MERIT RESEARCH JOURNALS
www.meritresearchjournals.org

Merit Research Journal of Medicine and Medical Sciences (ISSN: 2354-323X) Vol. 4(12) pp. 490-494, December, 2016
Available online http://www.meritresearchjournals.org/mms/index.htm

Case Report

A mental and motor retarded dysmorphic case with heterozygous 1p36 deletion: *Comparable results from cytogenetic, MicroArray-CGH, FISH and MLPA techniques*

Fatma Silan*, Onur Yildiz, Mine Urfali, Zeliha Guler and Ozturk Ozdemir

Canakkale Onsekiz Mart University, Faculty of Medicine Department of Medical Genetics, 17100, Canakkale / Turkey

***Corresponding Authors E-mail: fsilan@yahoo.com**
Tel: +90 286 2180018/2107

Abstract

Deletions of chromosome 1p36 ("1p36 deletion", "monosomy 1p36 deletion", or "1p36 deletion syndrome") affects approximately 1 in 5,000 newborns and are associated with mental retardation, developmental delay, hypotonia and craniofacial dysmorphisms. Here we report a mental and motor retarded case of 1p36 deletion with ISG15, AGRN, TNFRSF4, B3GALT, DVL1, TMEM240, GABRD and SKI affected genes. We report a 9 years old case of 46,XX,del1p36 karyotype. She has low-set ears, short middle finger, hand transverse lines and sparse teeth of dysmorphic findings. She has also mental and motor retardation, intellectual disability (few words in 6 years), autism spectrum, hypotonia, hypermetropia and obesity. She was misdiagnosed as Bardet Biedl Syndrome before referred our department. She was diagnosed by comparing different techniques of conventional cytogenetic karyotype analysis, MicroArray-CGH (Agilent 60 K platform, US), MLPA (microdeletion/ duplication P245 kit, MRC Holland) and FISH (1p36.33 *SKI* red-1qter green, Cytocell) methods. She had normal chromosomes and FISH profiles but 1440 kb heterozygous deletion in 1p36.33 region involving ISG15, AGRN, TNFRSF4, B3GALT, DVL1, TMEM240, GABRD, SKI genes by microarray and TNFRSF4, GNB1-3, GABRD2 genes in 1p36 locus were detected by MLPA techniques. Results showed the haploinsufficiency of more than 11 genes may contribute to above phenotypes of our case with 1p36 syndrome. Results also indicate the using of comparable techniques have a crucial role in the advance diagnosis of such cases with minor deletions that is not detectable by conventional cytogenetics and FISH techniques.

Keywords: Copy number variations, Dysmorphological features, Mental and motor retardation, MLPA, 46,XX karyotype, 1p36.33 deletion

INTRODUCTION

The patients with 1p36 deletion (MIM 607872) have multisystemic complications such as; mental and motor retardation, developmental delay, intellectual disability, distinctive craniofacial appearances, straight eyebrows, deep-set eyes, midface hypoplasia, hypo- or hypertelorism, pointed chins, large late-closing anterior

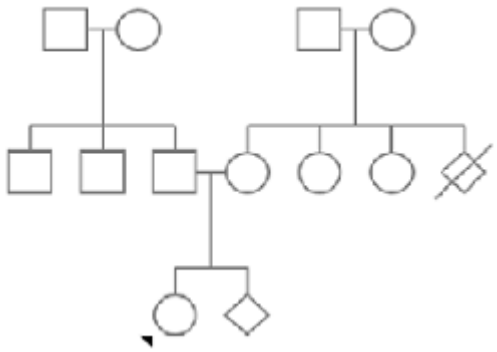

Figure 1. Shows the pedigree of the presented case.The arrow indicates the proband.

