

ORIGINAL PAPER

Genetic and clinical considerations in six cases with neurofibromatosis type 1

ELENA BUTEICĂ¹⁾, IRINA STOICESCU²⁾, F. BURADA¹⁾,
B. STĂNOIU¹⁾

¹⁾Department of Genetics

²⁾Department of Dermatology

University of Medicine and Pharmacy of Craiova

Abstract

Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder, caused by mutations in the NF1 gene. The NF1 gene encoding neurofibromin protein, which is strongly expressed in the nervous system and with the role as a negative regulator of the *ras* proteins signal. All six cases with neurofibromatosis type 1 were clinical and laboratory investigated. The frequently symptoms are “café au lait” spots and neurofibromas. In two cases, the disease is associated with essential hypertension and, in other two cases with kyphoscoliosis. The *novi* mutations in NF1 gene cause the disease in three cases, and in other three cases, the mutation is inherited (two cases on father side and one case on mother side).

Keywords: neurofibromatosis type I, gene, mutation, “café au lait” spots, neurofibromas.

Introduction

Neurofibromatosis type 1 (NF1) is one of the most common autosomal dominant disorder caused by mutations in the NF1 gene, with almost complete penetrance. The disease occurs in one in 3000 to 4000 people worldwide with no ethnic or gender-related variability.

The NF1 gene is a very large gene spanning over 350 kb of genomic DNA [1], with 60 exons, located in the long arm of chromosome 17 (17q11.2) [2].

NF1 gene encodes the protein neurofibromin. Neurofibromin has 2818 amino acids and predicted molecular size of 327 kD [1], but the observed molecular size is approximately 250 kD.

The NF1 protein is expressed in many cell types in adults and during embryonic development. The expression is most abundant in the nervous system including nerve cells [3], specialized cells called oligodendrocytes and Schwann cells.

Neurofibromin is a negative regulator of the *ras* signal transduction pathway, accelerating the switch of active *Ras*-GTP into inactive *Ras*-GDP [4].

The mutations in NF1 gene cause neurofibromin deficiency, which does not fulfill its role as suppressor protein. As result the *ras* signal will be transmitted permanently [5].

Multiple “café au lait” spots, axillary and inguinal freckling, multiple discrete dermal neurofibromas, and iris Lisch nodules frequently characterize clinical neurofibromatosis type 1.

Criteria for the diagnosis of NF1 developed by an *NIH Consensus Conference* in 1987 are generally accepted for routine clinical use [6]. NF1 patients should fulfill two or more of the following:

- six or more “café au lait” macules larger than 5 mm in prepubertal children and larger than 1.5 cm in postpubertal individuals;
- two or more neurofibromas of any type or one plexiform neurofibroma;
- multiple freckles (Crowe sign) in the axillary or inguinal region;
- a distinctive osseous lesion, such as sphenoid dysplasia or thinning of long bone cortex, with or without pseudoarthrosis;
- optic glioma;
- two or more iris hamartomas (Lisch nodules);
- a first-degree relative with NF1, diagnosed by using the criteria above.

Clinical and pathological reports

We investigated clinical (dermatological, neurological, ophthalmological) and laboratory six cases (two men and four women) with neurofibromatosis type 1. The pedigrees were created based on familial informations.

Case no. 1

A boy (L.R.), age 6 years, presents over six “café au lait” spots ≥ 1.5 cm in the greatest diameter, with different sizes and well delimited (Figure 1).

The spots still appear, most of them placed on thorax, abdomen and lower limbs. Multiple freckles are present in the axillary area.

The disease is not present to parents and other persons from family on mother or father side (Figure 2), but the mother work in a toxic medium with toluene, benzene and formaldehyde. Other tests were not made because the parents did not agree.

Case no. 2

A man (B.F.), age 21 years, gipsy ethnic, with mental retardation, have presented from early childhood multiple pigmented macules ("café au lait"), with different sizes and unorganized localization on all skin, more visible on thorax. In addition, he presents on limbs tumoral nodular formations, with different sizes and unpainful (Figures 3 and 4).

The histopathological examination from some formations revealed neurofibroma microscopic structure. Ophthalmological examination of patient did not proved the presence of Lisch nodules. Other members of family did not have skin lesions.

Case no. 3

Female patient (P.I.), age 52 years with essential hypertension and dermatological features: multiple "café au lait" spots and more neurofibromas with localization on anterior and posterior thorax (Figure 5).

The analysis of pedigree emphasized that mutation of the gene was inherited from generation to generation, neurofibromatosis type 1 being present at father and grand father on father side (Figure 6).

