

# Trisomy 9p. A brief clinical, diagnostic and therapeutic description

Prof. Francisco Cammarata-Scalisi<sup>a</sup>

## ABSTRACT

Trisomy 9p is characterized by the partial or complete duplication of the short arm of chromosome 9. It is one of the most common autosomal structural abnormalities in newborn infants. This is a relatively poor gene region, so it may be more compatible with survival. It is characterized by delayed mental and psychomotor growth, craniofacial dysmorphisms, skeletal alterations, central nervous system abnormalities, congenital heart disease, and, to a lesser extent, kidney disorders. To establish a diagnosis, it is necessary to perform a cytogenetic study with G bands and, if available, fluorescence *in situ* hybridization complemented with comparative genomic hybridization for a better understanding of the genotype-phenotype correlation. Assessment should be interdisciplinary and encompassing a timely family genetic counseling, together with available therapeutic options in an early manner. **Key words:** trisomy 9p, diagnosis, genetic counseling, treatment.

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## INTRODUCTION

Trisomy of the short arm of chromosome 9 (9p) is one of the most common autosomal structural abnormalities in newborn infants.<sup>1</sup> A potential explanation may be that this is a relatively poor gene region, so it may be more compatible with survival.<sup>1-3</sup> Trisomy 9p accounts for the fourth most frequent autosomal trisomy, after trisomies 21, 18, and 13.<sup>2,4</sup>

It was first described in 4 patients by Rethoré et al. in 1970<sup>1-5</sup> and then outlined by Centerwall and Beatty-DeSana in 1975.<sup>4</sup> It is a clinically recognizable entity and, to date, more than 200 cases have been reported in the bibliography.<sup>1-6</sup> It is characterized by the complete (*Figure 1*) or partial duplication of 9p.<sup>2</sup>

## CLINICAL FINDINGS

It is marked by delayed mental and psychomotor development. Craniofacial dysmorphisms include microbrachycephaly,<sup>1-4,7</sup> wide anterior fontanelle,<sup>2,7</sup> down and upward slant of palpebral fissures,<sup>1-3,7</sup> hypertelorism,<sup>1,2,3,8</sup> prominent nasal root, bulbous nose tip,<sup>1,3,7,9</sup> short philtrum,<sup>3</sup> down-turned corners of mouth,<sup>1,7-9</sup> micrognathia,<sup>2,7</sup> low-set ears,<sup>1,3</sup> and malformed, protruding ears.<sup>2,9</sup> The neck may be short and webbed,<sup>3</sup> and kyphoscoliosis, lordosis,<sup>2,6</sup> short stature<sup>3-5</sup> are evidenced in the pre- or post-natal period,<sup>5</sup> in association with delayed bone age.<sup>1,2,5</sup> Also, limb abnormalities characterized by short fingers,<sup>1,10</sup> clinodactyly of the fifth finger,<sup>9</sup> and hypoplastic toe nails<sup>1</sup> are part of the characteristics. Less commonly, central nervous system abnormalities,<sup>2,4,6,7</sup> congenital heart disease, and kidney disorders<sup>2,4,6,7</sup> may occur. Some studies have demonstrated an association with hepatoblastoma,<sup>7,9,11</sup> hepatocellular carcinoma,<sup>11,12</sup> seizures, self-harming behavior,<sup>8</sup> dysphagia,<sup>9</sup> lupus erythematosus, and the presence of keloids.<sup>8</sup> *Table 1*<sup>1-4,6,13</sup> shows potential clinical findings of trisomy 9p and their respective frequency.

Central nervous system disorders must be assessed, especially in patients with epilepsy and neuronal migration alterations.<sup>6</sup> For example, Dandy-Walker malformation, ventriculomegaly, agenesis and hypoplasia of the corpus callosum,<sup>14,15</sup> and large cisterna magna have been described.<sup>14</sup>

In addition, growth hormone deficiency has been characterized<sup>2</sup> and, less frequently, insulin-like growth factor-1 deficiency.<sup>2,16</sup>

a. Unit of Medical Genetics, Department of Pediatrics, School of Medicine of Universidad de Los Andes, Mérida, Venezuela.

