Diagnostic Yield of Molecular Karyotyping of Idiopathic Intellectual Disability Patients Ended with One Causative Anomaly; Duplication 9q34 Syndrome

İdiyopatik Entelektüel Yetersizliği olan Hastaların Moleküler Karyotiplemesinin Tanısal Kullanımı ile Saptanan bir Anomali Nedeni: 9q34 Duplikasyon Sendromu

Büşranur Çavdarlı [1,2], Emriye Ferda Perçin [1], Meral Yirmibeş Karaoğuz [1], Mehmet Ali Ergün [1]

[1] Gazi University Faculty of Medicine, Department of Medical Genetics, Ankara, Turkey
[2] Ankara Numune Training and Research Hospital, Medical Genetic Clinic, Ankara, Turkey

ABSTRACT

Objective: Clinical application of sequence comparative genomic hybridization has greatly contributed to the diagnosis of patients with multiple congenital anomalies, syndromic or non-syndromic intellectual disability. The idiopathic intellectual disability patients with normal karyotype and/or normal subtelomeric rearrangement analysis via Fluorescence *in situ* Hybridization (FISH), using genome-wide microarray platforms have detected chromosome abnormalities in up to 12% of cases. In this study, we aimed that evaluate the etiology of 9 patients with idiopathic intellectual disability and congenital malformations or dysmorphic features.
Methods: We performed genom wide SNP 2.7 array, in the evaluation of 9 patients with idiopathic intellectual disability and congenital malformations or dysmorphic features as well as normal karyotype and normal subtelomeric rearrangement analysis by the usage of FISH technique.
Results: As a causative anomaly, a 2.6 Mb microduplication on 9q34.2-q34.3 was observed only in one patient who has idiopathic mental retardation and multiple skeletal anomalies.
Conclusion: Microarray technology is a highly diagnostic method that is recommended for individuals with intellectual disability and multiple congenital anomalies. Microarray analysis revealed a causal anomaly in one of nine patients (11%) consistent with the literature.

Key Words: Intellectual disability, microarray analysis, chromosome 9q34 duplication, microduplication, FISH

Received: 02.04.2018 **Accepted:** 03.28.2019

ÖZET

Amaç: Dizi karşılaştırmalı genomik hibridizasyonun klinik uygulaması, çoklu konjenital anomalileri, sendromik veya sendromik olmayan entellektüel yetersizliği olan hastaların teşhisine büyük ölçüde katkıda bulunmuştur. Tüm genom mikrodizi platformları kullanılarak; normal karyotipli ve/ veya Floresans in situ Hibridizasyon (FISH) ile subtelomerik yeniden düzenlenmesi olmadığı saptanan, idiyopatik entellektüel yetersizliği olan olguların yaklaşık % 12'sine kromozomal anormallikler tespit edilebilmektedir. Bu çalışmada idiopatik entelektüel yetersizlik ve konjenital malformasyon ya da dismorfik özellikleri bulunan 9 hastanın etyolojisinin değerlendirilmesi amaçlanmıştır.
Yöntem: İdiyopatik entellektüel yetersizliği olan ve konjenital malformasyonlar veya dismorfik özellikler taşıyan; normal karyotipli, FISH tekniği ile subtelomerik yeniden düzenlenme olmadığı tespit edilen 9 hastanın değerlendirilmesinde tüm genom SNP array 2.7 tanısal uygulaması yapılmıştır.
Bulgular: Nedensel bir anomali olarak, idiyopatik entellektüel yetersizlik ve çok sayıda iskelet anomalisi olan bir hastada 9q34.2-q34.3 üzerinde 2,6 Mb'lık bir mikroduplikasyon gözlenmiştir.
Sonuç: Mikroarray teknolojisi, entellektüel yetersizlik ve birden fazla konjenital anomalisi bulunan bireyler için önerilen ve tanı gücü yüksek bir yöntemdir. Bu çalışmada; literatürle uyumlu olarak Mikroarray analizi ile dokuz hastadan birinde (% 11) nedensel bir anomali ortaya çıkarılmıştır.