The proband has two brothers with neurofibromatosis type 1 and one of hers two daughters inherited the disease from mother.

Case no. 4

A female patient (S.V.) with kyphoscoliosis and several "café au lait" macules in lumbar and sacrum area, together with various neurofibromas, which have different sizes (Figure 7).

Most of freckles are in the left axillary area. The pedigree analysis does not show the presence of disease to other persons from family (Figure 8).

Case no. 5

A female patient (D.C.V.), age 40 years, from rural area was hospitalized for multiple pigmented macules with different sizes and forms, with localization on all skin and many unpainful tumoral formations in the subcutaneous layer (Figure 9).

The ophthalmological examination showed the presence of Lisch nodules in both eyes. The neurological examination revealed dizziness, headaches, osteo-tendinous reflections diminished and endocrine exam acromegaly, latent tetany.

Cutaneous echographic examination revealed formations hypoechogenic, some situated intra-epidermically, size between 3–5 mm to 1–2 mm, without vascularization.

The analysis of pedigree revealed that mother of proband have neurofibromatosis type 1 associated with cardiac disease and grandfather from mother side has diabetes (Figure 10). The proband has two healthy daughters.

Case no. 6

A female patient (G.M.), age 71 years, gipsy ethnic, from rural area, with tumoral formations, localized on thorax and legs, and brown spots with varied intensity

of color. The tumoral formations were spherical, pediculate, elastic and unpainful (Figure 11).

The Lisch nodules were present on ophthalmological examination of patient. The patient has kyphoscoliosis and essential hypertension.

Microscopic structure of neurofibroma has shown by histopathological exam from tumoral formation. The pedigree showed the presence of some similar tumors on proband father and one daughter (Figure 12) (died by drowning).

Discussions

In three cases, the disease is caused by *de novo* mutations of NF1 gene. The mutation rate of the NF1 gene is one of the highest known in the human genome, $3.1\text{--}6.5 \times 10^5$ [7]. Thus, approximately 50% of all NF1 patients lack a family history of the disease [8].

It has been speculated that the high mutation rate is caused by the large size of the gene and the complexity of its processing [9].

There are no general hot spot areas for mutations in the NF1 gene, but the exons 10 and 37 have been shown to have the highest mutation rate and count for approximately 30% of the mutations [10].

About 90% of new mutations occur on the paternally derived chromosome [11, 12]. The exception is large deletions, which are usually of maternal origin [13].

In other three cases, the patients have inherited the disease from one of parents. Neurofibromatosis is the result of a single dominant gene. Once a person has the NF1 gene, whether by inheritance or mutation, he or she has a 50% chance of passing it on to each of his or her children.

The association between NF1 and essential hypertension is frequent but other features can occur: complete heart block, regressive cardiomyopathy in infancy, renal artery stenosis [14], coarctation of the aorta, or other vascular lesions [15].

The association between NF1 and essential hypertension was revealed in two cases investigated by us, and in other two cases, neurofibromatosis type 1 is associated with kyphoscoliosis. The musculoskeletal system is affected. Spinal rotational anomalies can include kyphoscoliosis, bowed legs, skull defects and anomalies of skull shape and thoracic cage deformities, such as *pectus excavatum* and pseudoarthrosis of bones [16].

"Café au lait" spots may be present at birth and increase in number in the future. When a child with NF1 is born, he or she may only have the brown spots. The size of the spots varies from 0.5 mm in diameter to several centimeters.

Sometimes newborns have freckles and, occasionally, neurofibromas. New brown spots often appear during infancy and early childhood.

The spots will not harm your child. As children grow older, the spots and tumors tend to increase in number and size. Discrete cutaneous and subcutaneous neurofibromas may develop at any time but are not frequent before puberty [17].



Figure 1 – “Café au lait” spot (case no. 1)

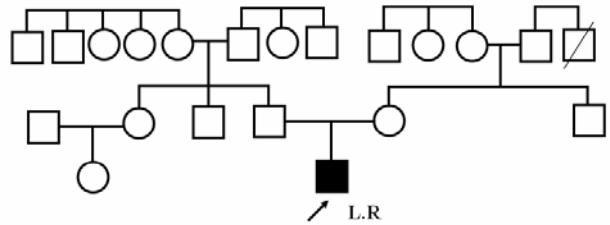


Figure 2 – The pedigree (case no. 1)



Figure 3 – Lower limb: “café au lait” spots and neurofibromas (case no. 2)



