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A Case Report of Neurofibromatosis Type 1 Diagnosed with a Noval Mutation Detection in NF1 Gene

NF1 Genindeki Yeni Bir Mutasyon Tespiti ile Nörofibromatozis Tip 1 Tanısı Konan Hasta: Olgu Sunumu

Nafiz Yasa[1]
Busra Eser Cavdartepe[1]
Fahrettin Duymus[1]
Nadir Kocak[1]
Tulin Cora[1]

[1]*Selçuk University, Faculty of Medicine, Department of Medical Genetic, Konya, Turkey*

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Address correspondence to: Nafiz Yasa, Selçuk University, Faculty of Medicine, Department of Medical Genetic, Konya, Turkey.

e-mail: yasanafiz@gmail.com

ORCID
Nafiz Yasa
https://orcid.org/0000-0003-1624-6745

Öz

Nörofibromatozis tip I (NF1), 17. kromozomda nörofibromin protein kodlayan genin mutasyonuna yol açan karmaşık bir hastalıktır. NF1 otozomal dominant bir hastalıktır. Bireylerde NF1 prevalansı yaklaşık 1: 2500 ila 1: 3500'tür. Erkekler ve kadınlarda eşit olarak görülür. Bu çalışmada çok sayıda hiperpigmente deri makülü, birden fazla café-au-lait lekesi, aksiller çillenmesi, optik gliomu, yüzlerce yumuşak deri nörofibromu ve her iki gözün irisinde lisch nodülleri bulunan 27 yaşında bir kadın hasta sunulmuştur. Klinik özelliklere göre, nörofibromatozis tip 1'den şüphelenilen hastadan, NF1 geninin dizi analizi yapıldı ve NF1 geninde bir heterozigot mutasyon c.980 T> G (p.L327R) tespit edildi. Bu mutasyon literatürde daha önce rapor edilmemiştir.

Anahtar Kelimeler: Yeni mutasyon, NF1, heterozigot mutasyon, yeni nesil sekans sistemi

Abstract

Neurofibromatosis type I (NF1) is a complex disorder caused by mutations of the neurofibromin protein-encoding gene on the chromosome 17. NF1 is an autosomal dominant disorder. The prevalence of NF1 is approximately 1:2500 to 1:3500. Both genders are equally affected. Herein, we report a 27-year-old female patient who had multiple hyperpigmented skin macules, multiple café-au-lait spots, axillary freckling, optic glioma, hundreds of soft cutaneous neurofibromas and lisch's nodules on the iris of both eyes. According to the clinical features, we suspect from NF1 and-then sequence analysis of NF1 gene was performed. A heterozygous c.980 T> G (p.L327R) mutation was detected in the NF1 gene. This mutation has not been reported previously.

Key words: A novel mutation, NF1, heterozygous mutation, NGS system

INTRODUCTION

Neurofibromatosis type I (NF1) is a complex disorder and mutations of the neurofibromin protein-encoding gene on the chromosome 17 causes NF1. NF1 is an autosomal dominant disorder. 50% of NF1 patients have an affected family member with NF1 (1). NF1 was previously known as von Recklinghausen disease. Robert William Smith first described the symptoms of NF1 in 1849. Friedrich Daniel von Recklinghausen was the first researcher who primarily published the disease in 1882 (2). The prevalence of NF1 is approximately 1:2500 to 1:3500. Both genders are equally affected (3). Symptoms in NF1 are usually seen at birth or before 10 years of age. While the case worsens with time, most NF1 patients have normal life time (4). The diagnostic criteria for NF1 was established in 1987 by the National Institutes of Health (NIH) in the consensus development conference and published further in 1997 (5).

The seven clinical and diagnostic criteria were defined for NF1 in this conference are as follows:

- Six or more café-au-lait spots or hyperpigmented macules greater than or equal to 5 mm in diameter in prepubertal children and 15 mm postpubertal
- Axillary or inguinal freckles (>2)
- Two or more typical neurofibromas or one plexiform neurofibroma
- Optic nerve glioma
- Two or more iris hamartomas (Lisch nodules), often identified only through slit-lamp examination by an ophthalmologist
- Sphenoid dysplasia or typical long-bone abnormalities such as pseudarthrosis

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• First-degree relative (eg, mother, father, sister, brother) with NF1
(Diagnostic criteria of the National Institute of Health Consensus Development Conference)

CASE

History:

Our patient is 27 -year-old woman. The disease started in childhood with the appearance of multiple hyperpigmented skin macules, multiple café-au-lait spots, axillary freckling and visual complaints. At the age of 25, optic glioma accompanied by visuel complaints were detected with brain MR.

