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Retrospective Study of Chromosome 1p36 Deletion Syndrome at Tertiary Care Centre with Literature Review

Rola M AL ANAZI[1*], Bashayer S ALAWAM[2], Zuhair Rahbeeni [3],

1. MD, king Fahad armed forces hospital-Jeddah.
2. MD, Imam Abdulrahman Bin Faisal university.
3. MD, King Faisal Specialist Hospital & Research Centre -Riyadh.

Corresponding Author: Rola M AL ANAZI, MD, king Fahad armed forces hospital-Jeddah.

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Abstract:

The constitutional deletion of chromosome 1p36 results in a syndrome with multiple congenital anomalies and mental retardation. Monosomy 1p36 is the most common terminal deletion syndrome in humans. is believed to affect between 1 in 5,000 - 10,000 newborns. However, this may be underestimate because some affected individuals are not diagnosed. The most common is terminal and interstitial deletions with varying lengths located throughout the 30 Mb of DNA which explain why the size of deletion can be variable. Medical problems commonly include developmental delay, intellectual disability, seizures, brain anomalies, vision problems, hearing loss, short stature, distinctive facial features, orofacial clefting, congenital heart defects, cardiomyopathy, and renal anomalies. Chromosome 1p36 deletion accounts for around 1% of cases of intellectual disability. In addition, haploinsufficiency of more than one gene may contribute to some phenotypes .In this article, we review of 6 families retrospectively with chromosome 1p36 deletion with phenotype and cytogenetics analysis at KFSHRC-Riyadh , Saudi Arabia .

As far as we know this is the 1st case series of 1p36 del in Arab world.

Keywords: *chromosome 1p36, chromosome deletion, 1p36 deletion syndrome, dysmorphic facial features*

Introduction

1p36 deletion syndrome (OMIM: 607872) is a chromosomal abnormality characterized by intrauterine growth retardation, a characteristic facial dysmorphism made up of straight eyebrows, sunken eyes, wide and flat nasal bridge, upper floor middle of the hypoplastic face, a long philtrum, a pointed chin and a frequent delay in closing the anterior fontanel, micro-brachycephaly, upturned ears of low implantation and malformed, brachydactyly, camptodactyly, short feet, hypotonia, developmental delay, intellectual deficit, seizures, heart defects and hearing and vision impairment. It is considered to be the most common terminal deletion in humans. It is estimated that the syndrome occurs in one every 5,000 to 10,000 births without differentiation of sex or ethnicity. The syndrome is caused by a partial heterozygous deletion of the most distal band of the short arm of chromosome 1 (1p36), with breakpoints ranging from 1p36.13 to 1p36.33. Fifty percent of the cases are de-novo terminal deletion, 29% are the interstitial deletion and the other cases are secondary to more complex chromosomal rearrangements. The first reports of individuals with partial monosomy of chromosome 1p36 were published in the early 1980s, starting with a report by Hain et al. Many of the individuals described in these reports had unbalanced translocations in which their 1p36 deletions were accompanied by a gain of material from a nonhomologous chromosome. While the addition of chromosomal material to the long arm of chromosome 1 made it easier to identify these 1p36 deletions, it also made it more difficult to delineate with certainty the clinical effects of monosomy 1p36. The syndrome comprises 4 cytogenetic groups including pure terminal deletions, interstitial deletions, complex rearrangements, and derivative chromosome 1 due to unbalanced translocations, where unbalanced translocations represent the least percentage of all cases of monosomy 1p36 (7%).

Fluorescence in situ hybridization (FISH) and comparative genomic hybridization (CGH-array) are currently the two best diagnostic techniques.

Methods

Here, we studied 6 families, Arab origin.

The probands of this study are affected female and male infants. Our study is retrospective with chart review of 6 patients that confirmed to have a ch1p36 deletion. We reviewed patient's files and cytogenetic result.

Cytogenetic Studies

Conventional cytogenetic analysis (CCA) of peripheral blood chromosomes was performed for patients to detect any numerical or structural chromosomal aberrations using the G banding technique.

