# Prenatal detection of *de novo* inversion of chromosome 9 with duplicated heterochromatic region and postnatal follow-up

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## Abstract

**We report the first *de novo* case of a heterochromatic duplication on the long arm of the chromosome 9, which then was pericentrically inverted at p11q13. This condition was detected prenatally and carry to term. We then performed the follow up for over 1 year. So far, there seems to be no phenotypical abnormalities.**

**Keywords:** heterochromatic duplication, pericentric inversion, *de novo* inversion

## Introduction

Pericentric inversions of chromosome 9 are among the most frequent chromosomal rearrangements in human, with a frequency of 1-2 percent (Nielson and Silesen, 1975). The majority of these inversions are inherited. Prenatal diagnosis of a *de novo* inversion poses a dilemma in providing the family with a best possible counselling. In the present case, we characterized the duplication of the classical satellite region and the pericentric inversion of chromosome 9 using FISH (fluorescence in situ hybridization) in prenatal diagnosis. And we report the physical and developmental follow-up of a patient documented with a *de novo* inversion of chromosome 9 with duplicated heterochromatic region.

## Case Report

Prenatal cytogenetic diagnosis was performed with amniocentesis in a 28-year-old woman (0-0-0-0) who had Down positive result on the triple test. GTG-banding showed abnormal extension of the long arm on the chromosome 9, which led to a suspicion of translocation of insertion (Figure 1A). To find the origin of the seeming extended region, CBG-banding was performed. We confirmed that the extended region was the duplication of the heterochromatic region (Figure 1B). Futhermore, RBG-banding was followed with the discovery of unstained negative band which confirmed the absence of euchromatic region (Figure 1C). In addition, there was no abnormality found by detailed fetal ultrasonography.

Chromosomal analyses on the lymphocytes from both parents were found to be a normal. The parents elected to continue the pregnancy. At 40 weeks, a 3.73 kg male baby was delivered. Vaginally Chromosome analysis on cord blood taken at birth confirmed the presence of a pericentrically inverted chromosome 9 in all cells examined. The PRINS (primed *in situ* hybridization) using D9Z1 on interphase and metaphase cells confirmed the chromo-some 9 and using classical alpha-satellite primer, we have found inverted region unobservable by convention-al banding technique (Figure 2). By the FISH method using WCP9, heterochromatic region of pericentrically invert-ed chromosome 9 didn't have observable signal (Figure 3).

Therefore, the duplication of the chromosome 9 of fetus was presumably occurred and then inversion rearrangement of the two break regions took place between the short arm (p11) and the long arm (q13) (Figure 4). On postnatal evaluation, up to now, the baby has been exhibiting a normal phenotypes, both mentally and physically.

## Discussion

The variable amount of heterochromatin present in the secondary constriction region of chromosome 9 (9qh), and its association with pericentric inversions have been the subject of scrutiny and debate (Verma, 1988).
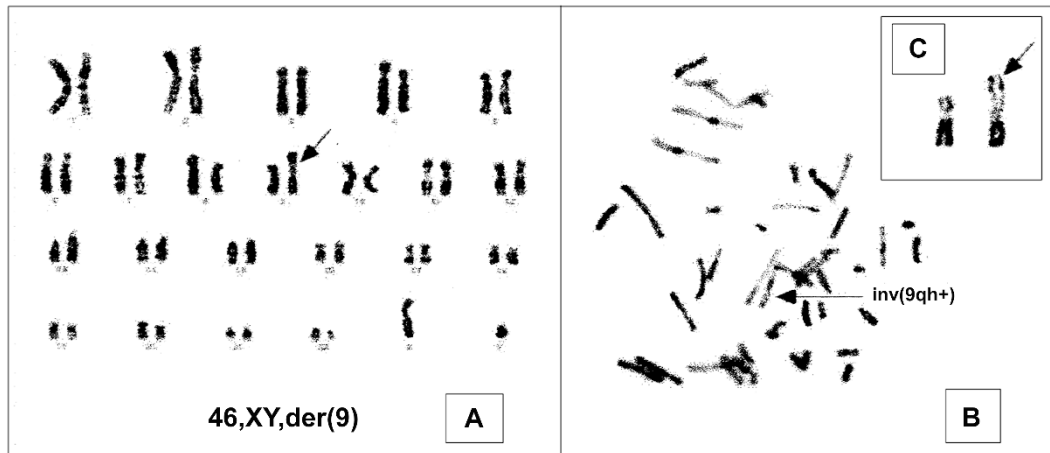
**Figure 1**. Prenatal diagnosis using GTG-, CBG- and RBG-banding. (A) The arrow indicates the added chromosome by GTG-banding. (B) The region indicated by the arrow is found to be a duplicate of heterochromatin region by CBG-banding. (C) And the arrow shows the absence of dark band (euchromatin negative) on the proximal region of the short arm of chromosome 9 by RBG-banding.
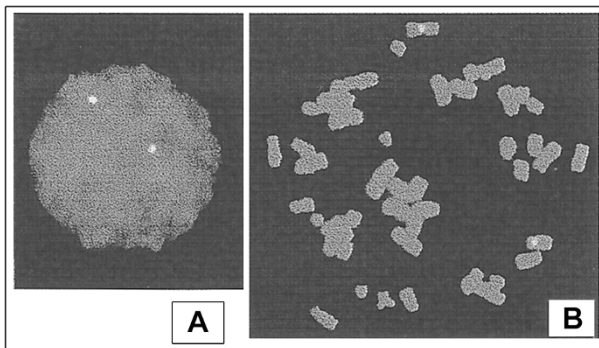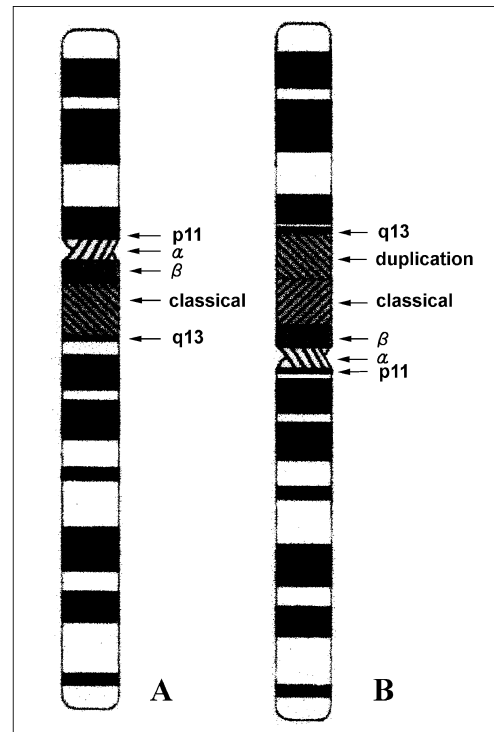


