



## Associations between the clinical findings of cases having submicroscopic chromosomal imbalances at chromosomal breakpoints of apparently balanced structural rearrangements



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### ARTICLE INFO

#### Article history:

Received 24 October 2016

Received in revised form 26 January 2017

Accepted 31 January 2017

Available online 2 February 2017

#### Keywords:

Mental retardation

Array-CGH

Congenital abnormalities

Apparently balanced chromosomal rearrangements

Inversions

Translocations

### ABSTRACT

Although the carriers with apparently balanced structural rearrangements have usually normal phenotype, phenotypic abnormalities can be seen in approximately 6% *de novo* cases. A number of different mechanisms are involved in the appearance of these phenotypic abnormalities, one of which is submicroscopic chromosomal imbalances at chromosomal breakpoints. Our goal was to unravel the possible submicroscopic chromosomal imbalances at chromosomal breakpoints by using array-CGH analysis in patients with apparently balanced structural rearrangements and to link these to the clinical findings. A total of nine patients with reciprocal translocation carriers (2 familial, 7 *de novo*) and six patients with inversion carriers (2 familial, 4 *de novo*) were included in this study. In order to evaluate the possible microdeletions and microduplications at the chromosomal breakpoints, DNA samples were isolated from the peripheral blood of the patients (and their parents) and investigated using array-CGH analysis. Array-CGH analysis revealed submicroscopic chromosomal imbalances at breakpoints in 3 of the 7 (43%) *de novo* reciprocal translocation carriers. Additionally, 1 out of 4 (25%) *de novo* inversion carriers were found to have a submicroscopic chromosomal imbalance in unrelated chromosome seen in cytogenetic analysis. Furthermore, no submicroscopic chromosomal imbalances were detected in either of the two familiarly transmitted reciprocal translocation carriers. Based on the results of both array-CGH analysis and conventional cytogenetic analysis, the karyotypes of the patients were designated as follows:

46,XY,t(13;16)(q14;q12.1)dn.arr[hg19]13q14.2-q21.1(50,131,521–57,306,322)x1dn;

46,XY,t(6;9)(q13;p12)dn.arr[hg19]6q14.1(78,016,882–83,293,127),9p23p22.3(12,249,507–15,939,627)x1dn;

46,XX,t(X;16)(p11.21;p11.2)dn.arr[hg19]Xp11.22(50,367,783–50,441,087)x3dn;

46,XX,inv.(18)(p11.23q11.2)dn.arr[hg19]22q11.21(18,706,001–21,505,417)x1mat.

Our results demonstrate the necessity of using array-CGH to evaluate patients with apparently balanced structural rearrangements in order to determine the submicroscopic chromosomal imbalances at chromosomal breakpoints that are related to the observed clinical abnormalities.

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**Abbreviations:** Array-CGH, array-based Comparative Genomic Hybridization; FISH, Fluorescence *In Situ* Hybridization; ISCN, International System for Human Cytogenomic Nomenclature; UCSC, University of California, Santa Cruz; TTK, TTK Protein Kinase; BCKDHB, Branched Chain Keto Acid Dehydrogenase E1, Beta Polypeptide; PHIP, Pleckstrin Homology Domain Interacting Protein; ELOVL4, ELOVL Fatty Acid Elongase 4; IBTK, Inhibitor Of Bruton Agammaglobulinemia Tyrosine Kinase; HMGN3, High Mobility Group Nucleosomal Binding Domain 3; 5HT-1B, 5-Hydroxytryptamine Receptor 1B; SIM1, Single-Minded Family BHLH Transcription Factor 1; PVL-like, Prader-Willi-like; FREM1, FRAS1 Related Extracellular Matrix 1; CER1, Cerberus 1, DAN Family BMP Antagonist; ZDHHC21, Zinc Finger, DHHC-Type Containing 21; NFIB, Nuclear Factor I/B; MPDZ, Multiple PDZ Domain Protein; LURAP1L, Leucine Rich Adaptor Protein 1-Like; TYRP1, Tyrosinase-Related Protein 1; TTC39B, Tetratricopeptide Repeat Domain 39B; SNAPC3, Small Nuclear RNA Activating Complex, Polypeptide 3, 50 kDa; PSIP1, PC4 And SFRS1 Interacting Protein 1; CCDC171, Coiled-Coil Domain Containing 171; CKAP2, Cytoskeleton Associated Protein 2; SUGT1, Suppressor of G2 Allele of SKP1; LECT1, Leukocyte Cell Derived Chemotaxin 1; DLC1, Doublecortin-Like Kinase 1; SMAD9, Mothers Against Decapentaplegic, Drosophila, Homolog of 9; RGCC, Regulator of cell cycle; SHROOM4, Shroom Family Member 4; KDM5C, Lysine Demethylase 5C; IQSEC2, IQ Motif and Sec7 domain 2; SMC1A, Structural Maintenance of Chromosomes 1A; HUWE1, HECT, UBA and WWE Domain Containing 1, E3 Ubiquitin Protein Ligase; FTSJ1, Ftsj RNA Methyltransferase homolog 1; PQBP1, Polyglutamine Binding Protein 1; SLC35A2, Solute Carrier Family 35 member A2.

