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Chromosome Polymorphism and Human Pathology: About 27 Cases of Chromosome 9 Inversion in the Beninese Population

Simon Azonbakin[1*], Alfred Ouedraogo[2], Alexis Ouedraogo[2], Daniel Sewadouno[1], Arnaud Agbanlinsou[1], Yannick Goussanou[1], Marius Adjagba[1], Jules Alao[3], Anatole Laleye[1]

[1]Laboratory of Histology-Reproductive Biology, Cytogenetics and Medical Genetics, Human Biology Unit, Faculty of Health Sciences, Abomey-Calavi University, Cotonou, Benin
[2]Laboratory of Histology-Embryology, Cytogenetics and Reproductive Biology, Teaching Hospital of Bogodogo, Ouagadougou, Burkina Faso
[3]Department of Pediatric and Medical Genetic, Faculty of Health Sciences, Abomey-Calavi University, Cotonou, Benin
Email: *azandeg@yahoo.fr

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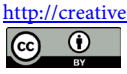

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Abstract

The chromosomal polymorphism defined by variations of some chromosomal regions of a person (the constitutive heterochromatin and the short arms of the acrocentric chromosomes (13 to 15 and 21 - 22)) sometimes highlighted problems with regard to their safety and their pathogenicity. Polymorphisms are usually found in the same family and transmitted in the dominant Mendelian. Chromosome 9 inversion is a frequent phenomenon that some cytogeneticists consider as a variant of normal. Despite its classification as a minor chromosome rearrangement which does not correspond to abnormal phenotypes, many reports have raised conflicting opinions as well, and its complete safety is controversial. 27 cases of inversion of chromosome 9 were identified in our laboratory. The main indications for karyotype of the case of inv (9) were congenital cardiopathy (18.5%), sex development disorders of (18.5%), down syndrome (18.5%), and infertility (14.8%). This study stood out the observations of many authors who highlighted the involvement of inv (9) in the genesis of several pathologies.

Keywords

Inversion, Chromosome 9, Karyotype, Abnormality, Fertility

1. Introduction

Constitutional chromosomal abnormalities are an important cause of miscar-

riage, infertility, congenital anomalies, and mental retardation in humans. Constitutional chromosomal abnormalities include numeral chromosomal aberrations that cause aneuploidy and structural chromosomal aberrations such as translocations, inversions, deletions, and duplications [1]. The frequency of structural chromosomal abnormalities has been estimated at 0.25% in live-born infants [2] [3]. Chromosomal polymorphisms of constitutive heterochromatin regions of chromosomes 1, 9, 16, and the Y chromosome were reported. The pericentric inversion of chromosome 9 (inv (9)) is one of the most common structural balanced chromosomal variations and was found in both normal and affected populations [4] [5]. The incidence is approximately 1% to 3% in the general population [3] [4]. Most cytogeneticists consider it as a normal variant because of the occurrence of inv (9). Despite its categorization as a minor chromosomal rearrangement, which is not related to abnormal phenotype, some reports described inv (9) in association with subfertility and recurrent abortions, abnormal clinical conditions, as well as other chromosomal abnormalities [6] [7] [8].

In order to study the frequency and the phenotype associated with inv (9), we reported 27 cases, in the Laboratory of Histology-Biology of Reproduction, Cytogenetics and Medical Genetics of Cotonou, Benin.

2. Methods

It was a retrospective study including cases of inv (9) at the Cytogenetics Laboratory of Cotonou from January 1, 2014 to June 30, 2020. The data were collected in the laboratory's registers. As they were routine patients, a written approval was not obtained from the ethical committee of Faculty of Health Science of Cotonou.

The study population includes all the patients admitted to laboratory during the study period. The karyotype was performed in a G band. The culture tubes were incubated for 72 hours at 37˚C, CO_2 5%. The culture was stopped at the 70th hour by adding 50 µl of colcemide (Sigma^{R}). Hypotonic treatment of the cells with KCl (0.075 M) followed by fixation in ethanol/glacial acetic acid (3:1 vol; vol). A concentrated suspension of cells was placed on slides and dried, for 25 minutes. The chromosomes were obtained by digestion in a trypsin bath and stained using 2% Giemsa solution. They were then dried and examined under the microscope using the programmed image analyzer (Cytovision 7.3.1). The metaphases were captured using a microscope and interpreted in accordance with the international system of Human Cytogenetic Nomenclature (ISCN).