*E-mail address:*  
Prof. Francisco Cammarata-Scalisi:  
francocammarata19@gmail.com

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Treatment with recombinant human growth hormone may be considered in patients with trisomy 9p with short stature, while taking into account the severity of intellectual disability and the potential for social inclusion. However, additional studies are required to establish the benefits of a taller stature in this group of patients.<sup>5</sup>

## ETIOLOGY

In most cases, partial trisomy 9p occurs as a result of parental reciprocal translocation between chromosome 9 and other autosome.<sup>2,3,8</sup> Therefore, phenotypic heterogeneity is correlated to the variable size of the duplicated segment (producing trisomy 9p) and the monosomy of the other chromosomal segment.<sup>3,4,8</sup> To a lower extent, it is the result of a spontaneous (*de novo*) genetic alteration occurring for unknown reasons during early embryonic development, i.e., it is not passed by any of the parents.<sup>2,8</sup>

Based on the aforementioned information, establishing the genotype-phenotype correlation may be hindered by the presence of small deletions or duplications affecting other chromosomes in most reported cases of trisomy 9p.<sup>2,10</sup> Such additional genetic alterations make it difficult to understand which abnormalities have been caused by trisomy 9p or by other chromosomal changes.<sup>10</sup> In some cases, an additional segment in the long arm of chromosome 9 may also be present.<sup>2</sup>

However, clinical severity is related to the size of the duplicated segment of 9p.<sup>3,4</sup> Studies on the genotype-phenotype correlation in cases of partial trisomy 9p suggested that the critical region for the phenotype was in 9p22 → p24, whereas Christ

et al. proposed a shorter region located in 9p22.1 → p23.<sup>3</sup>

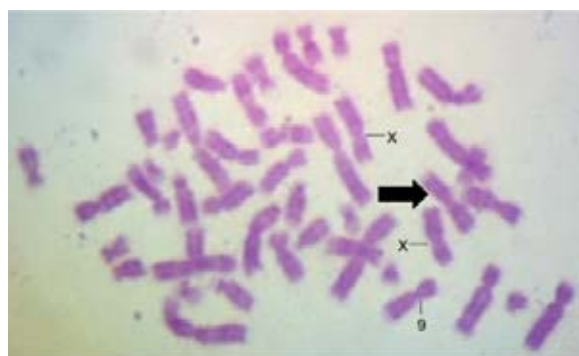
On its side, trisomy 9pter-p11 is associated with typical craniofacial characteristics,<sup>3</sup> whereas trisomy 9p21.1-q22-32 is related to more severe craniofacial characteristics.<sup>2</sup> Trisomy 9pter → q11-13 presents with skeletal and heart defects, in addition to craniofacial characteristics.<sup>3</sup> Facial clefts are uncommon, and the specific regions associated with this finding have not been clearly identified.<sup>10</sup>

TABLE 1. Clinical findings of trisomy 9p and their frequency (as a percentage)<sup>1-4,6,13</sup>

Finding	Frequency (%)
Short stature	99
Delayed bone age	99
Bulbous nose tip	95
Down-turned corners of mouth	95
Brachydactyly	90
Clinodactyly	90
Branchymesophalangy	90
Language disorder	90
Single palmar crease	80-95
Delayed puberty	70-90
Strabismus	70-80
Short philtrum	70-80
Hypertelorism	70-80
Malformed, low-set ears	70-80
Microbrachycephaly	70-75
Hypoplasia of phalanges	70-75
Hypoplastic nails	70-75
Enophthalmos	60-70
Down and upward slant of palpebral fissures	60-70
Gothic palate	60-70
Short, webbed neck	60-70
Hypotonia	60-70
Low birth weight	50-70
Kyphoscoliosis	60
Lordosis	60
Mental retardation	60
Hip luxation	30-40
Cerebral hypoplasia	< 30
Cerebellar hypoplasia	< 30
Ventriculomegaly	< 30
Agenesis and hypoplasia of the corpus callosum	< 30
Choroid plexus cysts	< 30
Epilepsy	< 30
Congenital heart disease	25
Ventricular septal defect	25
Ebstein's anomaly	10-20
Patent ductus arteriosus	10-20
Cleft lip and palate	5
Epicanthal folds	NS
Thin upper lip	NS
Microretrognathia	NS
Micropenis	NS
Kidney malformation	Infrequent
Umbilical hernia	Infrequent

NS: not specified.

FIGURE 1. Cytogenetic study with G bands in a female patient with complete duplication of 9p, as shown by the arrow



It has been suggested that the dosage effects of the genes located in 9pter-q22 contribute to the etiology of the already commented Dandy-Walker malformation.<sup>15</sup> Therefore, the genetic dosage effects, together with environmental influences, may be responsible for several abnormalities present in the central nervous system observed in this entity.<sup>14</sup>

