



*Mini-Review*

# Monosomy 1p36 syndrome: reviewing the correlation between deletion sizes and phenotypes

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**ABSTRACT.** The major clinical features of monosomy 1p36 deletion are developmental delay and hypotonia associated with short stature and craniofacial dysmorphisms. The objective of this study was to review the cases of 1p36 deletion that was reported between 1999 and 2014, in order to identify a possible correlation between the size of the 1p36-deleted segment and the clinical phenotype of the disease. Scientific articles published in the (National Center for Biotechnology Information; NCBI <http://www.ncbi.nlm.nih.gov/pubmed>) and Scientific Electronic Library Online ([www.scielo.com.br](http://www.scielo.com.br)) databases were searched using key word combinations, such as “1p36 deletion”, “monosomy 1p36 deletion”, and “1p36 deletion syndrome”. Articles in English or Spanish reporting the correlation between deletion sizes and the respective clinical phenotypes were retrieved, while letters, reviews, guidelines, and studies with mouse models were excluded. Among the 746 retrieved articles, only 17 (12 case reports and 5 series of cases), comprising

29 patients (9 males and 20 females, aged 0 months (neonate) to 22 years) bearing the 1p36 deletions and whose clinical phenotypes were described, met the inclusion criteria. The genotype-phenotype correlation in monosomy 1p36 is a challenge because of the variability in the size of the deleted segment, as well as in the clinical manifestations of similar size deletions. Therefore, the severity of the clinical features was not always associated with the deletion size, possibly because of the other influences, such as stochastic factors, epigenetic events, or reduced penetration of the deleted genes.

**Key words:** Monosomy 1p36 syndrome; 1p36 deletion syndrome; Deletion size; Phenotype

## INTRODUCTION

Monosomy 1p36, or the 1p36 deletion syndrome, is a subtelomeric monosomy with an incidence of 1 in every 5000 births. A majority of the cases (52-67%) have a terminal deletion on chromosome 1. Interstitial deletions (9.7-29%) and other abnormalities, such as derivative chromosomes (7-16.4%) and complex rearrangements, are less frequent (Shiba et al., 2013; Öiglanc-Shlik et al., 2014).

The major clinical features of 1p36 deletion syndrome include motor developmental delay and hypotonia associated with short stature and craniofacial dysmorphisms, such as large anterior fontanel, prominent forehead and chin, deep eyes, a flat nasal bridge, maxillary hypoplasia, and ear asymmetry (Zagalo et al., 2012). The patients may also show skeletal malformations, cardiac, gastrointestinal, and visual abnormalities, seizures, and behavioral disorders.

Monosomy 1p36 is the most common terminal deletion in human beings, responsible for about 1% of all cases of idiopathic mental retardation (Battaglia et al., 2008). Therefore, the objective of this paper was to review the cases of 1p36 deletion syndrome described in the literature from 1999 to 2014, and to correlate the size of the 1p36-deleted segments with the clinical phenotypes.

## MATERIAL AND METHODS

The scientific articles submitted to the database at the National Center for Biotechnology Information (NCBI; <http://www.ncbi.nlm.nih.gov/pubmed>) and the Scientific Electronic Library Online ([www.scielo.com.br](http://www.scielo.com.br)) websites were electronically searched using various combinations of key words, including "1p36 deletion", "monosomy 1p36 deletion", and "1p36 deletion syndrome".

Articles published between 1999 and 2014, written in English or Spanish, which reported an association between the size of the deletion in each patient and their respective clinical phenotypes, were retrieved. Articles showing an association with the phenotype while excluding the measurement of the size of the deletion were excluded from this review; additionally, those papers reporting changes on chromosomes other than chromosome 1p36 were also excluded. Letters, reviews, guidelines, and studies in mouse models were also excluded.