Anahtar Sözcükler: Entelektüel yetersizlik, mikroarray analizi, kromozom 9q34 duplikasyonu, mikroduplikasyon, FISH

Geliş Tarihi: 04.02.2018 **Kabul Tarihi:** 28.03.2019

A part of this study was presented at the 10th National Medical Genetics Congress in 2012 in Bursa, Turkey.

Address for Correspondence / Yazışma Adresi: Emriye Ferda Perçin, MD. Gazi University Faculty of Medicine Department of Medical Genetics, 06510, Ankara, Turkey
E-mail: ferdaep@yahoo.com

©Telif Hakkı 2019 Gazi Üniversitesi Tıp Fakültesi - Makale metnine http://medicaljournal.gazi.edu.tr/ web adresinden ulaşılabilir.
©Copyright 2019 by Gazi University Medical Faculty - Available on-line at web site http://medicaljournal.gazi.edu.tr/
doi:http://dx.doi.org/10.12996/gmj.2019.64

INTRODUCTI ON

The frequency of chromosome abnormalities and/or genomic rearrangements detected in patients with developmental delay/intellectual disability is quietly high, in the presence of additional malformations or dysmorphic features. Practice guidelines for the cytogenetic evaluation of patients with developmental delay/intellectual disability recommend high-resolution chromosome banding, Fluorescence *in situ* hybridization (FISH) analysis consisting subtelomeric regions and specific amplification methods such as multiplex ligation-dependent probe amplification (MLPA) to search primarily for the imbalances of the subtelomeric regions, and also array comperative genomic hybridisation (aCGH) analysis. There are advantages and disadvantages of the techniques compared to each other. While the rate of visible chromosome abnormalities in patients with intellectual disability is about three and half percent by the usage of conventional cytogenetic techniques, this ratio is come up to six percent (3–6%) by the usage of molecular techniques (1, 2). Array CGH has a 15–20% percent overall rate of detecting the genomic abnormalities that is mainly interstitial deletions and duplications, in patients with intellectual disability (3).

The detection ratio depends on the resolution of the techniques as conventional cytogenetic techniques is limited to approximately >5 Megabases (Mb) while array based methods can be useful to detect anomalies smaller than 3 Mb to kilobase levels.

In this study, nine idiopathic intellectual disability patients with normal karyotype and normal subtelomeric rearrangement analysis via Fluorescence *in situ* Hybridization (FISH), had been investigated for small deletions or duplications with "Genome Wide SNP 2.7 Array". The analyses ended with a causative anomaly in one of the patient, namely 9q34.2-34.3 duplication anomaly, and in this report the discussion of the similar cases in the literature was held on.

MATERIAL and METHODS

Patients

Nine patients with idiopathic intellectual disability and congenital anomaly or dysmorphic features who were referred to Medical Genetics Department of Gazi University Faculty of Medicine between 2005 and 2009 were included in the study. All the patients with normal cytogenetic and subtelomeric FISH analysis, whose clinical findings were summarized on Table 1, underwent to whole-genome microarray analysis. There were satisfying birth and postnatal informations to evaluate their clinical condition except Patient 8 (Table 1). Regarding the history of orphanage living, there was no prenatal, natal and postnatal information related with this patient.

This study was approved by the Gazi University Faculty of Medicine Ethics Committee in June 23, 2010 with the decision number 057.