Approximately 30 metaphases were analyzed and karyotyped for each of them, and cytogenetic nomenclature followed the International System for Human Cytogenetic Nomenclature [ISCN, 2016] recommendations.

FISH was done for the of probands and confirmed the presence of the 1p36 deletion as well as detecting the chromosomal breakpoints.

Family no.1. A 6-month-old that was referred complaining of Seizure, Multiple Congenital Anomalies, Congenital Heart Disease in form of VSD, and squint. This child was the first and only child of consanguineous 1st degree relative, apparently healthy parents. The pregnancy history was uneventful, with no specific remarkable family history of seizure, delayed development, hypotonia, or language delay. She had normal birth weight as mentioned by the parents.

At age of 12 months, her general clinical examination revealed weight of 8 kg (at 10 centiles), length of 57 cm (below 3ed entiles), and head circumference of 43 cm (at 5th centiles) intellectual disability, delayed motor and mental milestones in the form of delayed walking, hypotonia, and absent speech. She had dysmorphic facial features including brachycephaly, low anterior and posterior hairlines, hypotonic face, midface hypoplasia, straight eyebrows, deep-set eyes, strabismus, hypotelorism, down slanting palpebral fissures, low-set posteriorly rotated ears, prominent broad forehead, flat broad nose with downward columella, long philtrum, microstomia, pointed chin, short neck, skeletal abnormalities in the form of bilateral broad big toes, characteristic small feet, brachydactyly with talipes and bilateral broad thumbs. She had generalized hirsutism.

Neurological examination showed hypotonia, hyporeflexia, and inability to stand unsupported. Brain MRI revealed delayed white matter myelination related to age and minimal brain sub volume.

His echocardiography revealed Ventricle septal defect (VSD) and pulmonary hypertension (PTHN).

Pelvic- abdominal ultrasound and hearing test were normal. Complete eye and fundus examination revealed squint, myopia, and stigmatism. Thyroid function test was normal.

Follow-up at the age of 18 months revealed short stature for her age, but her weight and head circumference were appropriate for her age. The patient still showed severe global developmental delay and intellectual disability, remarkable hypotonia, and she could not walk unsupported. She regularly attended physiotherapy sessions. Dysmorphic features had become more obvious. Speech and language development were severely delayed. She even could not speak any words.

Her cytogenetic study shows 46, XX, subtelomeric deletion at 1p36.3 detected by Fluorescence in situ hybridization (FISH).

Family no.2. The Proband was female with severe IUGR with birth wight of 2kg, Hight of 35 cm & sever microcephaly 20cm below stander deviation The girl was the first and only child of consanguineous apparently, healthy parents. The pregnancy complicated with oligohydramnios at antenatally US, with no specific remarkable family history. She died at 3ed day of life.

Her cytogenetic study shows 46, XX, subtelomeric deletion at 1p36.3 detected by Fluorescence in situ hybridization (FISH).

Family no.3. The proband was a female infant. She was 12 months old when referred for the first time to medical genetics Clinic. The main concerns were that their child had global developmental delay (mental and motor) and hypotonia. The girl was the 5th child of consanguineous, apparently healthy parents. The pregnancy history was uneventful. No history of affected family members. She had normal birth weight as mentioned by the parents.

General clinical examination revealed delayed motor and mental milestones in the form of delayed walking, hypotonia, and absent speech only produce sounds. She was dysmorphic, showed facial features including brachycephaly, low anterior and posterior hairlines, hypotonic face, straight eyebrows, deep-set eyes, down slanting palpebral fissures, prominent broad forehead, flat broad nose, short neck, skeletal abnormalities in the form of bilateral broad big toes, characteristic small feet.

her weight was 9kg at 10th centile, length was 75 cm at 50 centile, and head circumference was 44 cm at 50 centile.

Neurological examination showed hypotonia, hyporeflexia, and inability to stand unsupported. Brain MRI revealed delayed white matter myelination related to age.

Echocardiography revealed atrial septal defect (ASD).

hearing test was normal. Complete eye and fundus examination was normal. Thyroid function test showed evidence of hypothyroidism.