fontanels hearing loss, obesity and seizure. (Shaffer and Lupski, 2000; Shapira et al., 1997; Battaglia et al., 2008; Shapira et al., 1997; Gajecka et al., 2007). The clinical features varie due to deletion size. Hypotonia and seizure are noted in approximately half the cases (Gajecka et al., 2007; Bahi-Buisson et al., 2008). Recently, there are advance molecular techniques for the correct detection of such minor deletions or duplication in the patients manifest the various clinical findings. Deletions mostly reported in telomeric region of the chromosome 1 in 1p36 syndrome (Shapira et al., 1997). Shapira et al. have identified 1p36 deletions by using G-banded chromosome analyses and Telomeric Fluorescence *In situ* Hybridization (T-FISH) techniques (Shapira et al., 1997). Nowadays, by the widespread clinical use of array-based copy number technique in the laboratory diagnosis of the small interstitial deletions (under 30 Mbp) widely reported in such cases (Bahi-Buisson et al., 2008; Heilstedt et al., 2003).

In the current case it was aimed to detect the affected genes for a case with various clinical spectrum of mental and motor retardation and autism. It was also aimed to compare different routine medical genetics laboratory techniques for detection of the possible chromosomal microdeletion or duplications in such a cases.

Case

We reported a 9 years old case of 46,XX,del1p36 karyotype. She was referred to Canakkale Onsekiz March University, Medical Genetics outpatient clinic for short status, developmental delay and her mother's pregnancy. She has diagnosed as Bardet Biedl Syndrome at another University's outpatient clinic. Proband is a sporadic case and parents were not consanguineous. Prenatal history was unremarkable. She has born by spontaneous vaginal delivery at the 37th week of gestation. Birth weight was 2300 g. Motor developmental milestones were mildly delayed (sits alone at 12th months, walks alone at 24th months; she start to say single words at 3th year and still she can't speak clearly.

On physical examination, her height was 116cm (<3rd centile), weight 36kg (>97th centile) and head circumference 49cm (2-50th centile) with minor dysmorphic facial features, low set ears, small hands and short fingers, transverse line in palm. She has stuck cerumen, chronic serous otitis media and total hearing loss at left ear, partial loss (40-50 dB) at right hear. Ophthalmologic examination shows strabismus, astigmatism, hyperopia, conjunctivitis and blepharitis. She has seasonal allergic rhinitis, chronic diseases of tonsils and adenoids. Our preliminary diagnosis was Prader Willi syndrome because she has truncal obesity, minör facial dysmorphism, hypotonia and mental and motor retardation (Figure 1). Cranial MRI and metabolic tests were normal.

Heparinized and blood-EDTA samples were used for lymphocyte culture and total genomic DNA isolation. Metaphase spreads were evaluated after trypsin-GTG banding technique. Genome-wide all chromosomes were also identified by Agilent SurePrint G3 Human CGH 60K MicroArray Platform (Agilent Technologies, CA, United States) chromosomal microarray analysis for the advance detection of affected gene or genes in the chromosomal break points for the presented case. She was diagnosed by comparing different techniques of conventional cytogenetic karyotype analysis, MicroArray-CGH (Agilent 60 K platform, US), MLPA (microdeletion/duplication P245 kit, MRC Holland) and FISH (1p36.33 *SKI* red-1qter green, Cytocell) methods. Whole genomic DNA was used as a template for MLPA and MicroArray-CGH analysis with 60-mer oligonucleotide CGH arrays (Agilent Technologies, Santa Clara, CA, USA). Total genomic DNA were digested using *AluI* and *RsaI* enzymes(Agilent Technologies), labeled with cyanine 3-dUTP (Cy3-dUTP) and cyanine 5-dUTP (Cy5-dUTP), respectively by using Klenow DNA enzyme following the manufacturer's instruction. Target DNA from patient, reference and human COt-1 DNAs were dissolved, denatured and hybridized to the CGH array at 65°C for 24 h. After hybridisation with oligoprobs with 60 K