Table 1. Clinical and laboratory findings of investigated patients.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9
Age, sex	2 years old, female	7 years old, female	11 years old, female	1 years old, female	15 years old, male	7 years old, female	13 years old, male	22 years old, male	10 years old, female
Weight	<3p	10-25p	25-50p	25-50p	10-25p	10-25p	3-10p	50-75p	3-10p
Length	<3p	<3p	<3p	25-50p	25-50p	10-25p	<3p	50-75p	10-25p
Head circumference	<3p	<3p	<3p	10-25p	10-25p	10-25p	<3p	10-25p	<3p
Parental consanguinity	-	3rd degree	-	-	3rd degree	-	5th degree	?	3rd degree
Intellectual disability (ID)	+	+	+	+	+	+	+	+	+
Other family members with ID	-	-	+	+	-	-	-	Unknown	+
Hypotonia	+	-	-	-	-	-	-	Unknown	+
Short stature	+	+	+	-	-	-	+	-	-
Microcephaly	+	+	+	-	-	-	+	-	+
Clinical Findings	Growth retardation, Brachycephaly, Downslanting palpebral fissures, Dyplastic ears, Hydronephrosis	Febril convulsion history Sleep disturbance Narrow forehead, Short philtrum, Pointed teeth, Short neck, Clinodactyly	Attention deficit / hyperactivity disorder Anteverted nostrils, Long philtrum, Thin upper lip	Epilepsy Short neck, Hemangioma on the back of the neck	Agressive behaviors, Speech delay, Long face, Broad eyebrows, Synophrys, Anteverted nostrils, Mitral valve prolapse	Hearing loss, Speech delay, Epicanthus, Lacrimal duct obstruction, High palate, Bilateral short fifth fingers, İnguinal hernia	Upsweep, Flat forehead, Curved and sparse eyebrows, Upslanting palpebral fissures, Distinctive columella, Long philtrum, Small mouth and ears, Thin upper lip	Epilepsy, Behavioral distrubance, Pain insensitivity, Narrow-long face, Starabismus, Prominent glabella, High nasal root and bridge, Short philtrum, Narrow and high palate, Crowded teeth, Retrognathia Joint contractures, Broad hallux Aracnodactyly, Scoliosis and Kyphosis	Hypotonia, Epilepsy, Swallowing difficulty, Brachycephaly, Trigonocephaly, Hemangioma, Fusiform fingers, 2-3 syndactyly on foot
Cranial MRI	Cerebral atrophy, Corpus callosum hypoplasia	Agenesis of corpus callosum	Not performed	Normal	Not performed	Agenesis of corpus callosum, Pontine hypoplasia	Not performed	Normal	Cerebellar hypoplasia, Cerebral atrophy, Dandy-Walker malformation

DNA extraction and molecular analysis

Peripheral blood samples were collected from the patients. Genomic DNA was extracted from blood, using a salting-out isolation method according to standard protocols. Whole-genome microarray was performed using The Affymetrix® Cytogenetics Whole-Genome 2.7M Array (Affymetrix, Santa Clara, CA, USA) system. DNA digestion, labeling, and hybridization were performed following the manufacturer instructions.

Each array contains approximately 2,761,979 oligonucleotide markers, including 2,316,876 CNV markers, 400,103 SNP markers and 2,370,000 non-polymorphic markers. SNPs used in this study were obtained from The Single Nucleotide Polymorphism Database (dbSNP) and are able to detect loss of heterozygosity (LOH). Non-polymorpic markers contain RefSeq genes, cytogentically critical points and frequent CNVs. In the study, a limit of 100 kb was determined for the losses and gains. CEL files obtained by scanning the arrays were analyzed using the Chromosome Analysis Suite (ChAS) v1.2.1 Software and Cytogenetics Array NetAffix® Analysis fileset version NA32 (hg19) (Affymetrix). Variants found in the results were evaluated with online databases and libraries, including DECIPHERv4.1 (DatabasE of Chromosome Imbalance and Phenotype in Humans using Ensembel Resources), Ensemble (Genome Browser), DGV (Database of Genomic Variants) and ECARUCA (European Cytogeneticists Association Register of Unbalanced Chromosome Aberrations) OMIM (Online Mendelian Inheritance in Man) and PubMed (the U.S. National Library of Medicine).

RESULTS

In all cases investigated, some changes were found clinically insignificant. But no literature-supported evidence was available at the clinical disclosure point except for the Patient 8. All the variants detected in the patients were analyzed with the algorithms specified in the literature (4). Some of these variants were classified as benign (polymorphism), and further studies have been planned for variants with uncertain significance. In patient 8, the detected variant was thought to be responsible of the phenotype (Figure 1, Table 2).