Follow-up at the age of 18 months showed that she was short stature for her age, but her weight and head circumference were appropriate. The patient still showed severe global developmental delay and intellectual disability, remarkable hypotonia, and she could not walk unsupported. She died at age 30 months from septicemia and respiratory failure.

Her cytogenetic study shows 46, XX, del (1) (p36.3) detected by Fluorescence in situ hybridization (FISH).

Family no.4. 37-year-old, primigravid woman was referred for amniocentesis at 20 gestational weeks because of abnormal ultrasound finding of affected fetus with Microcephaly, VSD, midface hypoplasia and oligohydramnios . the proband was a female infant with intrauterine growth restriction (IUGR), sever hypotonia, require ventilation since born, dysmorphic feature in form of straight eyebrows, deep-set eyes and short neck. She is product of consanguineous, apparently healthy parents. The pregnancy history was significant for oligohydramnios and IUGR. They had 2 children normally. She died at 14 days of life.

Brain MRI postnatally showed revealed a Cerebral hypoplasia.

Her cytogenetic study shows 46, XX, del (1) (p36.1p36.2) detected by Fluorescence in situ hybridization (FISH).

Family no.5 A proband was a female infant. died at 12 hours after birth with dysmorphic feature in form of brachycephaly, low anterior and posterior hairlines, hypotonic face, midface hypoplasia, straight eyebrows, deep-set eyes, down slanting palpebral fissures, low-set posteriorly rotated ears, prominent broad forehead, flat broad nose with downward columella, long philtrum, microstomia, pointed chin and Congenital Heart Disease VSD. She was product of consanguineous apparently, healthy parents, there is a second child normal. The pregnancy history was uneventful, with no specific family history. No history of affected family members.

Her cytogenetic study showed 46, XX, del (1) (p36.1p36.2) detected by Fluorescence in situ hybridization (FISH).

Family no.6. The proband was a male infant. Referred at age of 4 months with seizure, microcephaly with dysmorphic feature in form of midface hypoplasia, straight eyebrows, deep-set eyes, spastic quadriplegia, Upper Limb more affected than lower limbs, associated with generalized dystonia and bilateral hip dislocation. He is the only child of consanguineous, apparently healthy parents. The pregnancy history was uneventful, with no specific family history. There is no history of affected family members. He had low birth weight (2 kg).

His cytogenetic study shows 46, XY, del (1) (p36) detected by Fluorescence in situ hybridization (FISH).

Results:

Six patients with pure chromosome 1p36 deletion, Cytogenetic and FISH Analyses of 1p36 Deletiontions have been evaluated for their clinical phenotypes Syndrome Patients (table 1).

In the current study, we reports on our patients who are presented with clinical features suggestive of monosomy 1p36 syndrome. Patients with monosomy 1p36 syndrome showed distinctive craniofacial features, intellectual disability, and developmental delay with variable degrees of severity. Typical craniofacial features include microcephaly and/or brachycephaly, large, late-closing anterior fontanel, straight eyebrows, deep-set eyes, midface hypoplasia, broad nasal bridge, long philtrum, pointed chin, and low-set ears. rated dysmorphic features, intellectual disability, developmental delay, delayed or absent speech, and hypotonia as the cardinal features of monosomy 1p36 with a collective percentage of 50% of the patients. Subsequent important clinical data include seizures and cardiac abnormalities with a percentage of 16-50%, followed by other less frequent findings, e.g., spastic quadriplegia, Upper Limb more affected than lower limbs, associated with generalized dystonia and bilateral hip dislocation skeletal abnormalities, sensorineural deafness, ophthalmological finding revealed squint, myopia, and stigmatism and hypothyroidism. All craniofacial features reported in our study are in conformity to those described by previous literature's. apart from large, late-closing anterior fontanel. Dysmorphic features observed in our patient were also comparable to the previous studies. Intellectual disability and developmental delay, present in our patient, are principle findings in patients with monosomy 1p36. Our patient also manifested generalized hypotonia which is a prevailing feature reported in 16-33% of those patients Corresponding to multiple previous studies, seizures and cardiac abnormalities in the form of VSD and ASD were observed in our patient. Skeletal abnormalities have been identified in about 16% of monosomy 1p36 patients including clinodactyly, vertebral scoliosis, rib abnormalities, and asymmetry in lower limbs. Our patient revealed skeletal abnormality in the form of bilateral short feet, brachydactyly, mild talipes, and bilateral broad thumbs and toes. During the investigations our patient revealed hypothyroidism, which has been reported in about 15–20% of patients with this syndrome. Brain MRI showed defective white matter myelination for age in our proband. This finding is consistent that micro-rearrangement syndromes including 1p36 deletion syndrome should be considered in patients with delayed myelination.