Figure 4 – Posterior thorax: multiple neurofibromas (case no. 2)



Figure 5 – Posterior thorax: multiple neurofibromas and “café au lait” spots (case no. 3)

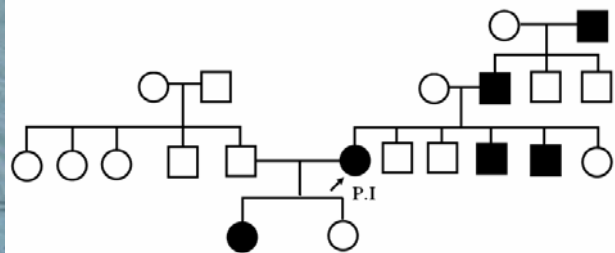


Figure 6 – The pedigree (case no. 3)



Figure 7 – Kyphoscoliosis (case no. 4)

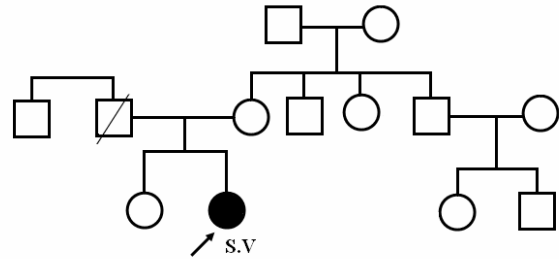


Figure 8 – The pedigree (case no. 4)



Figure 9 – Anterior thorax: multiple neurofibromas (case no. 5)

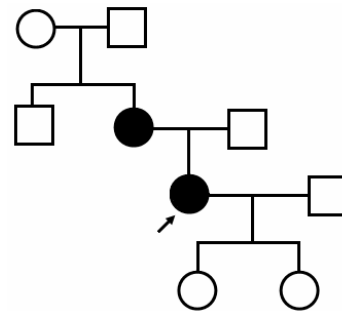


Figure 10 – The pedigree (case no. 5)



Figure 11 – Anterior thorax and abdomen: multiple neurofibromas (case no. 6)

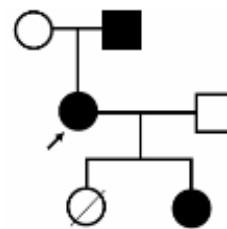


Figure 12 – The pedigree (case no. 6)

Total numbers of cutaneous and subcutaneous neurofibromas seen in adults vary from a few to thousands. Other cutaneous lesions include hemangiomas, xanthogranulomas, red-blue macules, giant hairy nevi, and depigmented macules.

A male patient (case no. 2) has mental retardation. In addition, abnormalities of nervous system may occur. Mental retardation is more frequently at patients with NF1 deleted [18].

Neurofibromin haplo-insufficiency is possible to cause mental retardation [19].

Other features are learning disabilities, behavioral disorders, hyperactivity, hypertelorism, abnormal hearing.

The structure of tumors from neurofibromatosis type 1 can be solitary tumor, plexiform neurofibroma or disseminated neurofibromatosis.

The microscope image in solitary neurofibroma can be different, in the classic forms, and it is formed by fusiform cells with hyperchrome nucleus and with fascicular organization.

Collagen bands, between them it is mucoid stroma, separate the cell fascicles. Nervous fillets can be observed between tumoral structures and in the stroma contains lymphocytes, mastocytes and xanthomatosis cells.

Plexiform neurofibroma contains Schwann cell proliferation, separated by large collagen bands. The disseminated neurofibromatosis is histological different from classic neurofibroma by morphology of tumoral cells and fine fibrillary collagen stroma [20].

☒ Conclusions

In three cases mutations in NF1 gene were not inherited from one of parents, these are de novo mutations and in others three cases the mutation is inherited. Clinical the features of disease are variable, but "café au lait" spots and neurofibromas are the frequently symptoms.

On some cases investigated by us, the neurofibromatosis type 1 is associated with essential hypertension, kyphoscoliosis and mental retardation. Even if in present neurofibromatosis type 1 has not available treatments, genetic counseling is very important and some of the symptoms of NF1 can be treated individually.

The diagnosis of neurofibromatosis type 1 and patient's monitorization impose multidisciplinary approach.

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Corresponding author

Elena Buteică, Associate Professor, PhD, Department of Genetics, University of Medicine and Pharmacy of Craiova, 2-4 Petru Rareș Street, 200 349 Craiova, Romania; Phone +40722-570 333, E-mail: buteicaelena@yahoo.com

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