Figure 1a. Dysmorphic facial features including microcephaly, narrow forehead, high nasal root and nasal bridge, short philtrum, retrognathia, **b.c.d.e.** Skeletal anomalies like thoracolumbar scoliosis, kyphosis, arachnodactyly and flexion contractures of proximal interphalangeal joints and broad hallux.

Table 2. Results of the microarray analyses of all investigated patients

Patient	Chromosomal position	Variant type	Size(kb)	The genes in the context	Marker count	Result
1	1:3002202-3163805	Gain	161,603	PRDM16 , MIR4251, GPR62, PCBP4,ABHD14B	42	Polymorphism
2	16:34476235-34731771	Gain	255.536	LOC283914 , LOC146481	66	Polymorphism
3	15:20175623-22752987	Loss	2.577.364	HERC2P3, GOLGA6L6, GOLGA8C, BCL8 ,POTEB, NF1P1, LOC646214, CXADRP2, LOC727924, OR4M2, OR4N4, OR4N3P, REREP3, GOLGA8DP, GOLGA6L1	53	Parental testing was planned
4	14:22408697-22961712	Loss	553.015	-	220	Polymorphism
5	15:20175623-22749949	Gain	2.574.326	HERC2P3, GOLGA6L6, GOLGA8C, BCL8, POTEB,NF1P1,LOC64214,CXA,DRP2, LOC727924, DR4M2,OR4N4, OR4N3P,REREP3, GOLGA8DP, GOLGA6L1	50	Parental testing was planned
6	12:129329020-130654618	Loss	1.325.598	GLT1D1, TMEM132D, LOC100190940, FLJ31485, FZD10	65	Polymorphism
7	7:64621287-65090561	Loss	469.274	INTS4L1, ZNF92	133	Polymorphism
8	**9:135920384-138520804**	**Gain**	**2600.42**	**GTF3C5, CEL, CELP, RALGDS, GBGT1, OBP2B, ABO, SURF6, MED22, RPL7A, SNORD24, SNORD36B, SNORD36A, SNORD36C, SURF1, SURF2, SURF4, C9orf96, REXO4, ADAMTS13, C9orf7, SLC2A6, TMEM8C, ADAMTSL2, FAM163B, DBH, SARDH, VAV2, NCRNA00094, BRD3, WDR5, RNU6ATAC, RXRA, COL5A1, FCN2, FCN1, OLFM1, KIAA0649, C9orf116, MRPS2, LCN1, OBP2A, PAEP, LOC100130954, GLT6D1**	**61**	**Likely Pathogenic**
9	16:18324884-18593111	Loss	268.227	MIR3180-1, MIR3180-3,MIR3180-2 MIR3179-3 MIR3179-2, MIR3179-1, NOMO2, ABCC6P1	61	Polymorphism

Array analysis of the Patient 8 revealed a 2,6 Mb microduplication on the distal part of long arm of chromosome 9 and molecular karyotype of the patient was "arr[GRCh38]9q34.2q34.3 (135920384-138520804)x3" (Figure 2). This interval includes 2,730 probes and there are 45 OMIM genes located on this duplicated site which was detected with 61 markers (Table 2).