## RESULTS

The search retrieved 746 articles. Among these, 17 scientific articles met the criteria for inclusion and were selected for this study (D'Angelo et al., 2006; Krepischi-Santos et al., 2006; Kang et al., 2007; Robinson et al., 2008; Bursztejn et al., 2009; El-Hattab et al., 2010; Gajecka

et al., 2010; Rosenfeld et al., 2010; Haimi et al., 2011; Mikhail et al., 2011; Nicoulaz et al., 2011; Giannikou et al., 2012; Gervasini et al., 2013; Shiba et al., 2013; Zhu et al., 2013; Shimada et al., 2014; Stagi et al., 2014). Among these, 12 were case reports and five reported series of cases. These articles included a total of 29 patients (9 males and 20 females aged 0 months (neonate) to 22 years) bearing the measured 1p36 deletions, and whose clinical phenotypes have been described. The deletion sizes ranged from 199 kb to 16 Mb.

All deletions and phenotypes are indicated in an ideogram of chromosome 1, with an amplified 1p36.11-1p36.33 region (Figure 1). Developmental delay, especially psychomotor delay (44.82%), was prominently observed. Additionally, the articles reported various neurological manifestations, such as failure in oral expression (55.17%), hypotonia (48.27%), intellectual disability (48.27%), and epilepsy (41.37%), among others.

## DISCUSSION

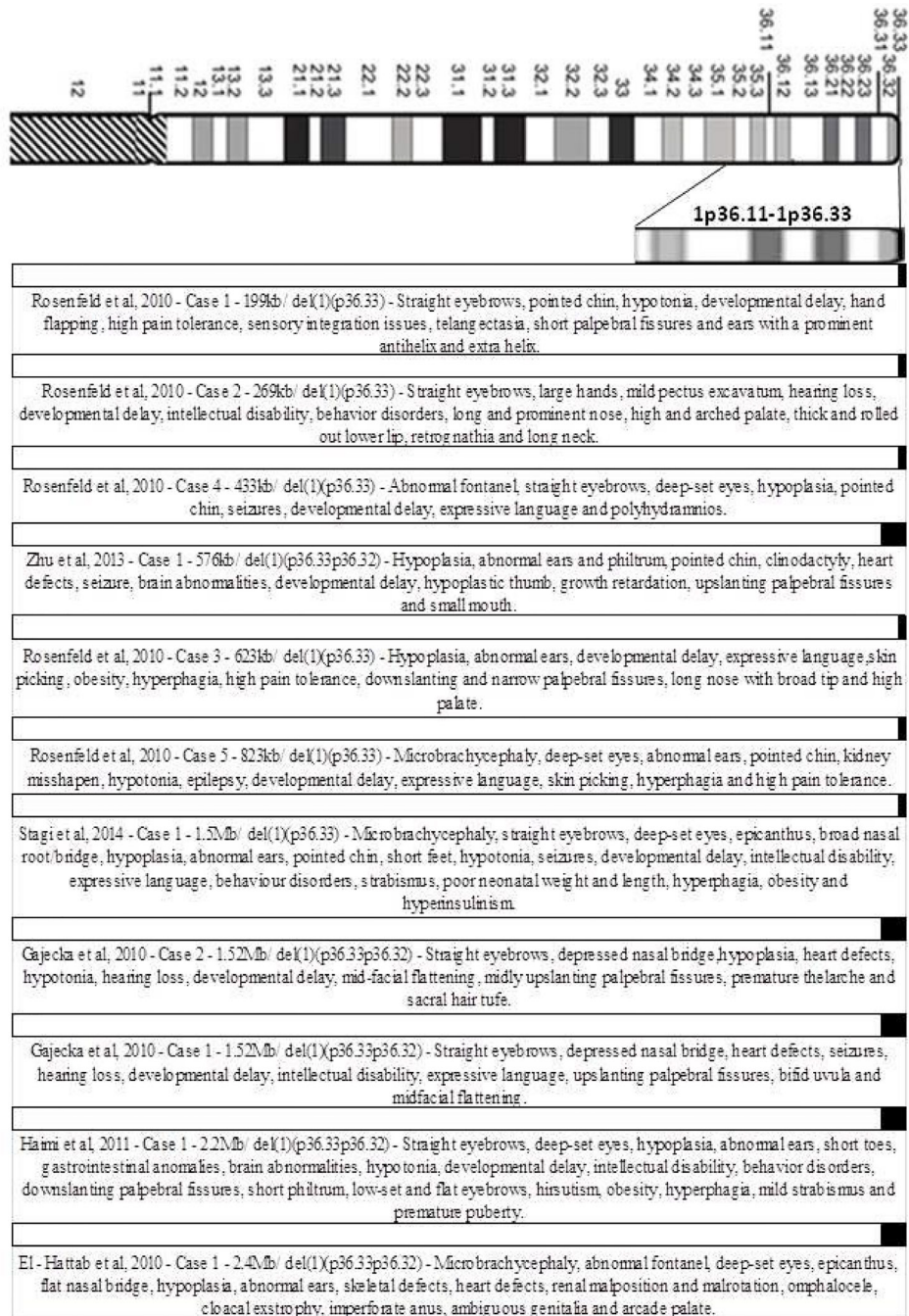
In this study, we selected 17 articles reporting a deletion in chromosome 1 (1p36). The majority of the patients analyzed in these articles were females, a finding that has been previously reported (Slavotinek et al., 1999).