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## 1. Introduction

Chromosomal abnormalities, whether numerical (trisomy, monosomy) or structural (deletion, duplication) in nature, and which can be detected by conventional cytogenetic analysis, are the major causes of mental retardation and congenital abnormalities. Although the great majority of cases with apparently balanced structural rearrangements have a normal phenotype, 0.6% of mentally retarded patients have apparently balanced structural rearrangements (Rauch et al., 2006). Phenotype can be affected due to the (1) disruption or dysregulation of a gene (or genes) at or near the breakpoint, (2) a microdeletion or microduplication at the breakpoint of the structural rearrangement, or (3) position effect of the gene (or genes) in the breakpoint region(s) of the balanced structural chromosomal abnormalities (Kalscheuer et al., 2003; Kenwrick et al., 1987).

The development of array-based Comparative Genomic Hybridization (Array-CGH) has served to overcome the limitations of both conventional cytogenetic analysis and Fluorescent *In Situ* Hybridization (FISH) by allowing for the ability to screen the entire genome for cryptic chromosomal imbalances (Shaw-Smith et al., 2004; Hayashi et al., 2005). In recent years, cryptic chromosomal imbalances have been detected in 30–50% of patients with apparently balanced translocations and abnormal phenotype by array-CGH (Baptista et al., 2008; De Gregori et al., 2007; Gribble et al., 2005). In this study, we used array-CGH in order to evaluate cryptic chromosomal imbalances in 15 patients with mental retardation and/or congenital abnormalities, all of whom carried an apparently balanced chromosomal rearrangement.

## 2. Methods

### 2.1. Study patients

Fifteen patients (9 males and 6 females) with mental retardation and/or congenital abnormalities were included in this study. Informed consent was obtained from each of the patients' families, and all patients were evaluated by two independent and experienced clinical geneticists. Conventional cytogenetic analysis was performed on peripheral blood samples from each patient and their parents using GTG-banding. At least 20 GTG-banded metaphases from each patient were analyzed at the 550 band level, and the karyotypes were designated according to the International System for Human Cytogenomic Nomenclature (ISCN 2016). Nine of the fifteen patients had an apparently balanced reciprocal translocation, seven of which were *de novo* while two were familial. Six of the fifteen patients had an apparently balanced inversion, including four which were *de novo* and two familial.

### 2.2. Array-CGH studies

Genomic DNA samples were isolated from peripheral blood lymphocytes using the salting-out procedure. Array-CGH analysis was performed on the samples using the NimbleGen CGX-3 array (which includes 134,829 oligonucleotide probes) according to the manufacturer's instructions. Genomic DNA samples and reference samples were labeled with Cy3 and Cy5, respectively, using NimbleGen Dual-Color DNA Labeling Kits. The hybridization protocol was carried out using the NimbleGen Hybridization System. After the hybridization protocol, slides were washed and then scanned using the NimbleGen MS 200 Microarray Scanner and MS 200 Data Collection Software. Additionally, genes located in the deleted and duplicated area were further investigated using the University of California, Santa Cruz (UCSC) human genome browser database (<http://genome.ucsc.edu>, hg19).