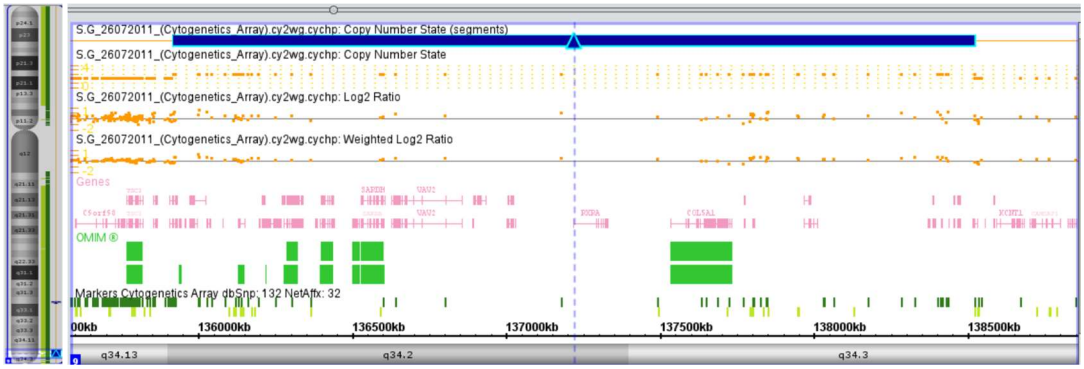


Figure 2. Duplicated region on chromosome 9 (9:135920384-1385208041) mentioned with blue bar, Green stics indicate the MIM genes linked with disease.

DISCUSSION

Conventional cytogenetic analysis allows for detection of numerical and structural chromosomal abnormalities present in the entire genome, but has a limited resolution of 5-10 megabases. Thus, submicroscopic aberrations cannot be detected, and interpretation of the test results remains subjective. FISH and MLPA can detect specific cytogenetic aberrations with a higher sensitivity than conventional cytogenetic techniques; but, they cannot cover entire regions of chromosomes (5). Array CGH has many advantages over conventional cytogenetic techniques in that it can provide rapid genome-wide assessments at a high resolution (≤1 Mb). It can also detect single-copy gains and losses across whole chromosomes, but balanced translocations cannot be detected. Nowadays, high-resolution array comparative genomic hybridization (array CGH) is a powerful and efficient method for diagnosis and research of intellectual disability because of it can be explain the etiology of intellectual disabilities in a rate of 15-20% (3). It has been suggested as a standard practice for children with diagnoses including unexplained developmental delay/intellectual disability (DD/ID), autism spectrum disorders (ASDs), and dysmorphic features (6-8). In this study, nine cases were studied with molecular karyotyping method (2.7 SNP Array) and only in one case (Patient 8) a duplication of about 2.6 Mb was detected, which could be figured out the clinical findings, located on the long arm of chromosome 9 (chr: 135920384-138520804) (Table 1, Figure 1 and 2).

Duplication of 9q34 is usually based on unbalanced meiotic segregation of the gametes of balanced translocation career healthy parents.

First association between clinical features and isolated duplication of 9q34 on seven patients in a translocation career family was described by Allerdice et al. and it was called as “Duplication 9q34 Syndrome” (9). In the literature, there are a few patients with de novo and/or whole 9q duplication of the chromosome 9. Clinical features of 9q34 duplication syndrome vary depending on the size of the duplicated region but common characteristic clinical features are consist of intellectual disability, motor retardation, long narrow asymmetric face, short palpebral fissures, high nasal root, dysplastic ears, tooth abnormalities and skeletal findings including scoliosis, kyphosis, arachnodactyly, camptodactyly, and joint contractures. Previous studies have suggested that a large number of functional genes are located on the 9q34 region causing multi systemic clinical findings, but that there is not yet a definitive candidate gene to explore the abnormalities presented in this syndrome (10, 11).

Comparison of the clinical findings of our case who has characteristic duplication 9q34 syndrome and other cases with 9q34 duplication diagnosed by microarray method which has overlapping duplication region are summarized in Table 3. As seen in the Figure 3 and Table 3 while clinical findings in the presented case and other cases in the literature with 9q34 duplication are quite similar, the duplicated regions do not overlap completely (11-13). Developmental delay and intellectual disability were found in four cases, but phenotypic features and skeletal findings were not found in all of them (Table 3). The case which is described by Mizuno et al. has the most different phenotypic findings from the other three reported ones, possibly because of the Japanese lineage (Table 3) (11).