Clinical findings	Patient no.1	Patient no.2	Patient no.3	Patient no.4	Patient no.5	Patient no.6
Dysmorphic features						
Microcephaly		+		+		+
Brachycephaly	+		+		+	
Large or late-closing anterior fontanel	+		+		+	
Midface hypoplasia	+			+	+	+
Straight eyebrows	+		+	+	+	+
Deep-set eyes	+		+	+	+	+
Low-set ears	+		+			
Broad nasal bridge	+		+			
Long philtrum	+				+	
Pointed chin	+				+	
Developmental findings						
Intellectual disability	+		+			
Developmental delay	+		+			
Neurological findings						
Hypotonia	+		+			
Seizures	++					++
Spasticity						+
Cardiac abnormalities						
Structural cardiac defects	+		+	+	+	
Pregnancy finding						
Oligohydramnios				+		
IUGR		+				

Table 1 Summary of phenotypes in our cases with chromosome 1p36 deletion

If we compare our patients with other literatures, there is a difference in percentage in dysmorphic feature and others clinical finding these could be explained by less numbers of patients which involved

in these retrospective review .although a different physions not geneticists how are assessed the patients.

Clinical findings	Frequency of findings in patients reported by Rosenfeld et al. [2010]	Frequency of findings in patients reported by Shimada et al. [2015]	Findings in our patients
Dysmorphic features			
Microcephaly	63%	83%	50%
Brachycephaly	NA	65%	50%
Large or late-closing anterior fontanel	75%	56%	50%
Midface hypoplasia	80%	NA	66%
Straight eyebrows	100%	84%	83%
Deep-set eyes	88%	93%	83%
Low-set ears	40%	88%	33%
Broad nasal bridge	88%	57%	33%
Long philtrum	NA	88%	33%
Pointed chin	84%	89%	33%
Developmental findings			
Intellectual disability	98%	98%	33%
Developmental delay	100%	68%	33%
Neurological findings			
Hypotonia	94%	92%	33%
Seizures	60%	70%	33%
spasticity			16%
Cardiac abnormalities			
Structural cardiac defects	0%	PDA 37%	VSD 50%
Cardiomyopathy	0%	ASD 16%	ASD 16%
		NA	

Table 2 Comparative for phenotypes of chromosome 1p36 deletion with other studies

karyotypes for the parents revealed normal, 46, XX and 46, XY for the mother and the father, respectively. In all probands, however, all cells showed 46, XX, subtelomeric deletion at 1p36.3 in proband 1-5 and in no.6 show 46, XY, del (1)(p36.3)which detected by FISH.

Discussion

From literature review only a case report from Morocco as far as we review this is the first Retrospective study of case series about chromosome 1p36 deletion syndrome at tertiary care centre.

Magenis et al published the first report (1987) of an individual with de-novo isolated 1p36 deletion. After that the publications emerged with additional case reports with the clinical descriptions of large cohorts of individuals with 1p36 deletions, a pattern of characteristic functional deficits, congenital anomalies, and physical features associated with 1p36 deletions emerged. This pattern included developmental delay, intellectual disability, seizures , vision problems, hearing loss, short stature, brain anomalies, orofacial clefting, congenital heart defects, cardiomyopathy, renal anomalies, and distinctive facial features that include straight eyebrows, deeply set eyes, midface retrusion, wide and depressed nasal bridge, long philtrum, pointed chin, large, late closing anterior fontanel, micro brachycephaly, epicanthal folds, and posteriorly rotated, low-set, abnormal ears . Defining this pattern made the 1p36 deletion syndrome a clinically recognizable entity. At the same time, these reports also highlighted the significant phenotypic variability seen between patients.