3. Results

Over 5-year, 1049 karyotypes were performed. Inv (9) was observed in 27 cases (2.57 %). The inv (9) was predominant in male subjects with a sex ratio of 1.17.The average age of the patients was 12.65 years with extremes from 03 months to 39 years. The majority (46.15%) of our patients were between 0 and 1 year of age. **Table 1** summarizes the clinical and genetypical information about the cases of inv (9). The main indications for karyotype of the case of inv (9)

were congenital cardiopathy (18.5%), sex development disorders of (18.5%), Down Syndrom (18.5%), and Infertility (14.8%). The other indication was facial dysmorphy (7.4%), Suspicion of Klinefelter syndrome (3.7%), psychomotor delay (3.7%), polymalformative syndrome (3.7%), recurrent abortions (3.7%) and hypotrophy (7.4%). Table 1 summarized clinical feature of patient with inv chr9 and genotypic finding.

The type of inversion observed was q11-q22.3. We also observed a case with mosaicism 46, XX (85%)/46, XX, inv (9), five cases associated with Down's syndrome and one case with duplication of chromosome 9 (46, XY, inv (9), dup (q13 P11). Figures 1-4 show metaphasic finding of some genotypics aspects of inv chr (9).

Table 1. Clinical and genetypical information about the cases of inv chr (9).

Case	Sex	Age (years)	Clinical aspects	Genotypics forms
Case 1	F	0.25 (3 months)	Congenital Cardiopathy	46, XX, inv (9)
Case 2	F	0.33 (4 months)	Developpement sexual disorders (DSD)	46, XX, inv (9)
Case 3	M	0.75 (9 months)	Congenital Cardiopathy	46, XY, inv (9)
Case 4	M	31	Infertility (severe oligospermia)	46, XY, inv (9)
Case 5	M	0.75 (9 months)	Developpement sexual disorders (DSD)	46, XY, inv (9)
Case 6	F	35	Infertility (primary amenorrhea)	46, XX, inv (9)
Case 7	M	0.75 (9 months)	Facial dysmorphia	46, XY, inv (9)
Case 8	F	1	Congenital Cardiopathy	46, XX, inv (9)
Case 9	M	38	Developpement sexual disorders (DSD)	46, XY, inv (9)
Case 10	M	15	Facial dysmorphia	46, XY, inv (9)
Case 11	M	39	Suspicion Klinefelter's syndrome	46, XY, inv (9)
Case 12	F	0.60 (8 months)	Congenital Cardiopathy	46, XX (85%)/46, XX, inv (9) (15%)
Case 13	F	2	Down syndrome	47, XX, +21, inv (9)
Case 14	F	14	Developpement sexual disorders (DSD)	46, XX, inv (9)
Case 15	M	0.75 (9 months)	Down syndrome	47, XY, + 21, inv (9)
Case 16	M	4	Congenital Cardiopathy	46, XY, inv (9)
Case 17	M	0.58 (7months)	Down syndrome	46, XY, +21, inv (9)
Case 18	M	10	Developpement sexual disorders (DSD)	46, XY, inv (9)
Case 19	M	0.75 (9 months)	hypotrophy	46, XY, inv (9)
Case 20	M	1.83 (22 months)	Psychomotor retardation	46, XY, inv (9)
Case 21	M	1.83 (22months)	Polymalformative syndrome	47, XY, +13, inv (9)
Case 22	M	35	recurrent abortions	46, XY, inv (9)
Case 23	M	0.25 (3 months)	Down syndrome	46, XY, +21, inv (9)
Case 24	F	0.33 (4 months)	Down syndrome	46, XX, +21, inv (9)
Case 25	M	46	Infertility (oligospermia)	46, XY, inv (9)
Case 26	M	33	Infertility (azoospermia hypogonadism)	46, XY, inv (9)
Case 27	M	0.75 (9 months)	Hypotrophy	46, XY, inv (9), dup (q13 P11)