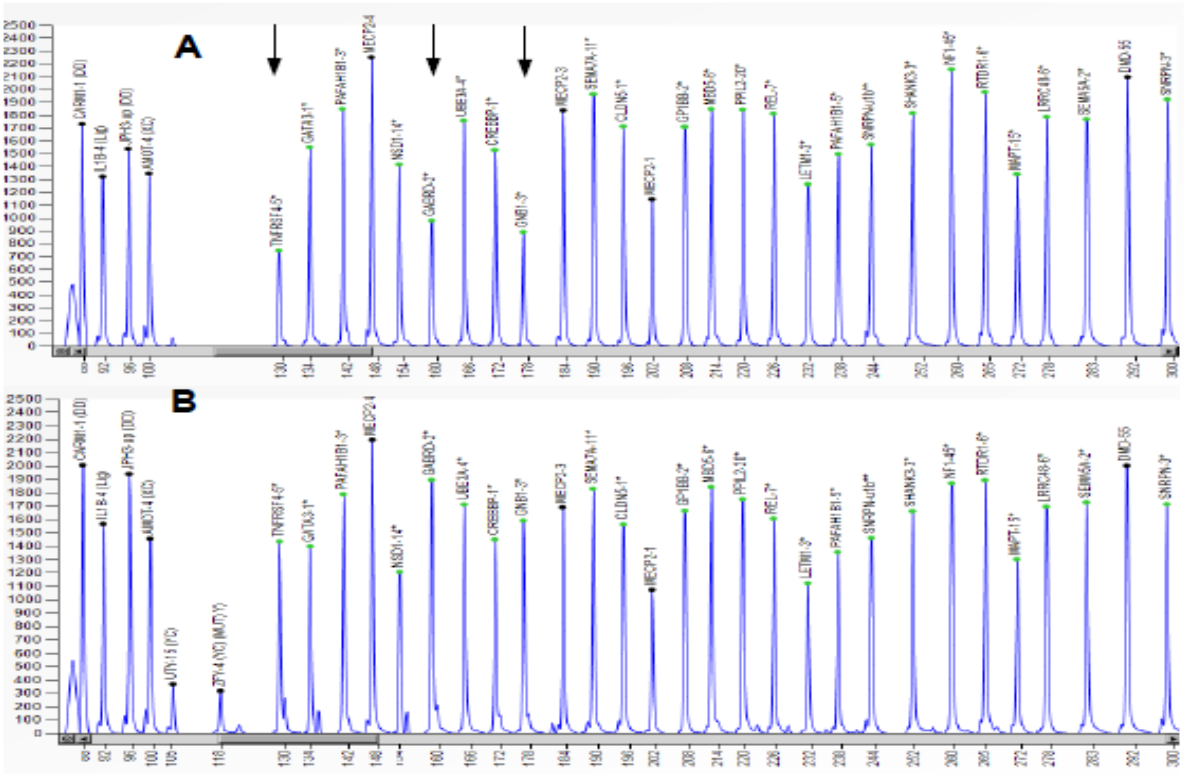

Figure 2. The MLPA pick profiles from proband case(A) and amnion sample from her sibling for the prenatal diagnosis(B). Heterozygous deletions were detected in TNFRSF4, GABRD and GNB1 genes in proband case (A, arrows). The heterozygous deleted genes that detected in proband case were in normal appearance in amnion sample from her sibling(B).