At first, it was suggested that the variable phenotypic expression of 1p36 deletions might be caused by a parent-of- origin effect in which deletions of the paternally derived copy of 1p36 were not equivalent to deletions of the maternally- derived copy due to differences in imprinting. However, DNA polymorphism analysis shows that there was no obvious parent of origin effect. Instead, they concluded that phenotypic variability was more likely to be caused by differences in the location and extent of the 1p36 deletions, which varied significantly in the patients they studied.

1p36 deletions were typically identified using G-banded chromosome analyses or telomere fluorescence in situ hybridization (FISH). As a result, most of the 1p36 deletion patients described in the literature had telomeric deletions. With the widespread clinical use of array-based copy number detection assays, an increasing number of small interstitial deletions are being identified throughout the 30 Mb of DNA that comprise chromosome 1p36. In many cases, the phenotypes of these individuals are distinct from those with terminal deletions since they are caused by haploinsufficiency of a discrete set of genes.

The clinical and genetic heterogeneity seen among individuals with 1p36 deletions present a significant challenge to physicians who are called upon to provide prognostic information to families and to generate individualized care plans for their patients that include appropriate diagnostic and surveillance testing.

Bedell et al. (1996) cited reports of 11 children who have been described with 2 or more syndromes with overlapping phenotypes and variations of the following features: short stature (9 of 10), prominent forehead (9 of 9), brachycephaly (7 of 7), microcephaly (10 of 11), midface hypoplasia (10 of 10), prominent jaw/chin (11 of 11), dysplastic pinna (6 of 7), hearing loss (3 of 11), congenital heart disease (7 of 11), hypotonia (11 of 11), DD/MR (11 of 11), facial clefting (4 of 11), and early demise (3 of 11). All patients were associated with a deletion of the terminal short arm of chromosome 1.

Shapira et al. (1997) described 13 subjects facial characteristics of the syndrome include deep-set eyes, flat nasal bridge, asymmetric ears, and pointed chin. Additional clinical characteristics include seizures, cardiomyopathy, developmental delay, and hearing impairment (Slavotinek et al., 1999; Shaffer and Heilstedt, 2001).

Heilstedt et al. (2003) reported 62 patients with monosomy 1p36. Thirty were systematically examined through a specific protocol including hearing evaluations, palatal and ophthalmologic examinations, echocardiograms, neurologic assessments, and thyroid function tests. Orofacial clefting anomalies were present in 5 of 30 (17%); hypermetropia was present in 20 of 30 (67%). Six of 30 (20%) had hypothyroidism. All 30 had developmental delay and mental retardation. Twenty-six of 30 (87%) had hypotonia. Oropharyngeal dysphasia was present in 21 of 29 (72%). A history of dilated cardiomyopathy in infancy was present in 7 subjects (23%). In none did the condition worsen over time. Thirteen subjects (43%) had a structural heart defect, most frequently patent ductus arteriosus. Some hearing impairment was present in 82% of the subjects, being sensorineural type in almost all.

Tan et al. (2005) reported a 16-year-old boy with features of Cantu syndrome (OMIM: 239850) who was found to have a distal 1p36 deletion. The boy also had features not previously described in either syndrome, including hypercholesterolemia, type II diabetes, recurrent bony fractures, and nonalcoholic steatohepatitis.

Neal et al. (2006) reported a 3-year-old girl who had developmental delay, Duane syndrome anomaly, hearing loss, mild dysmorphic facial features including posteriorly rotated and slightly low-set ears and a broad nasal bridge, and scoliosis. MRI brain imaging revealed left periventricular nodular heterotopia , truncation of the rostrum of the corpus callosum, slight ventricular enlargement, and patchy areas of hyperintensity consistent with delayed myelination. FISH analysis detected a deletion of 1p36 with loss of heterozygosity between D1S468 and D1S450, indicating at most a 9.6-Mb deletion region on 1pter-p36.22.

