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Short Communication

# Monosomy 9pter and trisomy 9q34.11qter in two sisters due to a maternal pericentric inversion

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ABSTRACT

Pericentric inversions of chromosome 9 leading to unbalanced live-born offspring are relatively rare and so far only four cases have been reported. Here we present two sisters with an unbalanced recombinant chromosome 9 which resulted from a large maternal pericentric inversion inv(9)(p24.3q34.1). Further molecular characterisation of the aberrant chromosome 9 by 250k SNP array analysis showed a terminal 460 kb loss of 9p24.3 and a terminal 8.9 Mb gain of 9q34.11. We compared the clinical features of these two patients with the previous reported four cases as well as with patients with similar sized 9pter deletions or 9qter duplications. Based upon this study, we suggest that the recombinant chromosome 9 phenotype is mainly the result of duplication of a 3.4 Mb region of chromosome 9q34.11q34.13.



## 1. Introduction

A small pericentric inversion of the heterochromatic region of chromosome 9 (9 ph) is a well-known rearrangement which occurs approximately in 1 out of 50 to100 people and is regarded as a relatively innocent polymorphism (Betz et al., 2005; Gersen and Keinanen, 2005). In contrast, a large pericentric inversion with breakpoints in the respective distal short and long arm of chromosome 9 is quite rare and may result in live-born offspring with a terminal deletion and a terminal duplication after a recombination event in the inversion loupe. So far, only four such cases have been reported; all but one were single cases and all were of paternal origin (Mattei et al., 1980, 1983; Shapira et al., 1997; Sonoda et al., 1991).

Here we present two sisters with a recombinant chromosome 9 due to a maternal pericentric inversion inv(9)(p24.3q34.1). The recombinant chromosome was further characterized by SNP array analysis and clinical features of both patients were compared to the previous four cases and with patients showing similar sized 9pter deletions or 9qter duplications.

## 2. Clinical report

### 2.1. Patient 1

The proband was a twenty-one-year-old female with moderate intellectual disability (ID). She was the first daughter of non-consanguineous, Javanese parents. Both parents were considered healthy and showed no dysmorphisms or behavioural disturbances. Furthermore, they had finished regular schooling indicating a normal cognitive function. Family history revealed a younger, intellectually disabled sister (Patient 2). Her mother had no history of miscarriages. The patient was born at term after an uneventful pregnancy with a weight of 2800 g (10th centile). She showed gross motor delay and hypotonia. She started to walk after 24 months and spoke her first words at the age of four years. Although she was able to understand others, she developed only limited active speech. On physical examination her weight was 25 kg (<3rd centile), height 145 cm (<3rd centile) and head circumference 52 cm (<3rd centile). Facial dysmorphisms included a slightly asymmetric face, severe microtia and aural atresia of the left ear, upslanting palpebral fissures, strabismus, cupid bow mouth shape, high arched palate and irregular position of teeth. In addition, she had a slender posture with scoliosis, cubitus valgus, arachnodactyly, clinodactyly and sandal gaps (Supplementary data, Fig. 1A). She showed shy behaviour and had an attention deficit disorder.

*Abbreviations:* CEBIOR, Center for Biomedical Research; CNAG, Copy Number Analyzer for Affymetrix Genechip mapping; DECIPHER, Database of chromosomal imbalance and phenotype in humans using Ensembl Resources; DGHE, Directorate of Higher Education; DGV, Database of Genomic Variants; ECARUCA, European Cytogeneticists Association Register of Unbalanced Chromosome Aberrations; FISH, Fluorescence *in situ* Hybridization; GTG, G-banding with trypsin-Giemsa; ID, intellectual disability; Kb, kilobase (thousand base pairs); Mb, megabase (million base pairs); MLPA, multiplex ligation-dependent probe amplification; OMIM, Online Mendelian Inheritance in Man; RUNMC, Radboud University Nijmegen Medical Centre; SNP, single nucleotide polymorphism; UCSC, University of California, Santa Cruz.

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### 2.2. Patient 2

At the time of investigation this girl was fifteen years old and had mild ID. She was born at term after an uneventful pregnancy with a weight of 2300 g (<3rd centile). She had an uncomplicated neonatal period and there was no significant medical history. She started to walk after 16 months and to speak at three years of age. She followed elementary school until 3rd grade. Due to the behavioural problems she had to leave school and stay at home with her family.

On physical examination her weight was 28 kg (<3rd centile), height 141 cm (<3rd centile) and head circumference 51 cm (<3rd centile). She had a thin posture and minor facial dysmorphisms including an asymmetric, long and narrow face, a flat nasal bridge, cupid bow mouth shape and a high arched palate. In addition, she had arachnodactyly, fetal finger pads, clinodactyly and sandal gaps (Supplementary data, Fig. 1B). She spoke with a nasal voice and showed shy and hyperactive behaviour. Genotype and phenotypic information of both patients have been submitted to the ECARUCA database (www.ecaruca.net).

## 3. Cytogenetic and molecular analysis

The index patient (patient 1) was part of a larger series of 527 Indonesian individuals with intellectual disability tested by conventional karyotyping as reported by (Mundhofir et al., 2012). GTG-banded cytogenetic analysis from lymphocytes at 400–500 bands revealed a 46,XX karyotype. Subsequently, subtelomeric MLPA analysis was performed, as previously described, and showed a deletion of chromosome 9pter and a duplication of 9qter in both sisters, but not in the parents (Schouten et al., 2002) (Supplementary data, Fig. 2). This indicated that both sisters were carrier of a recombinant chromosome 9.