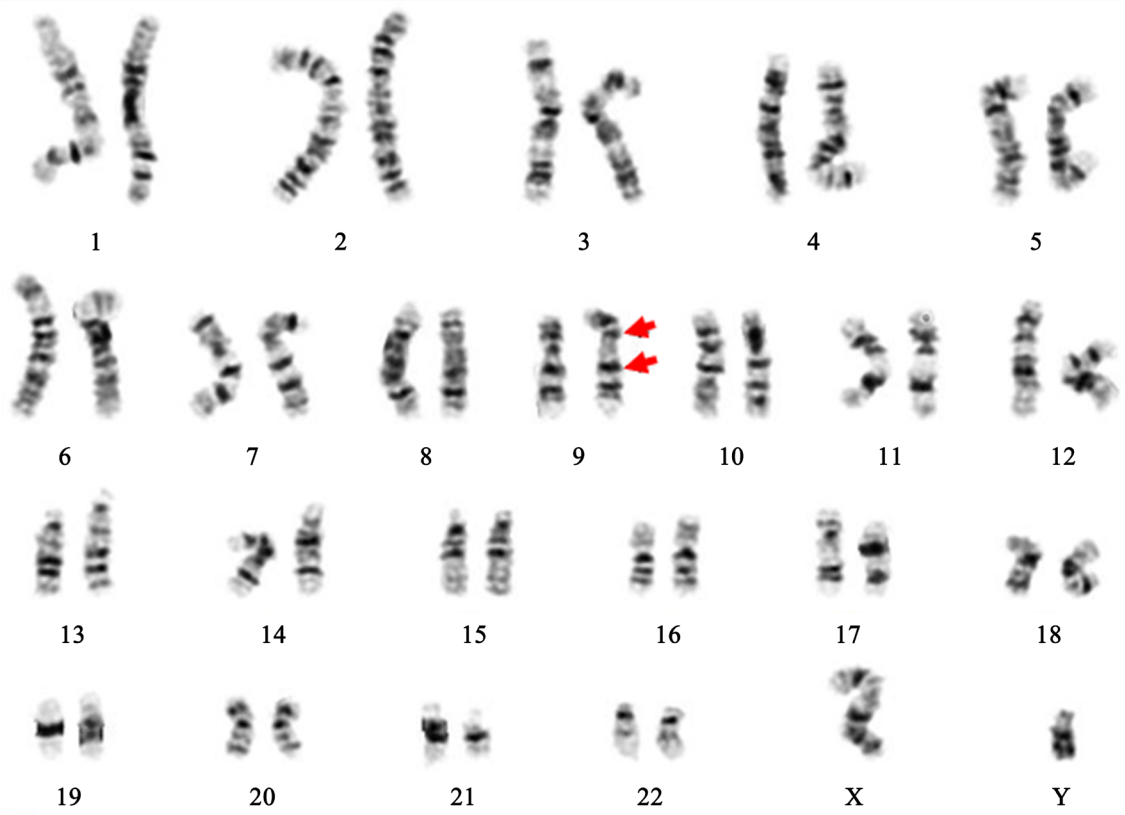

Figure 1. Karyotype showing a case of inv chr9 GTG-banded karyotypes of the lymphocytes from patients with pericentric inversion of chromosome 9.

