significance are still present. The fact that there are no uniform guidelines for determining the clinical significance of genetic variation identified by aCGH poses a challenge. In this context, poor correlation between phenotype and genotype remains a major issue that needs to be explored. In many cases, the benefits of CMA do not yet directly affect the patient.

## Further reading

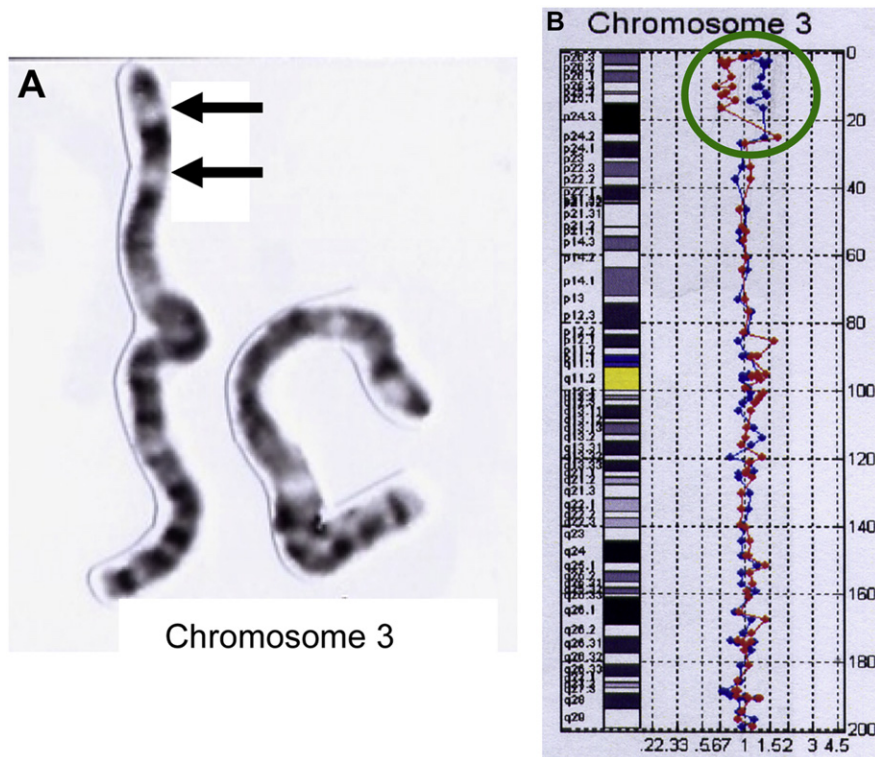
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**Fig. 1.** Dup(3) (p23p25) syndrome. (A) Flat face, full cheeks, fish mouth, flat nasal bridge, hypertelorism, temporal narrowing. (B) Flat occiput, retrognathia, low set dysplastic ears. (C) Prominent nuchal fold, short neck. (D, E) Overlapping fingers. (F) Prominent toetip pads. (G) Hypoplastic toenail (published with the parents' consent).



**Fig. 2.** (A) Karyotype result: 46,XX, dup(3) (p23p25). Double arrow indicates the duplication area. (B) Array-based comparative genomic hybridization result (circled) from 3p26 to 3p24.2 (2495414→16469054), which shows the presence of a 14 MB gene duplication.