Battaglia et al. (2008) evaluated 60 patients with the 1p36 deletion syndrome (41 females and 19 males). Microcephaly was reported in 95% of patients, and all patients had straight eyebrows, deep-set eyes, midface hypoplasia, broad nasal root/bridge, long philtrum, and pointed chin. Other dysmorphic features included micro-brachycephaly (65%), epicanthus (50%), large late-closing anterior fontanel (77%), and posteriorly rotated low-set abnormal ears (40%). Brachy/camptodactyly and short feet were prominent. Heart defects were present in 71%, including 23% with noncompaction cardiomyopathy. Other findings included visual inattentiveness (64%), visual abnormalities (52%), sensorineural deafness (28%), skeletal abnormalities (41%), abnormal genitalia (25%), and renal abnormalities (22%). Eighty-eight percent had central nervous system anomalies: 44% had seizures and 95% had hypotonia. All patients had developmental delay with poor or absent speech, and 47% had a behavior disorder. Gradual developmental progress was observed in all patients over time.

Bursztejn et al. (2009) reported an 8-year-old girl with an initial clinical diagnosis of Aicardi syndrome who was subsequently found to carry a de-novo 11.73-Mb terminal deletion of chromosome 1p36, thus revising the diagnosis. She had onset of infantile spasms at age 3 months, bilateral pupillary coloboma, agenesis of the corpus callosum, and delayed psychomotor development. Other features included deep-set eyes, low-set and posteriorly rotated ears, brachydactyly, and hypertrichosis. She also had interatrial and trabeculated interventricular communications. The deletion was found to occur on the maternal chromosome during oogenesis. The report emphasized the phenotypic overlap between the 2 disorders.

D'Angelo et al. (2010) described 9 unrelated patients with de novo deletions of distal 1p36 ranging in size from 2.2 to 10.2 Mb. Four deletions that could be studied occurred on the maternal allele. Four of the patients were ascertained from a larger group of 154 patients with psychomotor delay associated with hyperphagia and obesity, suggesting that this is an additional variable feature of monosomy 1p36. Five of the patients were ascertained from a larger group of 83 patients suspected to have monosomy 1p36 due to mental retardation. Three of the patients with obesity did not have the typical facial features of monosomy 1p36 and had slightly milder cognitive impairment. D'Angelo et al. (2010) suggested involvement of the PRKCZ gene, which was deleted in all patients, but also noted the possibility of a position effect.

Dod et al. (2010) reported a 25-year-old man with monosomy 1p36 who developed symptoms of left ventricular noncompaction as an adult. In infancy and childhood, he had severe developmental delay, facial dysmorphism, seizures, and a cardiomyopathy with a low ejection fraction (15 to 20%). He also had scoliosis and spastic quadriparesis.

Shimada et al. (2015) identified 50 Japanese patients with chromosome 1p36 deletions of various types. Most patients had craniofacial dysmorphism, including straight eyebrows (84%), deep-set eyes (93%), broad nasal bridge (97%), low-set ears (88%), and pointed chin (89%). Other commonly observed features included hypotelorism, hypotonia, poor sucking, seizures (70%), and infantile spasms (16%). Many patients had nonspecific findings on brain imaging, most commonly enlarged ventricles. Congenital heart defects and cardiac functional anomalies were found in 69% and 22% of patients, respectively. The most common findings were patent ductus arteriosus and ventricular septal defects. More variable features included cryptorchidism, hearing problems, and strabismus.