## 3. Results

Array-CGH analysis revealed cryptic chromosomal imbalances in 4 of the 15 patients with an apparently balanced chromosomal

rearrangement (26.7%), including three of seven patients with a *de novo* reciprocal translocation and one of four patients with a *de novo* inversion. The patient with a *de novo* inversion showed a familial cryptic deletion in another chromosome, yet with no cryptic rearrangements on the inversion breakpoints. The results of cytogenetics and array-CGH and the clinical findings are shown in Table 1. The results of cytogenetic and array-CGH analysis, as well as detailed clinical information about the patients, is provided below.

### 3.1. Patient 1

The clinical features of the 18-year-old boy were: neuromotor retardation, moderate intellectual disability, obesity, a rounded face with full cheeks, hypotelorism, bilateral temporal flatness, bilateral ptosis, down-slanting palpebral fissures, left epicanthal folds, strabismus, maxillary hypoplasia, small mouth, thin lips, high arched palate, micrognathia, a gap between the first and second toes, and behavioral problems. He also had left cryptorchidism and had previously undergone an operation for an inguinal hernia. Furthermore, cranial magnetic resonance imaging detected corpus callosum dysgenesis. Cytogenetic analysis showed that the patient had a *de novo* apparently balanced translocation between chromosomes 6 and 9. The initial karyotype of the patient was designated as: 46,XY,t(6;9)(q13;p12)dn. Array-CGH analysis revealed deletions of 5.27 Mb and 3.69 Mb in the 6q14.1 and 9p23p22.3 regions, respectively. 13 genes located in the 6q14.1 region and 11 genes located in the 9p23p22.3 region were found to be deleted, according to the International Standards for Cytogenomic Arrays (ISCA) Consortium database. The final karyotype of the patient was designated as: 46,XY,t(6;9)(q13;p12)dn.arr[hg19]6q14.1(78,016,882–83,293,127), 9p23p22.3(12,249,507–15,939,627)x1 dn. A picture of the patient, as well as the full and partial karyotypes and array-CGH results, are all shown in Fig. 1.

### 3.2. Patient 4

The clinical features of a 9-year-old boy were as follows: neuromotor retardation, moderate intellectual disability, a coarse face and high frontal hairline, hypertelorism, strabismus, a depressed nasal bridge, a wide forehead and high anterior hairline, anteverted nostrils, large ears and mouth, maxillary protrusion and gingival enlargement. Additionally, his mother had a history of recurrent abortions. Chromosomal analysis of the patient revealed an apparently balanced *de novo* translocation between chromosomes 13 and 16. The initial karyotype of the patient was designated as: 46,XY,t(13;16)(q14;q12.1)dn. Array CGH analysis showed a 7.17 Mb deletion in the 13q14.2–q21.1 region, which is comprised of 53 genes according to the ISCA database. Final karyotype of the patient was designated as: 46,XY,t(13;16)(q14;q12.1)dn.arr[hg19]13q14.2–q21.1(50,131,521–57,306,322)x1dn. A picture of the patient, as well as the full and partial karyotypes and array-CGH results, are shown in Fig. 2.

### 3.3. Patient 7

The clinical features of a 14-year-old girl were as follows: mild neurodevelopmental regression, moderate intellectual disability, epilepsy and 5th finger clinodactyly, kyphosis, scoliosis, and joint laxity. She also displayed aggressive behavior, attention deficit and hyperactivity, and stereotyped movements. Chromosomal analysis revealed a *de novo* apparently balanced translocation between chromosomes X and 16. The initial karyotype of the patient was designated as: 46,X,t(X;16)(p11.21;p11.2)dn. Array-CGH analysis showed the presence of a 73.30 kb microduplication in the Xp11.22 region, a region which includes 1 gene according to the ISCA database. The final karyotype of the patient was designated as: 46,X,t(X;16)(p11.21;p11.2)dn.arr[hg19]Xp11.22(50,367,783–50,441,087)x3 dn. A picture of the patient, her full and partial karyotype, and the results of array-CGH are shown in Fig. 3.

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