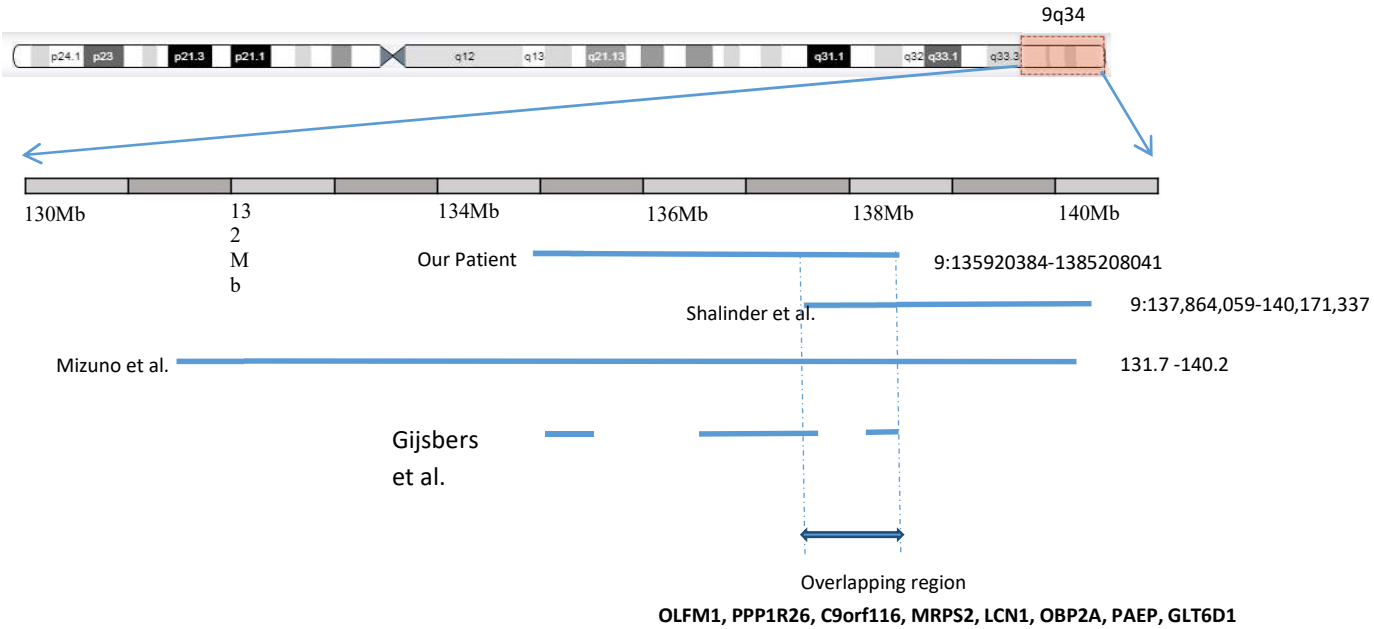


Figure 3. Common duplicated genes in patients with isolated duplication of chromosome 9q34.

Table 3. Comparison of the clinical features of other cases whose duplicated region of chromosome 9q coincide with the present case.

	Our patient (Patient 8)	Shalinder et al.	Mizuno et al.	Gijsbers et al.
Size of 9q duplication	2.6Mb	2.3 Mb	8.5 Mb	400kb duplication, 2.4 Mb triplication, 130kb duplication
Start and endpoints	9:135920384-1385208041	9:137,864,059-140,171,337	9:131.7 -140.2	9q34.3 1
Neurodevelopmental findings				
Developmental delay	+	+	+	+
Hypotonia	?	+	+	-
Intellectual disability	+	+	+	+
Dysmorphic features				
Long face	+	+	-	+
Facial asymmetry	+	+	-	+
Beaked nose	+	-	-	-
High nasal root	+	-	-	+
High palate	+	+	-	+
Retrognatia/micrognatia	+	+	+	+
Skelalet anomalies				
Aracnodactyly/camptodactyly	+	-	+	+
Scoliosis	+	+	-	-
Long hallux	+	+	+	?

