

A New de Novo Mutation Associated with Neurofibromatosis (NF-1)

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Abstract

Neurofibromatosis type 1 (NF-1) is the most common neurocutaneous disease with an autosomal dominant inheritance pattern and a frequency of 1:3,500 live births in the general population, regardless of race and sex. NF-1 is a progressive disorder characterized by multiple café-au-lait macules, neurofibromas, Lisch nodules and other manifestations such as bone abnormalities, short stature, epilepsy, learning disabilities, hyperactivity, with a highly variable and unpredictable expression. Half of its cause comes from different mutations in a gene on chromosome 17, resulting in less or performance neurofibromin having the regulatory domain of tumor activity. The other 50% of the case are caused by de novo mutation.

It is an infant 13 months old, no family history of neurofibromatosis, which features six café-au lait spots 1 cm of diameter in the legs, chest, auxiliary region and short stature.

The clinical diagnostic criteria of NF-1 were established by The National Institutes Health Consensus Development Conference in 1987. It has been suggested that pathogenic mutation in the NF-1 gene be added to the list of diagnostic criteria, but not yet accepted.

A molecular genetics study showed an alteration in exon 16 c.2540T>G (p.Leu847 Arg). No genetic alterations were found in phenotypic parents.

After six years of follow-up she was not observed clinical or radiographic abnormalities.

The genetic study is mandatory for confirmation of the suspected diagnosis and to monitor de novo mutations that knowledge and phenotypic expression thereof.

Keywords: Gene; Café-au-lait macules; Mutation; Neurofibromatosis; Neurofibromin; Genetic

disabilities, hyperactivity, short stature, hydrocephalus, scoliosis, epilepsy, headaches, bone abnormalities and cardiovascular lesions [6].

Introduction

The NF-1 was described by Von Recklinghausen in 1882, a German pathologist who recognized that tumors observed in the skin were composed of fibrous tissue surrounding the nerves, resulting in the name of neurofibroma [1]. NF-1 is the most common mendelian dominant autonomic disorder with a variable and unpredictable expression, caused by a mutation that inactivates the germline in a gene on chromosome 17q11.2 [2].

Clinical manifestations are the café-au-lait spots are the first sign in the affected children present at birth or in the first months of life, are flat brownish lesions of varying intensity, with a diameter of 0.5 cm, is found throughout the body except the scalp, eyebrows, and palms of hands and soles of the feet [3].

The freckles are spots smaller location in the armpits or groin and are not present at birth, appear between 3-5 years [3,4]. Cutaneous or subcutaneous neurofibromas and Lisch nodules or iris hamartomas appear within 5-10 years [3,5]. Other manifestations are learning

In 1988 the clinical criteria for the diagnosis of NF-1 are at least 2 of the following criteria: 1) Six or more café-au-lait macules with diameters >5 mm in prepubertal patients and >15 mm in postpubertal patients; 2) Two or more neurofibromas of any type or one plexiform neurofibroma; 3) Axillary or inguinal freckling; 4) Optic glioma; 5) Two or more Lisch nodules of the iris; 6) A distinctive osseous lesion, such as sphenoid wing dysplasia or pseudarthrosis; 7) A father or brother diagnosed with neurofibromatosis established [7].

The gene was identified by Cawthon [8] with positional cloning techniques, have been shown translocations, deletions and point mutations of the NF-1 gene on chromosome 17q11.2, chromosomal assignment previously established by genetic analysis of families carrying neurofibromatosis [8]. The NF-1 gene, 300 Kb consists of 60 exons in genomic DNA, mRNA encoding a 11-13 Kb and specifies a cytoplasmic localization protein, neurofibromin 2818 amino acids and 327 kD molecular weight [9].

The mutation rate for NF-1 is one of the highest known, probably due to large size of the gene conversions mediated genes and pseudogenes presence of repeated sequences [10]. In the present is considered that half of patients diagnosed with NF-1 are a spontaneous

mutation de novo where parents have no chromosomal abnormality, nor have the disease so there is talk of germline mutations [11,12].

Having identified a new de novo mutation in the gene for neurofibromatosis, a Venezuelan girl, motivated us to conduct this work. We to mark again the importance of molecular genetics study in clinically diagnosed patients to detect new mutations or simply to establish the evolution and behavior of the detected mutation.

Clinical case

The Infant 13 months, female who presents café-au-lait spots in various parts of the body and short stature.

Antecedent Important: One product gestation, pregnant 38 weeks to term controlled, obtained by cesarean, no consanguineous parents. Birth weight: 2900 Kg; Stature: 49 cm. Normal psychomotor development.

Physical examination: Weight: 10 kg (50th percentile) Stature: 69 (<10th percentile) Head circumference: 46 cm (50th percentile).

In the time of admission was in good general condition, no dysmorphic features were seen, they were observed skin six café au lait macules, flat oval greater than 1 cm in diameter in the lower limbs, chest and inguinal regions. Cardiopulmonary was normal. Abdomen no tumors were observed, nor visceromegaly. The tendon reflexes normal. Neurological was normal. Evaluation dermatological was confirmed the NF-1.

Laboratory Tests: See Table 1.

Hemoglobin	11.7 gr/dL
Hematocrit	39%
Leukocytes	5000 mM
Segmented	37%
Lymphocytes	63%
Glucose	78 mg/dL
Urea	14 mg/dL
Creatinine	4 mg/dL
T3	3.37 ng/dL
T4	1.50 ng/dL
Oxaloacetic Transaminase	7.1 U/L
Piruvica	18 U/L
Transaminase	
Calcium	9 mg/dL

Table 1: Laboratory tests.