**Figure 2**. PRINS with specific α-satellite DNA primer (D9Z1) for chromosome 9; Both showing two green spots in interphase (A) and metaphase (B).
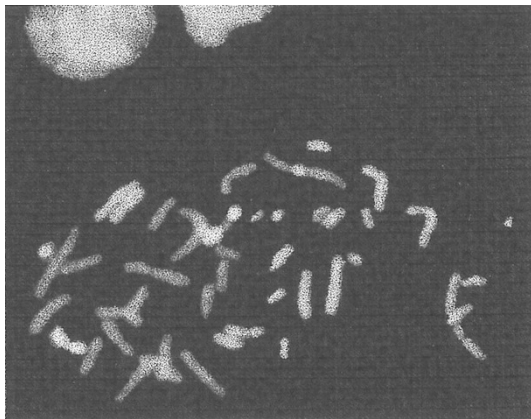


**Figure 3**. Both chromosomes 9 are painted by fluorescence in situ hybridization (FISH) using whole chromosome painting probe. One shows complete painting but the other incomplete; the unpainted region is the heterochromatin region.



**Figure 4**. Schematic diagram representing the duplication and the pericentric inversion occurring in chromosome 9. A is normal chromosome 9 and B is der(9)inv(9)(p11q13)dup(9)(q11q13).

Consequently, attempts have been made to evaluate these regions by various selective techniques. Recent molecular cytogenetic techniques involving FISH have become routine for the characterization of structural variations in the human genome (Bernardi, 1995). Other cytogenetic approaches do not allow in depth characterization and banding techniques reflect the homology at the DNA level (Lohe and Hilliker, 1995). Molecular cytogenetic techniques have unequivocally shown that pericentromeric heterochromatin is not homogeneous in spite of its uniform staining patterns by conventional

techniques (Singer, 1982). This heterogeneity is presumably due to the arrangement of different fractions of repeated satellite DNA sequences in the pericentromeric heterochromatin (Choo *et al.*, 1991; Tyler-Smith and Willard, 1993). Tandem repeated DNA families have been characterized by FISH analysis using a combination of loci and whole chromosome-specific probes (Adinolfi, 1992).

There are four unique types of pericentric inversions involving the secondary constriction region of chromosome 9 using by fluorescence *in situ* hybridization technique with human centromere specific α satellite, the β satellite (D9Z5) and classical satellite (D9Z1) human DNA probes. Type A inversion consist of breakpoints within the α and β satellite DNA regions; type B consist of breakpoints the β satellite DNA region 9q13; type C involve breakage within the β and classical satellite DNA regions, and type D have breakpoints within the α and classical satellite DNA regions. Like these, obviously, reshuffling of satellite DNA sequences occurred, which has given rise to a variety of heteromorphisms whose clinical significance remains obscure (Samonte *et al.*, 1996), few types of pericentric inversion have been observed due to the variable breakpoints within the qh regions, but their implications have also remained obscure (Verma *et al.*, 1993; Macera *et al.*, 1995).

But, it has been reported that various abnormalities appeared in individuals with the pericentric inversion 9. In the case of homozygosity for the pericentric inversion 9, the fetus showed severe intrauterine growth retardation (IUGR), oligohydramnios and subsequently expired in utero (Cotter *et al.*, 1997). Six infertile males with pericentric inversion of chromosome 9 have an abnormality in the hypothalmic-pituitary-testicular axis (Sasagawa *et al.*, 1998). In 2.3% of the couples with the history of recurrent spontaneous miscarriages, pericentric inversion of chromosome 9 was detected (Sasiadek *et al.*, 1997).

Since chromosomal variation may have an important role in genomic evolution (Houle *et al.*, 1992; Bernardi, 1995) the elucidation of the various heteromorphisms of chromosome 9 constitutive heterochromatin may shed light on this matter. The present study suggests that pericentric inversion have taken place involving the 9qh(+) region. The formation mechanism involved in the pericentric inversion may be due to the duplication of the classical satellite region (q11q13) of the chromosome 9 and the inversion of the region between the break points (p11 and q13) and its subsequent reunion.

The present case in the first report presenting the der(9)inv(9)(p11q13)dup(9)(q11q13) in Korea as there had been little information on this abnormality in chromosome 9 to make proper interpretation of fetal implication remain obscure. However, as a result of our follow up of this case, we believe that such abnormality alone can not lead to any observable phenotypical abnormalities.

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