Therefore, higher resolution chromosomal analysis was necessary. High resolution GTG banding chromosomal analysis (~600–700 bands) of both sisters showed a recombinant chromosome 9, with the same 46,XX, rec(9)dup(9q)inv(9)(p24.3q34.1)mat karyotype. Karyotyping of the parents showed that their mother was a carrier of a balanced pericentric inversion of chromosome 9, 46,XX,inv(9)(p24.3q34.1); while the father had a normal male karyotype. Fluorescence *in situ* Hybridisation (FISH) analysis with subtelomeric probes for 9pter (LSI 9pter) and 9qter (LSI 9qter) was performed according to manufacturer's recommendation (Vysis, Downers Grove, IL, USA). FISH analysis in both sisters showed two clear signals of telomere 9q at either end of the aberrant chromosome 9 and no signal with the 9pter probe (Fig. 1). FISH analysis in the mother confirmed an inversion of chromosome 9, This confirmed that the deletion and duplication of chromosome 9 in both sisters were indeed the results of a recombination event between the maternal inverted chromosome 9 and the normal chromosome 9.

Further characterization of the recombinant chromosome 9 was performed with genome wide SNP array analysis using the Affymetrix *NspI* 250K SNP array platform (Affymetrix, Santa Clara, CA, USA). Copy number estimates were determined using the Copy Number Analyzer for Affymetrix Genechip Mapping (CNAG) software package (version 2) (Nannya et al., 2005). A terminal 460 kb loss of 9p24.3 (0.03–0.49 Mb, hg18) and a 8.9 Mb gain of 9q34.11qter (131.3–140.2 Mb, hg18, http://genome.ucsc.edu/) were detected (Fig. 2). The 9pter deletion (SNP_A-2227623 → SNP_A-1898345) comprised four genes and the 9qter duplication (SNP_A-4223541 → SNP_A-1874845) comprised 162 genes.

## 4. Discussion

We report the fifth case of a large balanced, pericentric inversion of chromosome 9 in a healthy carrier, which was transmitted as an unbalanced recombinant chromosome to the offspring causing ID and dysmorphisms. SNP array, subtelomeric MLPA and FISH analyses allowed the characterizing of the recombinant chromosome that consists of a 460 kb 9pter deletion and an 8.9 Mb 9qter duplication.

Four previous cases of large pericentric inversions of chromosome 9 leading to an unbalanced karyotype have been reported. Three of these resulted in larger aberrations, including bands 9p22 and 9q32 (Mattei et al., 1980, 1983; Sonoda et al., 1991), hampering interpretation of the clinical overlap. Therefore, the current cases have been compared with the only patient with a comparable chromosomal aberration (Shapira et al., 1997) (Table 1).

To further correlate the genotype with the phenotype in the present cases, we also compared it with patients having a 9pter deletion or a 9qter duplication. Smaller 9pter deletions (below 500 kb) are very rare, and only two ID patients showing minimal dysmorphisms have been reported thus far (Griggs et al., 2008). In addition, two more ID patients are presented in DECIPHER (Database of Chromosomal Imbalance and Phenotype in Human using Ensembl Resources). One of the latter (Patient 249275) was not tested for *de novo* occurrence, while the other (Patient 256715) had inherited the deletion from a healthy parent. Furthermore, the Database of Genomic Variants (DGV; http://www.tcag.ca/) reports several variants in this region that can be found in the normal population. Therefore, the pathogenic significance of a small deletion of this terminal region still remains uncertain.

In recent years, seven cases of molecularly well characterized 9q34 duplications have been reported (Fig. 3; Table 1), of which three are presented in DECIPHER (Gawlik-Kuklinska et al., 2007; Mizuno et al., 2011; Ruiter et al., 2007; Youngs et al., 2010). Recently, Mizuno et al. proposed a 3 Mb critical region (131.7–134.7 Mb) for the most frequent clinical features of 9q34 duplications (Fig. 3). In accordance with the overlap of the current duplication with this region, our patients had most of these features in common, including ID, hypotonia,

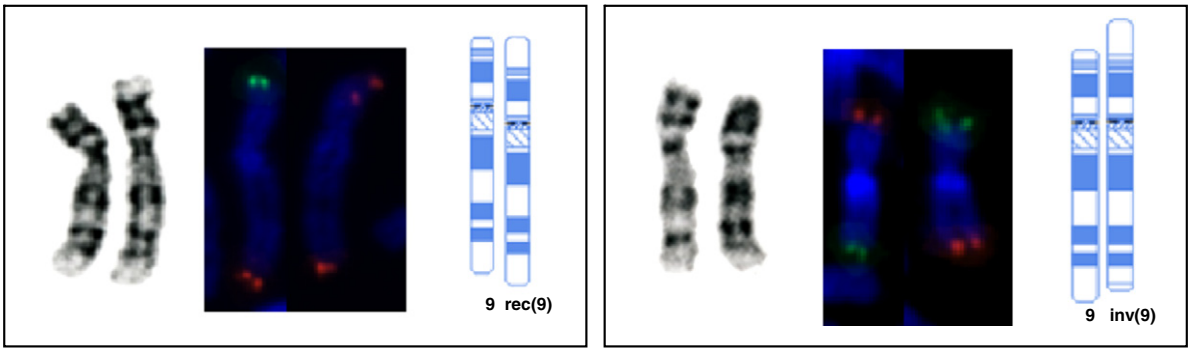


**Fig. 1.** Conventional cytogenetic analysis, FISH analysis and the ideogram of the aberration in the patient (left) and her mother (right). Chromosome 9 of the patient showed a duplication of 9q material attached to the p-arm of the chromosome (left). FISH results with chromosome 9p telomere-specific probe (green) and chromosome 9q telomere-specific probe (red); Note the two signals of 9q on the patient's aberrant chromosome 9.