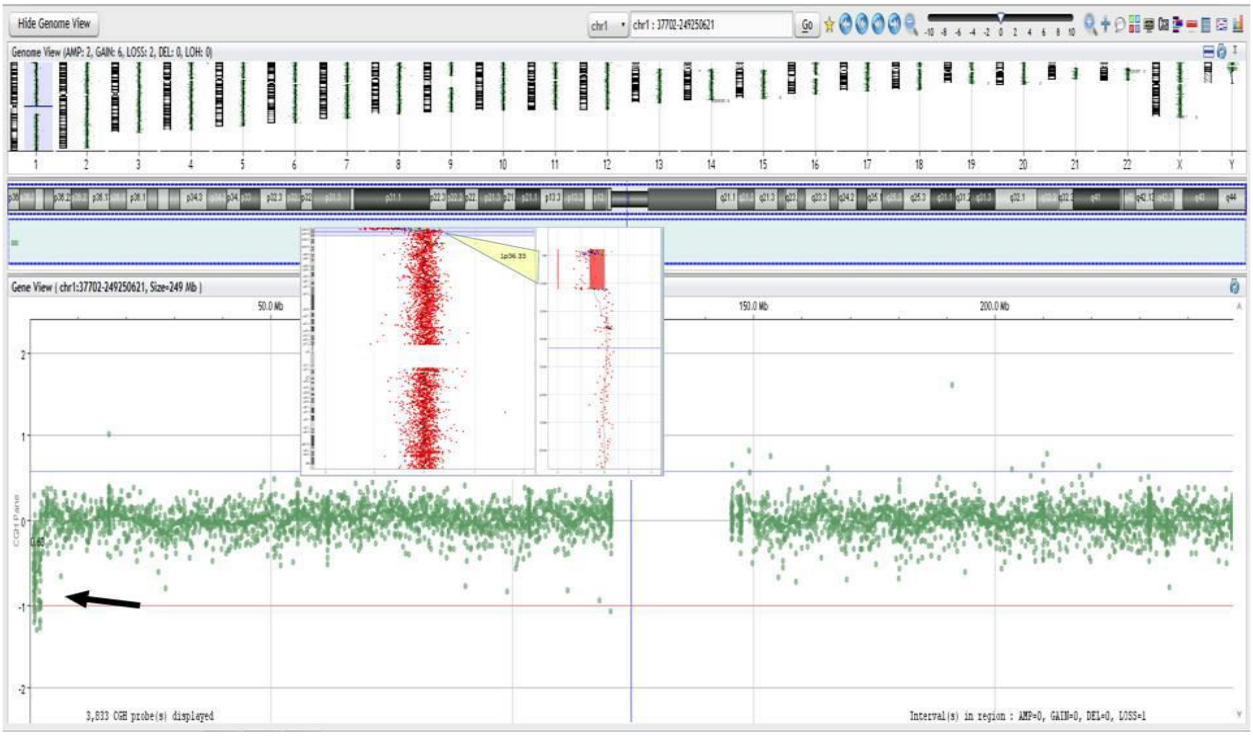

Figure 3. Shows the array-based copy number variation profiles for the chromosome 1 in the proband case. Arrows indicate the deleted terminal region of locus and size.

glass slides were washed, scanned and the microarray images were analyzed using Agilent C microarray scanner (model/tip Agilent Technologies, USA) and the data were imported into Default Analysis Method–CGH v2 (Agilent Technologies) for evaluation. Her mother was pregnant and amnion sample from her sibling was analysed for 1p36 deletion during the prenatal diagnosis.

She had normal chromosomes and FISH profiles but 1440 kb heterozygous deletion in 1p36.33 region involving ISG15, AGRN,TNFRSF4, B3GALT, DVL1, TMEM240, GABRD, SKI genes by microarray (Figure 2) and TNFRSF4, GNB1-3, GABRD2 genes in 1p36 locus were detected by MLPA techniques (Figure 3). The amnion sample from her sibling was in normal structure for 1p36 locus after MLPA and MicroArray-CGH analyses.

DISCUSSION

The clinical findings that caused by terminal deletions of 1p36 include short stature, intellectual disability, dental problems, hearing loss and distinctive facial features show patient based individual variations. In general, according to the recent literature findings there is a genetic heterogeneity in chromosome 1p36 syndrome (terminal and/or interstitial) and clinical variability (Heilstedt et al., 2003; Shapira et al., 1997; Kang et al., 2007; Wu et al., 1999). On the other hand, the severity of the clinical features was not always associated with the deletion size as reported by Jordan et al (Jordan et al., 2015). Jordan et al have claimed that the genotype-phenotype correlation in monosomy 1p36 syndrome shows variation due to the affected gene/genes and deleted chromosomal sizes (Jordan et al., 2015). Our findings showed deleted 11 genes in a case with clinical findings of chromosome 1p36 syndrome. In this report, we describe a patient with facial dysmorphism, obesity, autism spectrum and mental and motor retardation. Although, her chromosomes were in normal structure after FISH and conventional karyotype analyzes the 1440kb heterozygous deletion in 1p36.33 locus were detected involving ISG15, AGRN,TNFRSF4, B3GALT, DVL1, TMEM240, GABRD, SKI genes by microarray and TNFRSF4, GNB1-3, GABRD2 genes by MLPA techniques. The chromosome 1p36 deletion syndrome mainly involves the chromosomal rearrangements such as; terminal and/or interstitial deletions, combined re-arrangements of more than one deletions with duplication, triplication, insertion, and/or inversions that resulted with derivativeted chromosome 1.