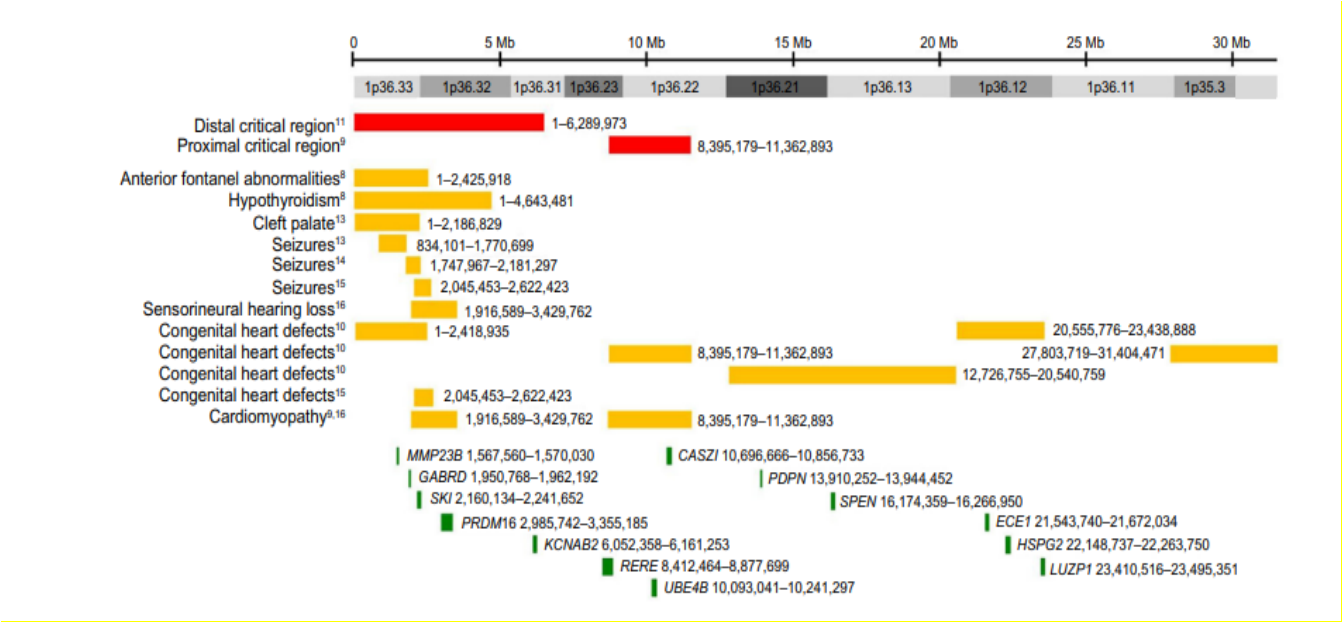

Figure 2 based on human genome build GRCh37/hg19.

Critical regions and selected genes on chromosome 1p36. Spans approximately 30 Mb. Red bars represent the approximate locations of the distal and proximal critical regions. Orange bars represent the approximate locations of critical regions defined for various 1p36-related phenotypes. Green bars represent the approximate locations of selected genes whose haploinsufficiency is likely to contribute to phenotypes associated with 1p36 deletions. Coordinates.

Conclusion

In the current study, we have analyzed the clinical and cytogenetic data of a probands who presenting with manifestations of 1p36 deletion syndrome. Phenotype-genotype correlation for monosomy 1p36 could be performed for the core clinical features of the syndrome. Nevertheless, the final aspect of the syndrome depends on complex factors rather than a simple contiguous gene deletion. Monosomy 1p36

syndrome due to unbalanced translocation can present either with the classical picture of the syndrome or with additional phenotype according to the disrupted genes in the other involved chromosome.

The identification of this microdeletion allowed us to confirm the diagnosis in this patient, guide the clinical management and formulate adequate genetic counseling for the parents. Researchers' efforts still continue to provide important evidence for the contribution of the different genes involved in this syndrome and to identify a complete deletion/phenotype map for the 1p36 region that will allow physicians to provide the prognostic information desired by families and generate individualized care plans for patients with these deletions.

Most of the genes currently implicated in the development of 1p36 deletion-related phenotypes have been identified through a combination of molecular cytogenetic study. At the same time, exome and genome sequencing efforts will help identify genes whose haploinsufficiency contributes significantly to an increased risk of developing specific 1p36-related phenotypes. As a comprehensive deletion/phenotype map of the 1p36 region emerges from these efforts, physicians will find it easier to provide the prognostic information desired by families affected by 1p36 deletions and to generate individualized care plans for their patients who carry these deletions.

Finally, this case series in purpose to increase awareness for the health care provider with phenotype 1p36 deletion syndrome.

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