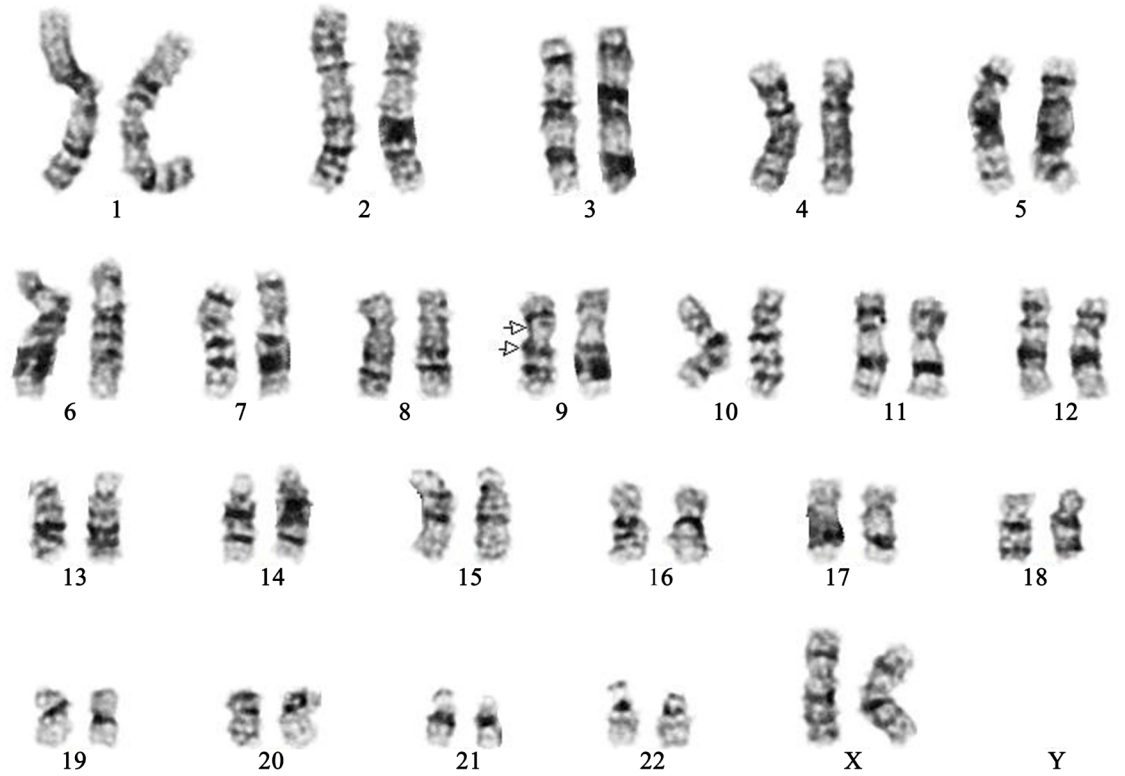

Figure 2. Karyotype showing a case of inv chr9 from a femelle. 46, XX, inv (9).

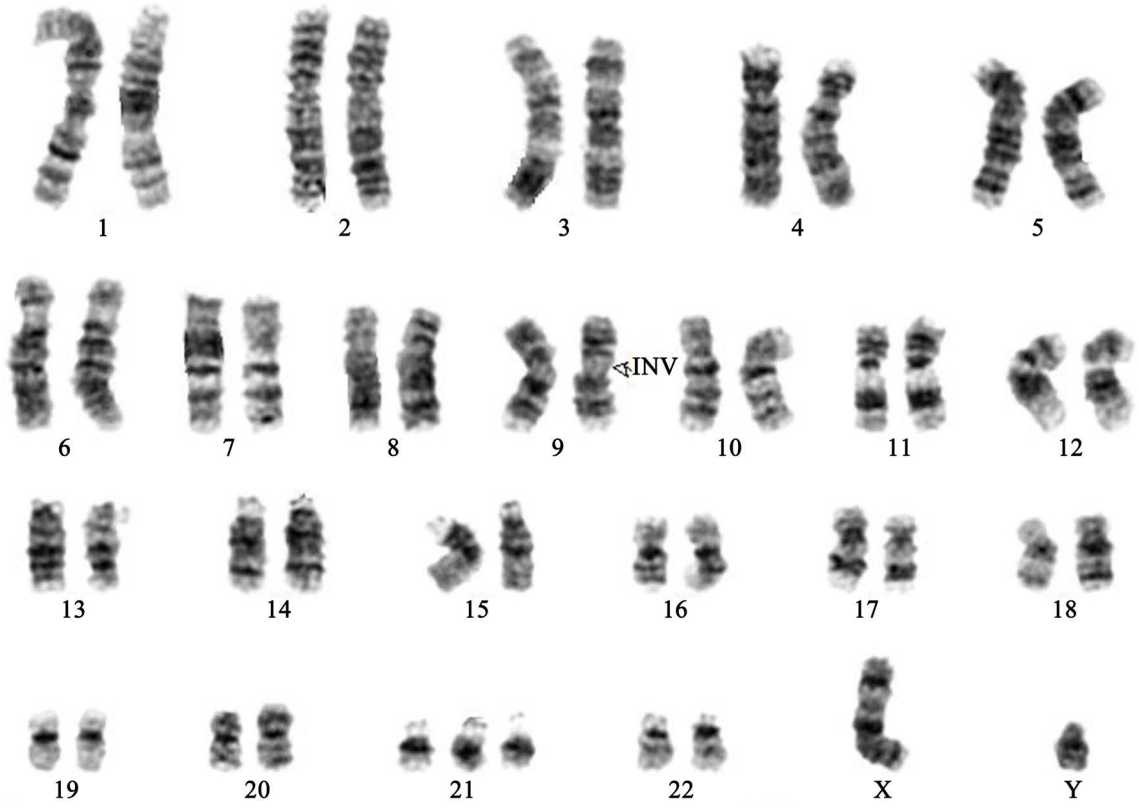

Figure 3. Karyotype showing a case of inv chr9 from a femelle with trisomy 21. 47, XY, +21, inv (9).