Various techniques are employed to detect chromosomal deletions; array comparative genome hybridization (aCGH) is a technique that covers the whole genome. This technique is more effective than the multiplex ligation probe amplification (MLPA) method, used to detect other chromosomal alterations when 1p36 deletion was not clinically suspected (D'Angelo et al., 2010). The aCGH method can also be used to determine the break points and measure the size of chromosomal loss (Battaglia et al., 2008), allowing the investigation of genotype-phenotype association.

Another technique used to identify chromosomal deletions is conventional or high-resolution karyotype analysis; however, these methods are often unable to detect small changes in the 1p36 segment, as it is a clear G-band on the tip of the terminal region of the short arm of chromosome 1 (Slavotinek et al., 1999); moreover, deletions smaller than 2-3 Mb are not visible with common optical microscopy. Fluorescence *in situ* hybridization (FISH), as well as some other techniques, can be used to complement the cytogenetic study, confirming a partial monosomy in metaphases and/or interphases. FISH can be used to confirm the microdeletion, discovered using other methods such as CGH array or MLPA, when the karyotype is normal and when there is a strong clinical suspicion of the syndrome.

Cunha et al. (2014) also described a technique, using real-time quantitative PCR with a sensitivity and specificity of 100%, for the detection of monosomy 1p36. This technique was validated in two genes, *PRKCZ* and *SKI*, which were absent in most of their patients: eight of the patients (8/29) presented these deleted genes.

The deletion size can be used to explain the clinical variability of phenotypes such as the ones observed in other structural chromosomal syndromes (Gajecka et al., 2007). Deletions ranging from 199 kb to 16 Mb have been previously reported (Rosenfeld et al., 2010; Nicoulaz et al., 2011). Patients bearing 1p36 deletions of different sizes have been shown to express similar phenotypes. This indicated that the final aspect of the syndrome is governed by more complex causes than a simple contiguous gene deletion (Öiglanc-Shlik et al., 2014) (Figure 1), such as the effect of the position of one or more genes, genetic and/or environmental factors that may aggravate or mitigate the phenotype, and copy number variations or other genetic mutations other than 1p36. For example, Öiglanc-Shlik et al. (2014) reported that only one of four patients with the same deletion on 1p36 presented congenital heart defect, seizures, and behavioral changes.



**Figure 1.** Ideogram of the short arm of chromosome 1, and the amplified 1p36.11-1p36.33 region, depicting the different deleted bands and their respective clinical aspects.

