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Familial intragenic X-linked OPHN1 gene deletion in a newborn male infant with low birth weight and distinctive facial appearance that diagnosed by advanced microarray-CGH method

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Case Report

History

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ABSTRACT

The oligophrenin-1 (OPHN1) gene is localized in the Xq12 region and it encodes the rho-GTPase-activating protein which spans 500 kb in size and consists of 25 exons. Gene plays crucial role in synaptic function and dendritic morphogenesis.

Here we report a 391 kb deletion in OPHN1 gene in a mother and her newborn male child with recognizable pattern of clinical and neuroradiological hallmarks. Mother has short stature, and her son has distinctive facial appearance, bilateral choroid plexus cysts and low birth weight (1600 g).

After clinical evaluation, the current large intragenic gene deletion was identified by microarray-CGH and confirmed by MLPA techniques. The P106 MRX probemix kit (MRC Holland C1- 0416, Amsterdam) and Coffalyser software were used for MLPA and Agilent sure print G3 HUMAN CGH 60k Microarray platform and Agilent cytogenomics 4.0.2.21 software (Singapore) were used for advance chromosomal genotyping for mother and his son in the presented results.

Presented results showed that mother with X chromosome deletion has a great risk to have a son with mental retardation due to deleted X chromosome transmission in 50% possibility. If the son has clinical findings, the genotype should be screened by using the advanced genetic methodology. Results also showed that once these cases are first diagnosed correctly, they may be candidate to IVF for preimplantation genetic diagnosis by giving appropriate genetic counseling. It is also comment that pregnant women who have the history of having X-linked mental retarded child or a mentally retarded brother need to be tested genetically for prenatal diagnosis.

Keywords: Distinctive facial appearance; low birth weight; mental retardation; microarray; newborn; X-linked OPHN1 gene.

Düşük doğum ağırlıklı ve belirgin yüz görünümüne sahip yenidoğan erkek bebekte gelişmiş mikroarray-CGH yöntemi ile teşhis edilen ailesel intragenik X'e bağlı OPHN1 gen delesyonu

ÖZ

Oligophrenin-1 (OPHN1) geni Xq12 bölgesinde lokalize olup, 500 kb büyüklüğünde ve 25 ekzondan oluşan rho-GTPaz aktive edici proteini kodlamaktadır. Gen, sinaptik fonksiyon ve dendritik morfogenezde çok önemli bir rol oynar. Burada, tanınabilir klinik ve nöroradyolojik özellikler paterniyle bir annede ve yeni doğan erkek çocuğunda OPHN1 geninde 391 kb'lik bir delesyon bildiriyoruz. Annede boy kısalığı, oğlunda belirgin bir yüz görünümü, bilateral koroid pleksus kistleri ve düşük doğum ağırlığı (1600 g) vardı. Klinik değerlendirmeden sonra, mevcut büyük intragenik gen delesyonu, mikroarray-CGH ile tanımlandı ve MLPA tekniği ile doğrulandı. Anne ve oğlunun ileri kromozomal genotiplemesi için P106 MRX probemix kiti (MRC Holland C1- 0416, Amsterdam) ve Coffalyser yazılımı kullanılarak MLPA analizi ve Agilent sure print G3 HUMAN CGH 60k Microarray platformu ve Agilent cytogenomics 4.0.2.21 software (Singapore) kullanıldı. Sunulan sonuçlar, X kromozomu delesyonu olan annenin %50 olasılıkla delesyona uğramış X kromozomu aktarımı nedeniyle zihinsel geriliği olan bir erkek çocuk sahibi olma riskinin büyük olduğunu göstermiştir. Erkek çocuğun klinik bulguları varsa ileri genetik metodoloji kullanılarak genotip taranmalıdır. Sonuçlar ayrıca, bu vakaların doğru şekilde tanı konulduktan sonra, uygun genetik danışmanlık verilerek preimplantasyon genetik tanı için IVF'e aday olabileceklerini göstermiştir. Ayrıca X'e bağlı zihinsel engelli çocuk ya da zihinsel engelli erkek kardeş öyküsü olan gebelerin prenatal tanı için genetik olarak test edilmesi gerektiği yorumu da yapılmıştır.