Family history : Patient with neurofibromatosis was not detected in her family. She has one healthy girl.

Physical examination

Dermatological status: Hundreds of soft cutaneous neurofibromas, most of these were on the trunk and limbs, ranging from a few millimeters to several centimeters in diameter (Figure 1); multiple café-au-lait spots about 3,5 cm (Figure 1); axillary and inguinal freckling (Figure 2). The mucous membranes were not affected.

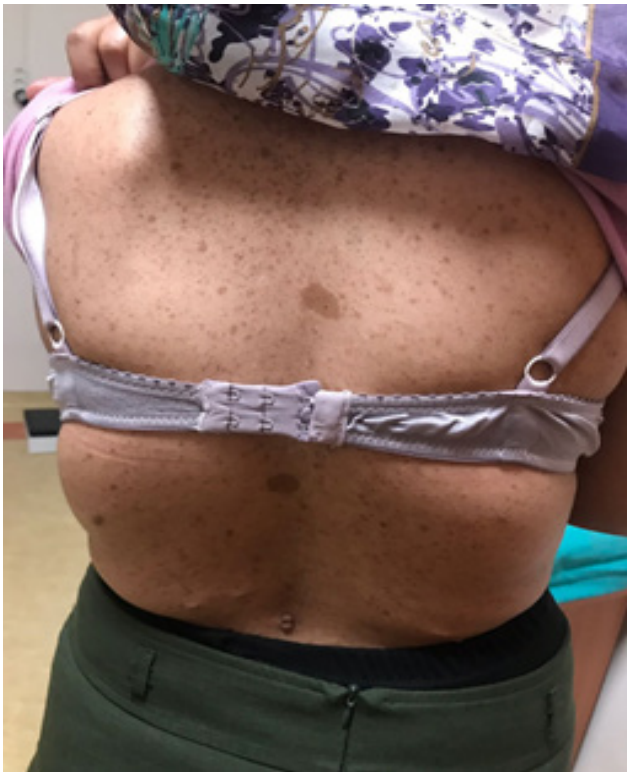

Figure 1. Soft cutaneous neurofibromas and multiple café-au-lait spots.

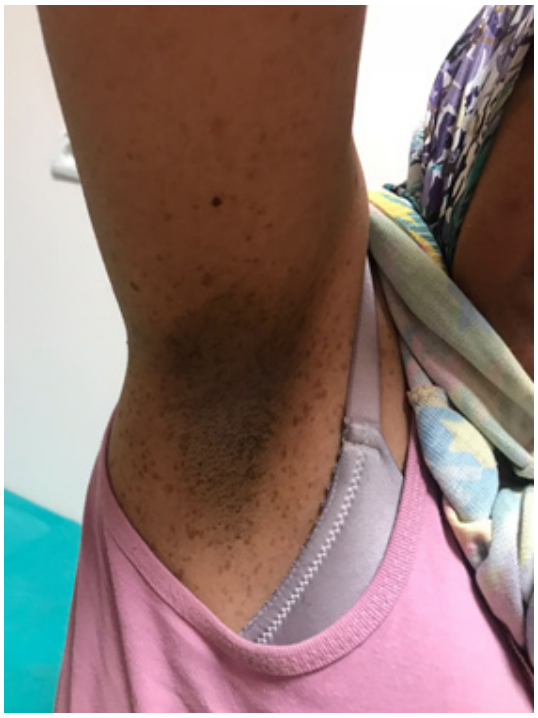

Figure 2. Axillary freckling

Ophthalmological status: Lisch's nodules on irises of eyes were accompanied by clinical visual impairment.

Laboratory and imaging:

Genetic Report: A heterozygous mutation c.980 T> G (p.L327R) was detected in the NF-1 gene (NM_001042492) of the patient using BioScientific kit on NGS system (Figure 3). The result was confirmed by sanger sequencing. The mutation has been evaluated as pathogenic according to mutationtester and polyphen databases. This mutation has not been reported previously.