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Figure 1. Continued

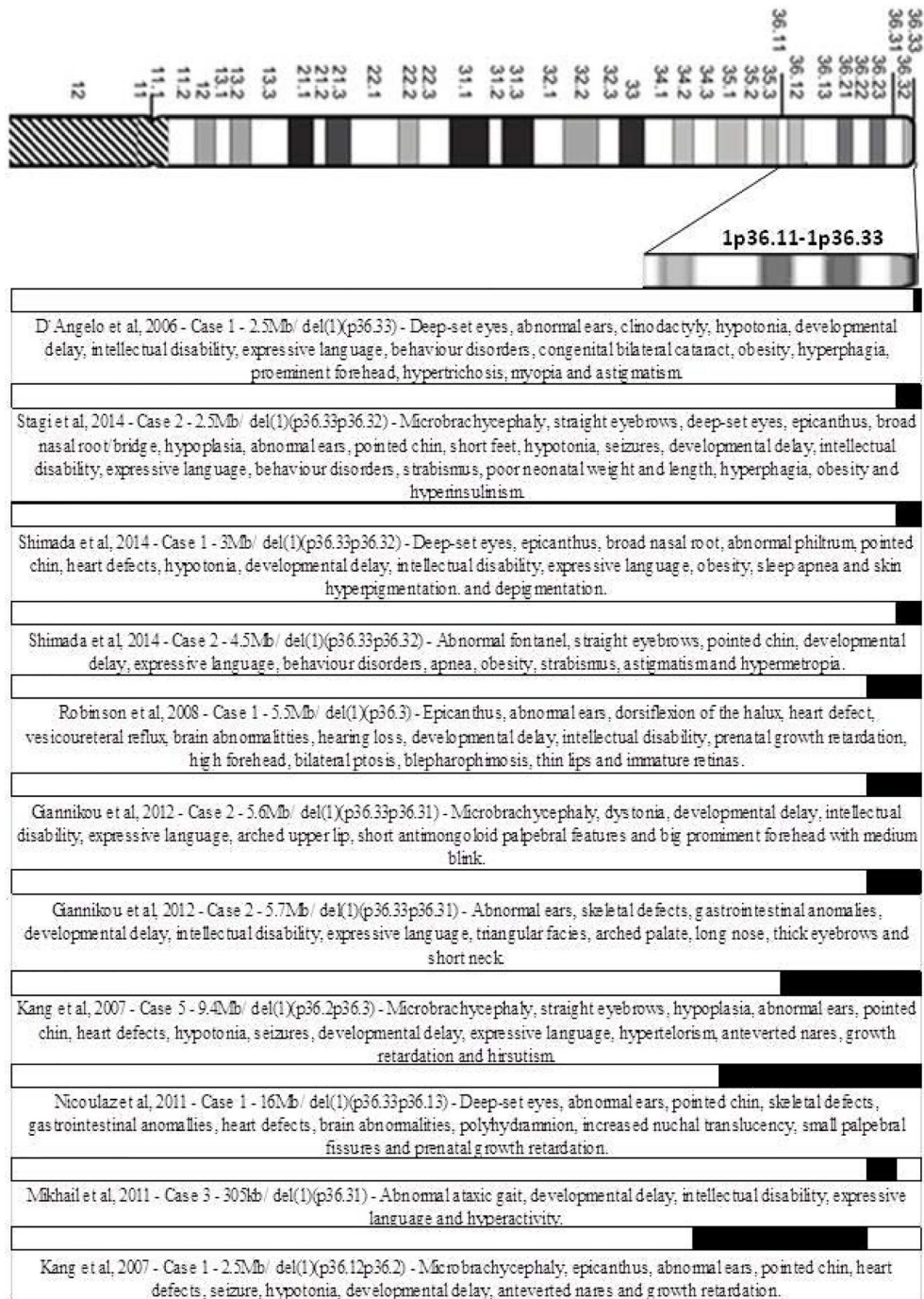
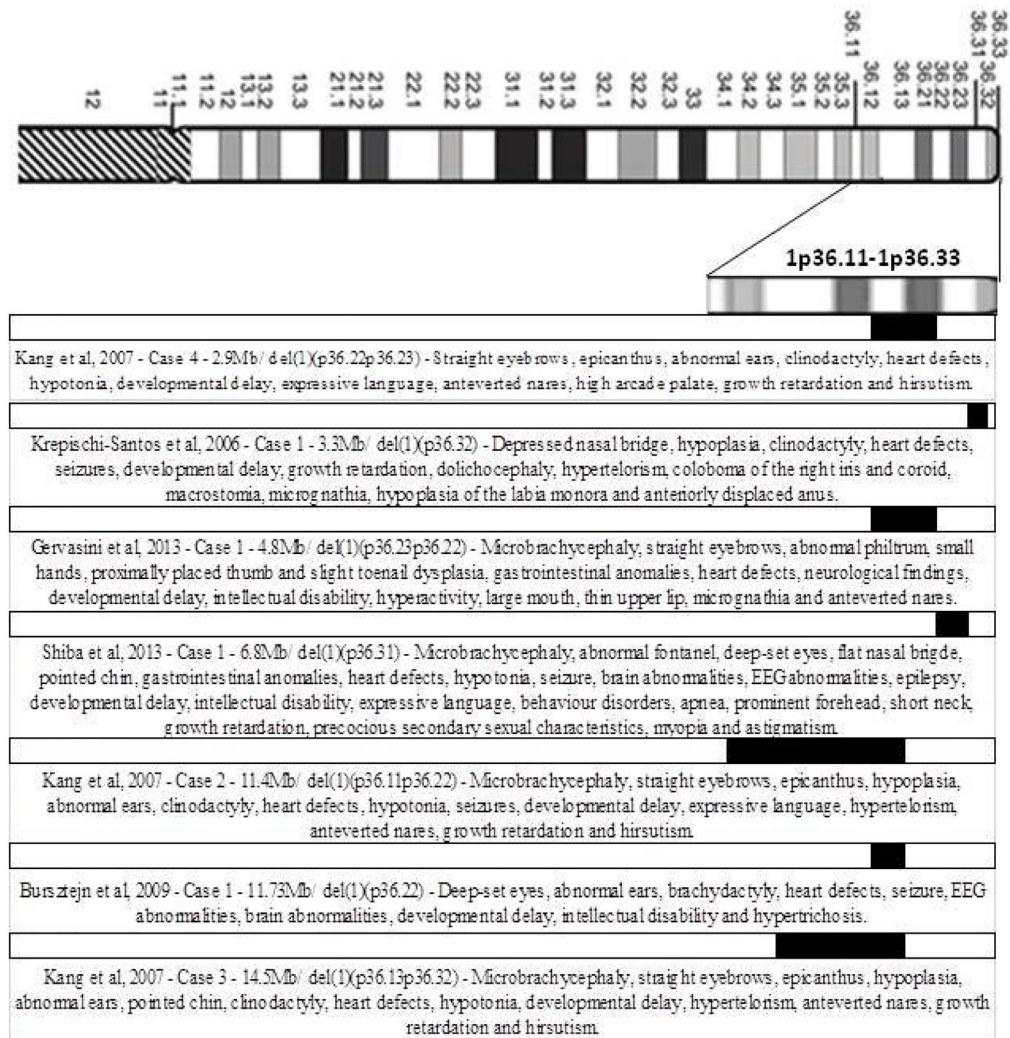