Anahtar sözcükler: Belirgin yüz görünümü; düşük doğum ağırlığı; zeka geriliği; mikroarray; yenidoğan; X'e bağlı OPHN1 geni

Süreç

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Introduction

Mental retardation (MR) is typically defined as an overall IQ below 70 associated with a functional deficit in adaptive behaviors such as self-care, daily activities, and social skills. It is an important clinical problem encountered in many individuals in a various level in large human populations all over the World 1-3. The severity of MR is classified as mild, moderate, severe, and profound 4. X-linked MR or intellectual disability (XLID) is a polygenic multifactorial genetic entity that one or more genes play crucial role on that phenomena in human 5-8. Recent literature findings showed some distinct genes such as GDI1, OPHN1, PAK3, ARHGEF6, IL1RAPL, ACSL4, MECP2, HNRNPH2, RPS6KA3, ARX, AP1S2 and ATRX that associated with XLID and MR 8-11. Specifically, Billuart,P et al have showed association between oligophrenin-1 (OPHN1) gene mutations and non-specific X-linked mental retardation (MRX) 12. The OPHN1 gene was also screened for point mutations (substitutions and frameshifts), duplications and deletions in subjects with non-specific mental retardation 13,14. Various substitutions in exons 2 and 10 13, and one deletion 14 were reported .

In the current results we aimed to present the pedigree diagram and OPHN1 gene profiling in newborn male baby and his mother with X-linked oligophrenin-1 (OPHN1) gene deletion for the correct and effective diagnosis.

Case Report

Here we report a male newborn baby with some distinctive facial appearance (low-set ears, long philtrum, high and broad forehead). Father (40y) was normal clinical appearance and mother (39y) was in short stature (139cm). The current proband case was born with caesarean at 33 gestation weeks. Mother has short stature, and her son has IUGR, distinctive facial appearance, bilateral choroid plexus cysts and low birth weight (1600 gr <10P, ponderal index:2,32). The birth measurements were consistent with 28 weeks. The birth weight was 1600 gr (<10 P), the height was 41cm (<10 P) and head circumference was 28.5 cm (<10 P) for the current proband case. Mother has preeclampsia story for the current proband case and there was no consanguinity between the parents. The GTG banded metaphases, subtelomeric FISH, QF- PCR, MLPA and

Microarray-CGH techniques were used for the specific chromosomal identification and genotype-phenotype correlation in the current proband and his mother with X-linked oligophrenin-1 (OPHN1) gene deletion. Trypsin - GTG banded metaphases were evaluated, and no structural abnormalities were detected in the current proband case (46, XY) and his mother with short stature (46, XX) after conventional lymphocyte cell culture. While the QF-PCR and subtelomeric FISH results were also in normal structure for both cases large intragenic large deletion was detected in OPHN1gene in mother and her newborn son after microarray-CGH and MLPA profiling. The P106 MRX probemix kit (MRC Holland C1- 0416, Amsterdam) and Coffalyser software were used for MLPA and Agilent sure print G3 HUMAN CGH 60k Microarray platform and Agilent cytogenomics 4.0.2.21 software (Singapore) were used for advance chromosomal genotyping for mother and his son in the presented results. The pedigree analysis showed us mother has heterozygous deletion of OPHN1 gene that located one of Xq12 region (Fig. 1, II 4) and transmitted that X chromosome to her newborn son (Fig.1, proband case, III 1). Pedigree diagram also indicate one mentally retarded male individual (Fig. 1, II 8) as an affected patient in second generation of the family (uncle of the proband case). Most possibly that deleted X chromosome may be transmitted from grandmother in first generation (Fig. 1, I4). Large heterozygous intragenic 391 kb deletion was detected in one of X chromosomes from mother (Fig. 2B) when compared to the healthy control individual (Fig. 2A). Mother shows short pick profiles (heterozygously deleted) for the target OPHN1-12, OPHN1-21 and OPHN1-3* genes that located on Xq12 (Fig. 2, arrows) due to one normal (50 percent signal in Coffalyser evaluation,small square diagram) and one deleted X chromosomes. Null picks and Coffalyser (Arrows and red dots in square diagram) profiles were detected for the target OPHN1-12, OPHN1-21 and OPHN1-3* genes in proband case (Fig. 2, C). The MLPA test profiles for the presented proband case and his mother were correlated by 60k microarray-CGH chromosomal microdissection profiles that evaluated by Agilent cytogenomics 4.0.2.21 software. Results showed a large intragenic 391 kb deletion in Xq12 that encompassing the OPHN1-12, OPHN1- 21 and OPHN1-3 genes in heterozygous type for mother and hemizygous type for the current presented case (Fig. 3, arrows).