The 1p36del syndrome is the most common terminal deletion observed in humans (Caliebe et al., 2010; Firth et al., 2009; Feenstra et al., 2006; Klaassen et al., 2008; Shaffer and Lupski, 2000). The disruption or dose reduction of multiple different gene may contribute to the various phenotypes observed in this syndrome and to the pleiotropic manifestations reported. (Shapira et al., 1997; Heilstedt et al., 2003; Battalia et al., 2008). As recommended by Seo et al. and Karaer et al. the advance molecular diagnosis techniques such as Sanger sequencing, MLPA, MicroArray-CGH and NGS should be used in the correct diagnosis of 1p36 deletion syndrome (Seo et al., 2016; Karaer et al., 2011). Kang et al have identified interstitial deletions affecting 1p36.23–1p36 in five patients by array comparative genomic analysis (Kang et al., 2007). Wu et al. were also reported various deleted genes that contributing to the phenotypic features of 1p36 deletion syndrome in 30 patients (Wu et al., 1999). Here we also aimed to report a case of chromosome 1p36 syndrome with various clinical findings. In the presented case the 1440 kb in size 1p36 deletion could not be detected by conventional karyotype – chromosome and FISH analyses. Some specific genes deletion that located in terminal region of chromosome 1 were detected by MLPA (Figure 2) and the other some were detected by MicroArray-CGH method (Figure 3). The amnion sample from sibling of the proband case was in normal structure for the above genes. The genetic counseling was given to both parents according to the above normal conditions during the prenatal diagnosis procedure. Without advance molecular findings the current case was suspiciously diagnosed as Bardet Biedl syndrome due to the some clinical findings of retarded conditions. After MLPA and array-based copy number variation analyses terminal microdeletion was detected chromosome 1 and she was diagnosed as chromosome 1p36 syndrome in the presented results.

CONCLUSION

The current case was diagnosed as 1p36 syndrome, due to some clinical findings of hypodontia, dysmorphic facial features, obesity, mental and growth retardation, low-set ears, visual and hearing impairments.Results showed the haploinsufficiency of more than 11 genes may contribute to above phenotypes of our case of 1p36 syndrome. The microdeletion was detected by the combined use of MLPA and array-based copy number variant analysis. Results also indicate the using of comparable techniques have a crucial role in the advance diagnosis of such cases with minor deletions that is not detectable by conventional cytogenetics and FISH techniques.

ACKNOWLEDGEMENTS

Authors give thanks to scientific research and project supporting unit – BAP for their kind contrubution towards obtaining the current results (Grant no: TAY-445/2015), Canakkale Onsekiz Mart University, Canakkale/TURKEY.

REFERENCES

Bahi-Buisson N, Guttierrez-Delicado E, Soufflet C, Rio M, Daire VC, Lacombe D, et al. (2008). Spectrum of epilepsy in terminal 1p36 deletion syndrome. Epilepsia 49,509-515.

Battaglia A, Hoyme HE, Dallapiccola B, Zackai E, Hudgins L, McDonald-McGinn D, Bahi-Buisson N, Romano C, Williams CA, Brailey LL, et al. (2008). Further delineation. Delineation of deletion 1p36 syndrome in 60 patients: a recognizable phenotype and common cause of developmental delay and mental retardation. Pediatrics 121, 404–410.