Figure 1. Continued



On the other hand, Rosenfeld et al. (2010) reported a deletion in the *GABRD* gene, which encodes the delta subunit of the gamma-aminobutyric acid (GABA)<sub>A</sub> receptors, in three 1p36 deletion patients. GABA is the major inhibitory neurotransmitter in the mammalian brain where it acts at GABA<sub>A</sub>. Mutations in this gene have been associated with susceptibility to generalized epilepsy with febrile seizures. Two of the three patients also presented convulsive frames. This could be explained by mechanisms such as stochastic factors, epigenetic factors, and/or the lack of complete penetrance of the gene, which could influence the clinical picture and avoid the precise phenotype-genotype correlation.

One possible explanation for the emergence of deletions causing monosomy 1p36 is the

presence of repetitive DNA sequence elements that can generate and/or stabilize these deletions.

The presence of mosaicism in 1p36 deletion has also been described in two patients with developmental delay, syndromic facies, obesity, and mild neurological disabilities. These mosaic individuals did not present speech disabilities and could walk without help, features that are milder compared to those shown by patients with the typical deletion (Shimada et al., 2014).

The most prevalent clinical feature observed in the patients analyzed in this review was developmental delay (psychomotor, motor, or global); this was followed by neurological disorders, such as hypotonia, epilepsy, brain malformation, hearing loss, dystonia, and ataxic gait. The proto-oncogene *SKI*, involved in myelination and the development of Schwann cells (Atanasoski et al., 2004), was one of the deleted genes; the *CAMTA1* gene, which encodes a member of the transcription activator family connected to calmodulin, expressed in some regions of the brain involved with embryo development and growth control (Finkler et al., 2007) also expressed deletions. The other genes implicated in neurological development are *GNB1*, associated with the size of the brain; *TP73*, connected to brain malformation; and *GABRD*, which plays a role in the development of seizures.

Patients with partial monosomy are at a greater risk of developing neoplasms, although this does not always occur. It is noteworthy that the suppression of other candidate genes for cancer susceptibility located in the same region, such as the *CDC2L2*, *TNFRSF25*, *AJAP1*, *TP73*, *CAMTA1*, may also contribute to the development of malignancies.

In this review, we identified 17 patients with cardiac anomalies, such as ventricular septal defect, persistence of the arterial duct, atrial septal defect, cardiac enlargement, defective mitral valve, changes in deployment of the pulmonary vein, and puff, among others. These abnormalities are commonly found in monosomy 1p36. Deletions in the *SKI* (Rosenfeld et al., 2010) or *PRDM16* genes can lead to cardiomegaly, which is the most common abnormality found in patients according to the literature (Slavotinek et al., 1999). However, only one of the patients included in this review presented a deleted *SKI* gene and cardiomegaly. In addition to these genes, region 1p36.22 has at least 23 known genes, many of which are expressed in the heart (Kang et al., 2007).

Several clinical features of monosomy 1p36, such as overeating, obesity, hypotonia, cognitive deficits and psychomotor delay, overlap with those of Prader-Willi syndrome (PWS). Patients showing the PW phenotype, but who present a negative result when tested for PWS, were believed to express a Prader-Willi-like phenotype. Therefore, monosomy 1p36 should also be investigated in Prader-Willi-like patients. Not only 1p36 deletion symptoms overlap with those of PWS, but also the symptoms of various other syndromes and chromosomal abnormalities overlap with PWS (Rocha and Paiva, 2014). Here, we identified four cases of monosomy 1p36 showing the Prader-Willi-like phenotype. According to Tsuyusaki et al. (2010), such a phenotype is associated with the 4-Mb 1p36 terminal deletion.

Even small deletions in 1p36 monosomy have been shown to lead to phenotypic alterations; the patient expressing the smallest deletion described in this review (199 kb) presented phenotypes such as straight eyebrows, pointed chin, hypotonia, developmental delay, intellectual and behavioral changes, high tolerance to pain, short palpebral fissure, telangiectasia, and pinna abnormalities (Rosenfeld et al., 2010). On the other hand, the patient showing the largest chromosomal loss (16 Mb) featured deep eyes, skeletal, gastrointestinal, cardiac and cerebral abnormalities, prenatal growth delay, polyhydramnios, and increased nuchal translucency (Nicoulaz et al., 2011).

The genotype-phenotype correlation in monosomy 1p36 syndrome is a challenge because of the variability in the size of the deleted segment, as well as in the clinical manifestations, which were not always related to the size of the deleted chromosome. In addition, the severity of the clinical

pictures were not always associated with the deletion size, probably because of other influences such as, stochastic factors, epigenetic events, or reduced penetration of the deleted genes.

## Conflicts of interest

The authors declare no conflict of interest.

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