Although the case reported by Gijbers et al. was clinically similar to other cases, mentioned patient had a heavier phenotype (severe mental retardation) and this can be attributed to possible sub-regions that are triplicated within the duplex region at 9q34 (13). In the literature most phenotypically similar case to our patient, which is not represented on the Table 3 due to having an extra chromosomal deletion. This patient reported by Young et al. who had 13.79 Mb duplication (126.42–140.20 Mb) at 9q33.3-q34.3 and a 155 kb deletion at 12p13.33 that contains only *IQSEC3* gene. Features of monosomy chromosome 12p13.33 reported in the literature include developmental delay, protruding tongue, strabismus, slightly unusual facies, slight micrognathia, and speech delay (14). The neurological findings of the case described by Young et al. may have been caused by both genomic alterations. However, dysmorphic facial findings and skeletal system anomalies of their and our patients may thought to be due to 9q34 duplication. As seen at Figure 3 in a total of four cases including our case, there are a total 8 common duplicated genes including *OLFM1, PPP1R26, C9ORF116, MRPS2, LCN1, OBP2A, PAEP* and *GLT6D1* genes in the common duplicated region. *OLFM1* gene (MIM *605366) was found to encode a deduced 135-amino acid protein, which the authors termed AMY that may have an essential role in nerve tissue (15). Overexpression of *PPP1R26* gene (Protein Phosphatase 1, Regulatory Subunit 26; MIM * 614056) has been shown to be associated with proliferation and tumor formation (16). Other common genes are not associated with any phenotypes and their functions are as follows: *C9ORF116* gene (MIM * 614502) as a target of *P53*; *MRPS2* gene (MIM * 611971) as a protein component of mitochondrial ribosomes that are encoded by the nuclear genome; *LCN1* gene (MIM * 151675) as having a role in the non-immunologic defense; *OBP2A* gene (MIM * 164320) as odorant-binding protein which is found in nasal epithelium; *PAEP* gene (MIM * 173310) as inducer for angiogenesis; *GLT6D1* gene (MIM * 613699) as a susceptibility locus for periodontitis.

There are 45 genes within the 2.6 Mb region in 9q34.2-q34.3 which is duplicated in our case; the functions of the 38 of them were determined and seven of these were associated with a phenotype/disease. These genes and their associated phenotypes are; *ADAMSTS13* with Thrombotic Thrombocytopenic Purpura (OMIM#274150), *ADAMSTSL2* with Geleophysical Dysplasia 1 (OMIM#231050), *CEL* with MODY8 (Maturity-Onset Diabetes of the Young, Type 8, with Exocrine Dysfunction, OMIM #609812), *COL5A1* with Ehler Danlos Sydrome Type 1 and 2 (OMIM#130000-130010), *DBH* with Congenital Beta Hydroxylase Deficiency (OMIM#223360), *SARDH* with Sarcosinemia (OMIM#268900) and *SURF1* with Leigh Syndrome (OMIM#256000). Although the deletion and mutation of these genes are known to cause related diseases, there is no information in case of duplication occurred. The clinical findings of the Patient number 8, do not compatible with the reported diseases.

Only skeletal system anomalies in patient may be thought to be caused by the duplication of *COL5A1* gene which is responsible for fibrillogenesis. Although skeletal system anomalies are shared by all of the patients, *COL5A1* gene is not found in the duplicated region of the patient reported by Shalinder et al. (12). These conflicting results cause difficulty to suggest a candidate gene for clinical findings in 9q34 duplication.

CONCLUSION

Microarray technology is a highly diagnostic method that is recommended for individuals with intellectual disability and multiple congenital anomalies. In our study, microarray analysis were performed in nine patients and in one patient, a pathologic change was found that explained the etiology of the disease. Clinical findings that result in 9q34 region duplication; it is thought to depend on the genes that express proteins that function in tasks such as cell cycle and metabolism in this region, signal control in protein transport, fibrinogenesis, connective tissue formation, and brain and nerve tissue development. The genotype-phenotype correlations to be made with the publication of new cases will contribute to the determination of gene/ genes responsible for clinical manifestations caused by duplication of the region.

Conflict of interest

No conflict of interest was declared by the authors.

Acknowledgments

The authors want to thank all patients for participating in the study. This work was funded by the Gazi University Scientific Research Foundation, under grant agreement SBE 01/2010-66.