MR imaging: An optic glioma 7mm in diameter was detected in the left eye (Figure 4).

Figure 3. NF1 sequence result

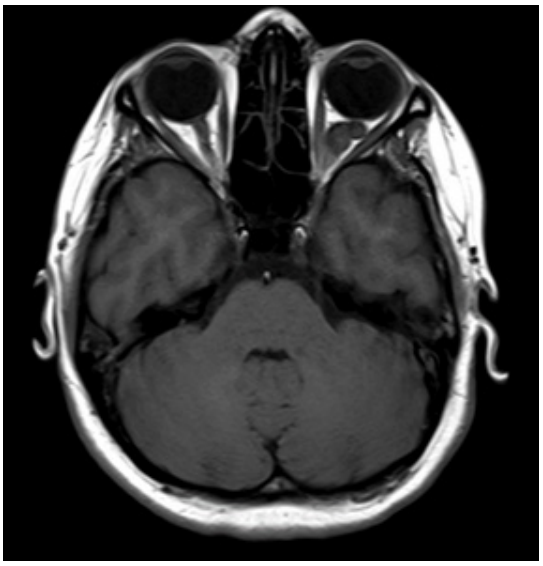

Figure 4. Optic glioma in her left eye

The findings of our patient were reviewed according to the National Criteria of the National Conference on Development of Health Adaptation. Two or more findings consistent with these criteria were evaluated in favor of NF1. There are 5 out of 7 criteria in this case (Table 1).

Table 1. NF1 diagnosis criteria of National Criteria of the National Conference on Development of Health Adaptation (5).

Criteria	In Our Case
Six or more café-au-lait spots or hyperpigmented macules greater than or equal to 5 mm in diameter in prepubertal children and 15 mm postpubertal	+
Axillary or inguinal freckles (>2)	+
Two or more typical neurofibromas or one plexiform neurofibroma	+
Optic nerve glioma	+
Two or more iris hamartomas (Lisch nodules), often identified only through slit-lamp examination by an ophthalmologist	+
Sphenoid dysplasia or typical long-bone abnormalities such as pseudarthrosis	-
First-degree relative (eg, mother, father, sister, brother) with NF1	-

DISCUSSION

NF1 is a large gene including 57 exons and approximately 350 kBp length. NF1 gene codes for at least three alternatively spliced transcripts. The protein product of the gene named neurofibromin which has 2,818 amino acids (6). The function of neurofibromin is not fully understood. It activates ras GTPase, controlling cellular proliferation and acting as a tumor suppressor (7). Neurofibromin also has other functions, including somatic cell division (8) and regulation of adenylyl-cyclase activity (9).

In our case, a heterozygous mutation in the NF1 gene (NM_001042492) has been identified and this mutation has not been previously reported in literature. This mutation is shown to be pathogenic in mutation tester and polyphen databases. NF1 is caused by variants of the loss of function of Neurofibromin. More than 2000 different pathogenic variants in NF1 have been identified. Many pathogenic variant were observed over and over again. Several different variants have been observed, including stop variants, amino acid substitutions, deletions (which may involve only one or a few base pairs, multiple exons, or the entire gene), insertions, intronic changes affecting splicing, alterations of the 3'-untranslated region of the gene, and gross chromosome rearrangements (9). Most of the pathogenic variant of the germline NF1 described in individuals appears to be severely hamper the formation of the gene product (11).

Only two NF1 diagnostic criteria were not exist in this patient. One of the missing criteria was there was no NF1 affected individual in her family. Half of affected individuals have NF1 as the result of a de novo NF1 pathogenic variant. The autosomal dominant type of NF constitutes 90% of all cases. (12). Another NF criterion that could not be detected in our case was sphenoid dysplasia. Sphenoid dysplasia is a prominent but not entirely pathognomonic feature of NF1 (13). As a result, this case is presented to show that this new mutation causes NF1 disease and can be used for diagnosis by introducing it into the literature.

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Address correspondence to: *Nafiz Yasa, Selçuk University, Faculty of Medicine, Department of Medical Genetic, Konya, Turkey.*

e-mail: *yasanafiz@gmail.com*

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