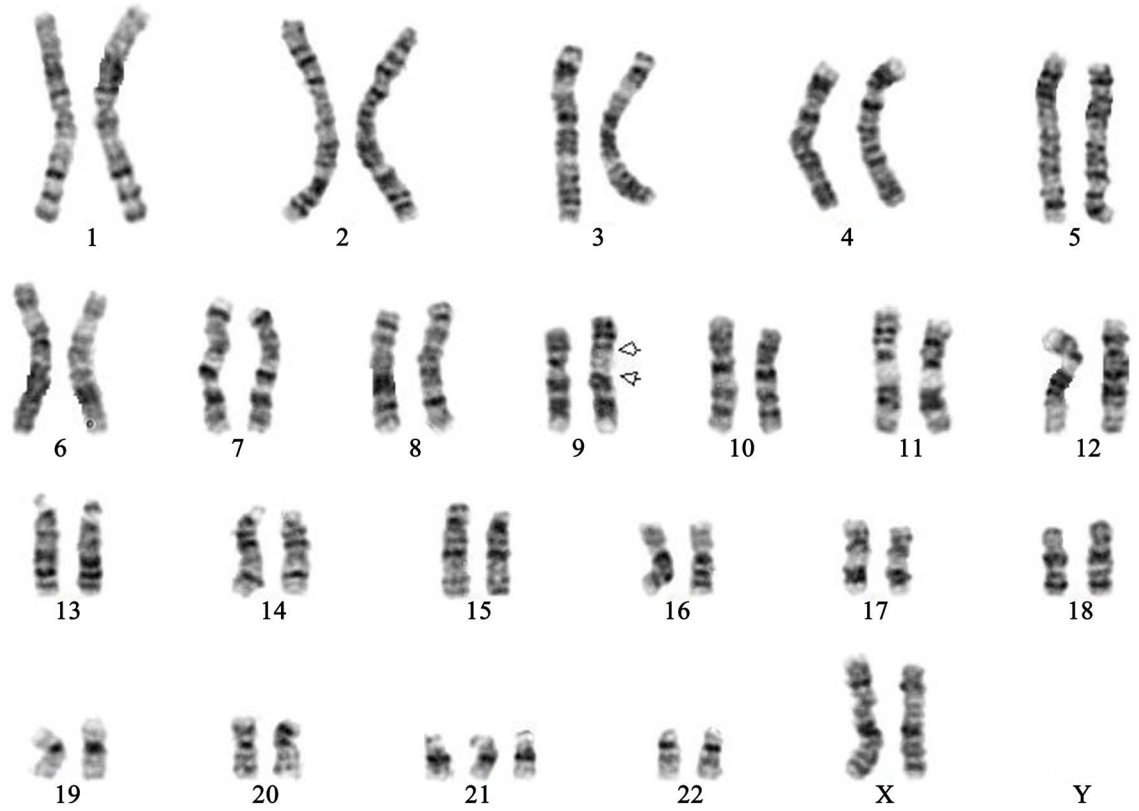

Figure 4. Karyotype showing a case of inv chr9 from a femelle with trisomy 21. 47, XX,+ 21, (inv) 9.

4. Discussion

The inv (9) is a frequent phenomenon, sometimes considered to be a chromosomal polymorphism [7] [9] [10]. Although it does not seem to be correlated with abnormal phenotypes, many controversial reports have been published indicating that it could lead to abnormal clinical conditions. However, when a breakpoint is located in a gene, the inversion affects the phenotype and causes the disease [11].