REFERENCES

1. Shaffer LG. American College of Medical Genetics guideline on the cytogenetic evaluation of the individual with developmental delay or mental retardation. Genet Med 2005; 7(9): 650-4.
2. Ravnan JB, Tepperberg JH, Papenhausen P, Lamb AN. Hedrick J, Eash D et al. Subtelomere FISH analysis of 11 688 cases: an evaluation of the frequency and pattern of subtelomere rearrangements in individuals with developmental disabilities. J Med Genet 2006; 43(6), 478-89.

3. Miller DT, Adam MP, Aradhya S, Biesecker LG, Brothman AR, Carter NP, et al. Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. Am J Hum Genet 2010; 86:749–64.

4. Gijsbers ACJ, Schoumans J, Ruivenkamp CAL. Interpretation of Array Comparative Genome Hybridization Data: A Major Challenge. Cytogenet Genome Res 2011; 135: 222–7.

5. Vissers LE, Vries BB, Veltman JA, Genomic microarrays in mental retardation: from CNV to gene, from research to diagnosis. J Med Genet 2010; 47(5): 289-97.

6. Sagoo GS, Butterworth AS, Sanderson S, Shaw-Smith C, Higgins JP, Burton H. Array CGH in patients with learning disability (mental retardation) and congenital anomalies: updated systematic review and meta-analysis of 19 studies and 13,926 subjects. Genet Med 2009; 11: 139-46.

7. Lybaek H, Meza-Zepeda LA, Kresse SH, Høysaeter T, Steen VM, Houge G. Array-CGH finemapping of minor and cryptic HR-CGH detected genomic imbalances in 80 out of 590 patients with abnormal development. Eur J Hum Genet 2008; 16: 1318-28. https://www.nature.com/articles/ejhg200878

8. Shin S, Yu N, Choi J R, Jeong S, Lee KA. Routine chromosomal microarray analysis is necessary in Korean patients with unexplained developmental delay/mental retardation/autism spectrum disorder. Ann Lab Med 2015; 35(5): 510-8.

9. Allerdice PW, Eales B, Onyett H, Sprague W, Henderson K, Lefeuvre PA, Pal G. Duplication 9q34 syndrome. Am J Hum Genet 1983; 35 (5): 1005-19.

10. Youngs EL, McCord T, Hellings JA, Spinner NB, Schneider A, Butler MG. An 18-year follow-up report on an infant with a duplication of 9q34. Am J Med Genet A 2010; 152A (1): 230-3.

11. Mizuno S, Fukushi D, Kimura R, Yamada K, Yamada Y, Kumagai T, Wakamatsu N. Clinical and genomic characterization of siblings with a distal duplication of chromosome 9q (9q34.1-qter). Am J Med Genet A 2011; 155A (9): 2274-80.

12. Shalinder S, Ashton F, Marquis-Nicholson R, Love JM, Lan CC, Aftimos S et al. A novel 2.3 Mb microduplication of 9q34. 3 inserted into 19q13. 4 in a patient with learning disabilities. Case Reports in Pediatrics 2012.

13. Gijsbers AC, Bijlsma EK, Weiss MM, Bakker E, Breuning MH, Hoffer MJ, Ruivenkamp CA. A 400kb duplication, 2.4Mb triplication and 130kb duplication of 9q34.3 in a patient with severe mental retardation. Eur J Med Genet 2008; 51(5): 479-87.

14. Romain DR, Goldsmith J, Columbano-Green LM, Chapman CJ, Smythe RH, Parfitt RG. Partial monosomy 12p13.1-13.3. J Med Genet 1987; 24: 434–6.

15. Yokoyama M, Nishi Y, Yoshii J, Okubo K, Matsubara K. Identification and cloning of neuroblastoma-specific and nerve tissue-specific genes through compiled expression profiles. DNA Res 1996; 3: 311-20.

16. Yang L, Zhao J, Lu W, Li Y, Du X, Ning T et al. KIAA0649, a 1A6/DRIM-interacting protein with the oncogenic potential. Biochem Biophys Res Commun 2005; 334: 884-90.