Chest radiography was normal, brain MRI was normal. Evaluation ophthalmological was normal.

Molecular genetics study for direct cycle sequencing of NF1 exon 16, was practiced in UAB Medical Genomics Laboratory (Dr Ludwine Messiaen) showed an alteration in exon 16 c.2540T> G (p.Leu847Arg).

A heterozygous missense alteration in exon 16 of the NF-1 gene was identified in the patient c2540T>G (p.Leu847 Arg).

This alteration was noted reported before and we have never observed it in our cohort of patients and controls.

We have finalized analysis in the parents, both reported to be an unaffected and did not find the missense alteration c.2540T>G (p.Leu847 Arg) in them.

This indicates that c.250T>G (p.Leu847 Arg) occurred de novo in the patient. Taking into account all evidence available at this time, we conclude that the missense alteration is very likely a pathogenic mutation.

The genetic study was performed both parents giving negative for the disease NF-1.

Discussion

NF-1 is a common dominant multisystem progressive disease, autosomal with complete penetrance, which occurs in childhood with heterogeneous manifestations [13]. The earliest and most common manifestations are café au lait spots that are present at birth or appear in the first months, which are detected by a simple visual inspection, as in our patient [14].

The distribution of the symptoms and signs of multisystem or behavior may be related to the defect in the protein neurofibromin at various stages of differentiation of the affected cells. The clinical features are highly variable even within a family, some children just have areas of skin hyperpigmentation (spots), but others suffer severe and disabling involvement characterized by central nervous system tumors, scoliosis, dysplasia of long bones, peripheral vascular lesions and rapidly growing tumors that can cause dysfunction and disfigurement [15].

The most common complications are short stature, which was found in the patient. The penetrance of neurofibromatosis is 100% means that all patients with neurofibromatosis NF-1 have a mutation. A molecular genetic analysis can detect a genetic mutation in over 92% of the examined patients who meet the diagnostic criteria. It is very important in children with negative family history and that only partially meet the diagnostic criteria [16].

The mutation rate in germ cells, calculated for gene NF1 neurofibromatosis type is one of the highest reported in humans, is above 50% of cases are due to de novo mutations. Mutations of neurofibromatosis type 1 appear to be evenly distributed along the gene. However some exons have a density higher mutation and most of these are recurrent mutations. Therefore these exons may have priority in mutation detection [10].

Although several mutations descriptions, there is no clear phenotype-genotype correlation, except NF1 patients with neurofibromatosis type, due to a complete deletion of the NF1 gene [15]. The wide variability of phenotype expression, even among affected members of my own family, is another hallmark of neurofibromatosis type 1 neurofibromatosis mild forms of mosaicism is caused by a situation in which the NF-1 mutation occurs after fertilization.

Somatic mutations occur early during embryonic development and produce a generalized mosaicism which is characterized by a slight indistinguishable form of the classical form of type 1 [14]

neurofibromatosis. Gonadal mosaicism is a rare form of mosaicism, the mutation is present only in the gonads and may be suspected in children with NF-1 unaffected parents, or family history, as in our case.

In a study by Yunus et al. [10] analyzing 4b exon were performed, 16, 29, 31 and 37 to investigate recurrent mutations in 100 patients in Turkey with neurofibromatosis type NF1, these analysis allowed to identify two different mutations in exon 4b, 496delGT and 499delTGTT and unknown mutation in exon 31, 5866delA. Han et al, found three mutations in exon 4b but none in exon 37.

Messiaen et al. [16] describes a comprehensive analysis of mutations in the NF1 neurofibromatosis type, 30% of the mutations found in their study were recurrent. These data support the contention that different populations have different sets of exons that contain recurrent mutation.

The molecular test to NF-1 is also useful in confirming the diagnosis in the case in patients with café-au-lait spots (98%) and with or without freckling (30%) and absence of a high prevalence of nervous system tumors Central [17]. They may be associated with learning disabilities and behavioral problems such attention disorder/hyperactivity (TADH) but with less severe than NF1 [18-20] cognitive phenotype. Dysmorphic features as macrocephaly (42%), short stature and less frequent Noonan-like facial features, achromic spots, pectus excavatum, headache, convulsions, deafness, scoliosis.

In these patients with a mild phenotype but with the diagnostic criteria for NF1 successful, they could have a Legius syndrome or NF1-like described in 2007 by Breems et al [21], which is due to an autosomal dominant mutation in the SPRED1 gene in the 15q13.2 chromosome which implies a loss of function of proteins involved in the pathogenic pathway RAS-MAPK1, neurofibromin like and therefore can be considered as a rasopathy [22].

Approximately at 1-2% of patients with neurofibromatosis criteria for NF1 has mutations in SPRED1 [18]. In addition this gene described a potential increased risk of developing leukemia (17.22) SPRED1 that the gene is also expressed in hematopoietic cells that down regulate the process of hematopoietic by suppressing stem cell stimulating factor and interleukin [17].

Early detection is a better prognosis and to evaluate the clinical follow these novo mutations that allow phenotypic knowledge of them and the expression of the disease.

The case presented was a minimal expression of the disease.

Throughout this reason it is important that pediatricians, pediatric neurologists, geneticist, dermatologists, ophthalmologists and oncologists who are involved in the diagnosis and treatment of patients with NF-1, forces us to change the management of patients with café-au-lait spots and perform molecular genetics study.

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