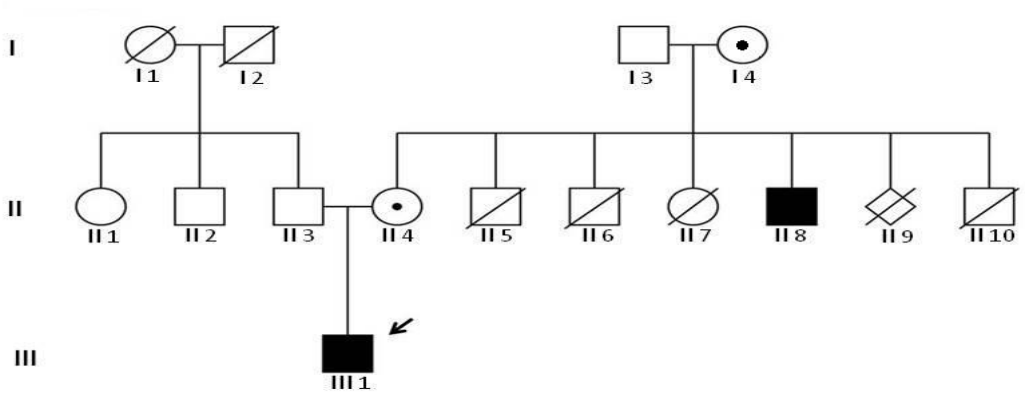

Figure 1. The pedigree and clinical diagram for the presented proband. Family members are recognized by generations and numbers. Square indicates male family member; circle, female member; circle with dot, X-linked trait; closed symbol, affected member; open symbol, unaffected member; symbols with crossline, ex members. Arrow shows the proband. Five teen family members were clinically evaluated and proband mother was diagnosed X-linked trait (II 4) and two (II 8 and III 1) were diagnosed as having mental retardation.