Caliebe A, Kroes HY, van-der Smagt JJ, Martin-Subero JI, To¨nnies H, van 't Slot R, Nievelstein RA, Muhle H, Stephani U, Alfke K, et al. (2010). Four patients with speech delay, seizures and variable corpus callosum thickness sharing a 0.440 Mb deletion in region 1q44 containing the HNRPU gene. Eur J Med Genet. 53, 179–185.

Chen D, Xu W, Bales E, et al.(2003). SKI activates Wnt/beta-catenin signaling in human melanoma. Cancer Res. 63(20), 6626–6634.

Feenstra I, Fang J, Koolen DA, Siezen A, Evans C, Winter RM, Lees MM, Riegel M, de Vries BB, Van Ravenswaaij CM, Schinzel A. (2006). European Cytogeneticists Association Register of Unbalanced Chromosome Aberrations (ECARUCA); an online database for rare chromosome abnormalities. Eur J Med Genet. 49, 279–291.

Firth HV, Richards SM, Bevan AP, Clayton S, Corpas M, Rajan D, Van Vooren S, Moreau Y, Pettett RM, Carter NP. (2009). DECIPHER: Database of Chromosomal Imbalance and Phenotype in Humans Using Ensembl Resources. Am J Hum Genet. 84, 524–533.

Gajecka M, Mackay KL, Shaffer LG (2007). Monosomy 1p36 deletion syndrome. Am J Med Genet C Semin Med Genet. 145©,346-356.

Go Hun Seo, Ja Hye Kim, Ja Hyang Cho, Gu-Hwan Kim, Eul-Ju Seo, Beom Hee Lee, Jin-Ho Choi, Han-Wook Yoo. (2016).Identification of 1p36 deletion syndrome in patients with facial dysmorphism and developmental delay. Korean J Pediatr. 59(1):16-23.

Heilstedt HA, Ballif BC, Howard LA, et al.(2003). Physical map of 1p36, placement of breakpoints in monosomy 1p36, and clinical characterization of the syndrome. Am J Hum Genet. 72(5),1200-1212.

Jordan VK, Zaveri H, Scott DA.(2015). 1p36 deletion syndrome: an update. The Application of Clinical Genetics. 8,189-200.

Kang SH, Scheffer A, Ou Z, et al. (2007). Identification of proximal 1p36 deletions using array-CGH: a possible new syndrome. Clin Genet. 72(4), 329-338.

Klaassen S, Probst S, Oechslin E, Gerull B, Krings G, Schuler P, Greutmann M, Hu¨rlimann D, Yegitbasi M, Pons L, et al. (2008). Mutations in sarcomere protein genes in left ventricular noncompaction. Circulation. 117, 2893– 2901.

Karaer K, Karaoguz MY, Percin EF.(2011). Monosomy 1p36 Syndrome: The First Case Report from Turkey. Turkiye Klinikleri J Med Sci. 31(1).

Medrano EE. (2003). Repression of TGF-beta signaling by the oncogenic protein SKI in human melanomas: consequences for proliferation, survival, and metastasis. Oncogene. 22(20), 3123–3129.

Shaffer LG, Lupski JR.(2000). Molecular mechanisms for constitutional chromosomal rearrangements in humans. Annu Rev Genet. 34, 297–329.

Shapira SK, McCaskill C, Northrup H, Spikes AS, Elder FF, Sutton VR, Korenberg JR, Greenberg F, Shaffer LG. (1997). Chromosome 1p36 deletions: the clinical phenotype and molecular characterization of a common newly delineated syndrome. Am J Hum Genet. 61, 642–650.

Wu YQ, Heilstedt HA, Bedell JA, et al. (1999). Molecular refinement of the 1p36 deletion syndrome reveals size diversity and a preponderance of maternally derived deletions. Hum Mol Genet. 8(2),313–321.

Zhu X, Zhang Y, Wang J, Yang JF, Yang YF, Tan ZP. (2013). 576 kb deletion in 1p36.33-p36.32 containing SKI is associated with limb malformation, congenital heart disease and epilepsy. Gene. 528(2),352–355.