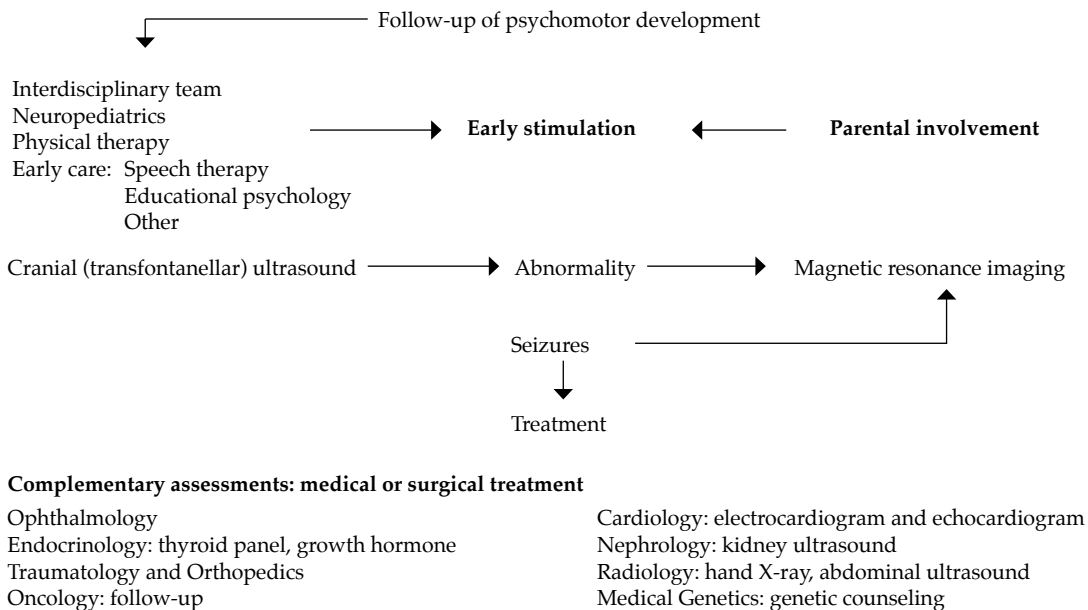
**DIAGNOSIS, MANAGEMENT AND TREATMENT**

Diagnostic guidance should be aimed at confirming the existence of chromosome disease, initially through a cytogenetic study with G bands and, if available, with a fluorescence *in situ* hybridization<sup>6</sup> complemented with comparative genomic hybridization, which is a more accurate method to measure changes in the number of copies across the genome. This method is useful to determine the region of chromosome 9 and its size, as well as other chromosomes involved, thus facilitating a more comprehensive understanding of genotype-phenotype correlations.<sup>10,17</sup> In the presence of a structural chromosomal abnormality, these studies should be done in both patients and their parents to identify the source of the translocation, thus warranting an adequate genetic counseling. If one of the parents carries the abnormality, the risk for recurrence ranges from 2 % to 15 %.<sup>6</sup>

One of the basic, complementary exams that is recommended to define the phenotypic expression is a cranial (transfontanellar) ultrasound and, in the presence of an abnormality or signs suggestive of a structural abnormality, such as seizures, a brain magnetic resonance imaging should be done. For the management of seizures, the most adequate drug for this type of crises should be indicated. In addition, psychomotor development should be monitored by an interdisciplinary team, including a pediatric neurologist, a physical therapist, and different health care providers from the early care team, such as a speech therapist and an educational psychologist, among others. For treatment, it is critical to conduct interventions in relation to delayed psychomotor development through early stimulation, which should be started as early as possible. On their part, parents' involvement in stimulation is decisive to obtain the best outcomes.<sup>6</sup>

Likewise, the Departments of Ophthalmology, Cardiology, Endocrinology, Nephrology, Traumatology and Orthopedics, and Radiology should perform assessments for the presence of hypoplasia of phalanges, among other signs, while the Departments of Oncology, Medical Genetics, and Pediatrics should provide follow-up, as shown in *Figure 2*. Prognosis is highly variable depending on the severity of delayed

FIGURE 2 Assessments required in a patient with trisomy 9p<sup>6</sup>



psychomotor development and the presence of seizures or heart disease, which are the most determining factors.<sup>6</sup>

## CONCLUSIONS

Trisomy 9p, also known as Rethore syndrome, is a recognizable clinical entity, and the craniofacial findings of this abnormality may determine its diagnosis.<sup>2,18</sup> This is due to the complete or partial duplication of 9p.<sup>6</sup> It is a relatively infrequent entity compatible with life.<sup>5</sup> However, language, swallowing, pulmonary, and nutritional alterations may affect patients' quality of life.<sup>9</sup> Phenotypic variability seems to depend on the magnitude of the genetic imbalance in each case.<sup>5</sup>

Finally, few references have been made in relation to differential diagnoses, which may be intricate due to the wide variety of clinical features. In this case, it is necessary to rule out other chromosomal entities, such as Turner syndrome, or genetic entities, like Smith-Magenis syndrome, which may present with coexisting alterations in growth, psychomotor development, intelligence quotient, language, as well as dysmorphisms, skeletal disorders, and various organ involvement.

The objective of this review is to guide clinical and cytogenetic diagnosis with available conventional or molecular methods in order to provide a timely family genetic counseling, together with available therapeutic options in an early manner.<sup>6</sup> ■

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