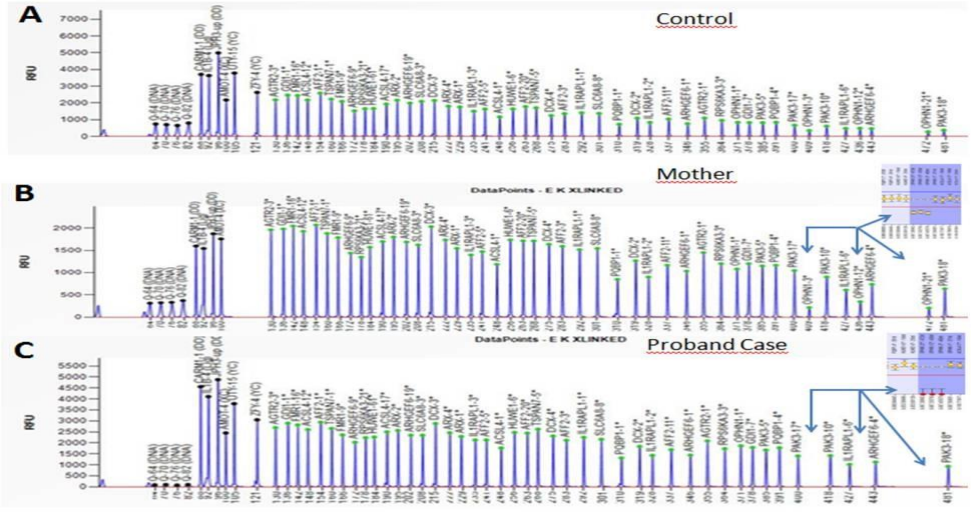

Figure 2. Shows the MLPA P106 MRX mental retardation detection kit picks and Coffalyser diagrams for the current proband case his mother and a healthy control individual. MLPA pick profiles for all target genes were in regular size and numbers in healthy control individual (A). Mother shows short pick profiles for the target OPHN1-12, OPHN1-21 and OPHN1-3* genes (arrows) due to one normal (50 percent signal in Coffalyser evaluation, small square diagram) and one deleted X chromosomes(B). Null picks and Coffalyser (Arrows and red dots in square diagram) profiles were detected for the target OPHN1-12, OPHN1-21 and OPHN1-3* genes in proband case(C).

Figure 3. Shows the 60k microarray-CGH profile of X chromosome in the current proband case. A large intragenic 391 kb deletion in Xq12 that encompassing the OPHN1-12, OPHN1-21 and OPHN1-3 genes (arrows) was detected in the current presented case.

Discussion

The oligophrenin-1 (OPHN1) gene is localized in the Xq12 region and it encodes the rho-GTPase-activating protein which spans 500 kb in size and consists of 25 exons. Gene plays crucial role in synaptic function and dendritic morphogenesis [15-19]. The OPHN1 gene is expressed at low levels in all tissues. It is expressed especially in neurons during development and higher in regions such as the olfactory bulb and hippocampus in later stages [20]. X- linked OPHN1 gene mutations cause MR with epilepsy, ventricular enlargement, and cerebellar hypoplasia [21,22]. Piton et al have also reported the various gene mutations on wide autistic spectrum and schizophrenia after X-chromosome sequencing by direct Sanger sequencing technique [23]. Redolfi et al and Nakano-Kobayashi et al have claimed that the Rho-linked mental retardation protein that encompassing from OPHN1 gene regulates the synaptic vesicle endocytosis and synaptic properties of adult-born inhibitory interneurons in the olfactory bulb [24,25]. Various types of variants in the OPHN1 gene have been reported in patients with mental retardation [8, 26-28]. Large intragenic deletion was also reported by Madrigal et al after aCGH technique [29].

Here, we report a large intragenic OPHN1 gene deletion in a newborn boy with some clinical hallmarks such as distinctive facial appearance (Low-set ears, long philtrum, high and broad forehead), bilateral choroid plexus cysts and low birth weight (1600 gr). The pedigree and genetic profiling of the X chromosome from current proband case showed us that he and his mother have 391 kb intragenic OPHN1 gene deletion. The pedigree diagram showed two affected individuals (one is newborn case - proband and his uncle) recognizable pattern of clinical and neuroradiological hallmarks for the OPHN1 gene deletion. Proband case's mother shows heterozygously deleted profiles for the target OPHN1-12, OPHN1-21 and OPHN1-3* genes that located on Xq12.

Conclusion

In conclusion, the presented results have showed that mother with X chromosome deletion has a great risk to have a son with mental retardation due to deleted X chromosome transmission in 50% possibility. If the son has clinical findings, the genotype should be screened by using the advanced genetic methodology. Results also have showed that once these cases are first diagnosed correctly, they may be candidate to IVF for preimplantation genetic diagnosis by giving appropriate genetic counseling. It is possible to expect sporadic MR in heterozygously affected female patients who have X-linked OPHN1 gene deletion after skewed X-inactivation. Current result shows that pregnant women who have the history of having X-linked mental retarded child and a mentally retarded brother need to be tested genetically for advance prenatal diagnosis tests.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Ethical Approval

Family consent was obtained. This article does not contain any studies with animals performed by any of the authors.

Author contributions

Hakan Aylanc, Oztürk Ozdemir, Fatma Silan: Conceptualization, methodology, data curation, writing-original draft preparation. Turgay Çokyaman, Fatma Silan: Visualization, Investigation. Fatma Silan: Supervision: Fatma Silan, Mehmet Berkay Akcan: Software, Validation: Oztürk Ozdemir, Hakan Aylanc: Writing- Reviewing and Editing the MN

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