4.1. Frequency

Inv (9), is one of the most common balanced structural chromosomal aberrations and occurs in approximatively 1% - 1.65% within a normal population. It's important to notice that the prevalence of the inv chr9 in the general population varies with ethnicity [12]. The pericentric inversion of the Heterochromatic region of chromosome 9 [inv (9)], inv (9) (p11q13), or inv (9) (p12q13), is the most common pericentric inversion found in the human karyotype [11].

In our study, the prevalence of inv Chr9 was 1.64%. Many other authors have reported the same observation in their studies with an incidence between 1 and 3% [13]. This incidence may depend on the type of genotipic abnormality associated with inv (9). In Japan, Kiyomi Yamada has reported an incidence of 1.65% of inv (9) among the whole population and 1.52% due to Down syndrome patient group. Furthermore, male subjects were predominant in our study as well as reported by some authors [14] [15].

4.2. Mechanism

The human chromosome 9 displays the highest degree of structural variability [4]. Pericentric inversion involving the secondary constriction region of chromosome 9 is considered to be a normal variant. A recent study described four unique types of pericentric inversions involving the 9qh region and suggested that the mechanism leading to appearance of this phenomenon involves break and reunion at the proposed breakpoints [10] [11]. Study of the heterochromatin organization in the pericentromeric region has revealed homology between 9p11-12 and 9q13-21.1. Such homologous sequences could be involved in the mechanism that generates the inversion [10] [11]. In our study, the most common variant is 9p11.1-q13.

4.3. Clinical Feature

Chr 9 pericentric inversions are very rare phenomena. In our series, 27 cases, the most common clinical sign were: heart disease, abnormalities in sexual development and infertility. In Korea, Seon-Yong Jeong *et al.* reported 8 patients with inv (9) presenting various congenital abnormalities, in particular: polydactyly, giant Meckel's diverticulum, poor rotation of the small intestine, cardiomyopathy, pulmonary stenosis [12] [15].

Here, we summarized the literature reviews of some clinical feature on inv (9)

[16].

Inv (9) and heart disease

We described 5 cases in our series. Few cases of this association were reported. The gène CFA9 on chromosome 9 is a succeptibility gène involved in the congenital heart defect [12].

Inv (9) and Infertility

Inv (9) is considered to be a predisposing factor for infertility. Five cases were observed in our study (Oligospermia, azoospermia and primary amenorrhea). Literature has raised divergent views regarding its correlation with hypofertility, recurrent abortions, spermatogenesis disorders and/or unbalanced offspring [9] [17] [18]. Moreover, inv (9), like the other chromosomal polymorphisms, remains an important risk factor of failure in Assistance Reproductive Technology. Many cases of miscarriages were reported to be associated with inv (9) [6] [7]. However, no statistical analyses were performed in these studies.

Inv (9) and Disorders of Sex Development

Five cases of sex development disturbances were observed in our study. Cases of micropenis and hypospadias associated with inv (9) have been reported [19] [20]. The phenotype can be explained by a disruption in the matching of homologous chromosomes during meiosis and or by the existence of genes of interest at breakpoints. Variants of the SRD5A2 gene are thought to be associated with the occurrence of abnormal sexual development [21].

Inv 9 and Malignant Hematological Disease

The link between inv (9) and leukemia were frequently reported. Indeed, in a series of 3809 cases of patients with malignant hematological disease, Sang Guk Lee has recorded 586 malignant pathologies and 55 chromosome 9 reversals [22]. This allowed them to conclude that chr9 inv are isolated anomalies that have no connection with malignant hemopathies. No case of malignant was found in our study.

Inv (9) and psychiatic disorders

Though some authors in literature have mentioned association of inv (9) and psychiatric disorders [8]; none case was recorded in our study

Inv chr9 and prenatal pathology

Inv (9) is considered as a polymorphic variation and is one of the most common forms of autosomal inversion diagnosed prenatally in amniocytes. Yet its clinical significance remains uncertain. Most publications suggest that this finding is insignificant. However, some articles report on abnormal ultrasonic findings in association, such as hydramnios, anhydramnios, hydroureter, hydronephrosis, encephalocele, and prune belly syndromes [23].

5. Conclusion

This study reinforced the observations of several authors who underline the involvement of chromosome 9 inversion in occurring of various pathologies. Molecular cytogenetic examinations such as comparative genomic hybridization

may prove essential to establish the relationship between the genetic abnormalities of this condition and the consequences on the phenotype of the subject.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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