



## Original Contribution

# CLINICAL POLYMORPHISM IN NEUROFIBROMATOSIS TYPE 1

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## SUMMARY

We report 9 patients with NF1 - 5 with positive family history and 4 sporadic cases. The von Recklinghausen disease is a common autosomal dominant disorder affecting about 1 in 5000 to 3000 people. It exhibits full penetrance and a high mutation rate. About 30 to 50% of NF1 patients representing a new mutations. Its distribution is higher than Huntington's chorea, muscular dystrophies Duchenne and myotonic dystrophy all together. The offspring of the affected people has 50% risk for inheriting the disease, which leads to different levels of disability and/or death. The aim of this article is to increase the knowledge and awareness of physicians. The NF1 is in the scope of interest of different medical specialities, because of the high heterogeneity of the clinical symptoms and complications, which require a multidisciplinary approach to the disease.

**Key words:** Neurofibromatosis type 1, Genetic counselling, Expression, Clinical heterogeneity.

## INTRODUCTION

The von Recklinghausen disease or peripheral neurofibromatosis is a common autosomal dominant disorder affecting about 1 in 5000 to 3000 people. It exhibits full penetrance and a high mutation rate. About 30 to 50% of NF1 patients represent a new mutation (1, 2). Its distribution is higher than Huntington's chorea, muscular dystrophies Duchenne and myotonic dystrophy all together. The offspring of the affected people has 50% risk for inheriting the disease, which leads to different levels of disability and/or death. The Neurofibromatosis type 1 is in the scope of interest of more than 10 medical speciality, because of the high heterogeneity of the clinical symptoms and complications, which require a multidisciplinary approach to the disease.

Neurofibromatosis type 1 (NF1, Morbus Recklinghausen) is a genetic disease with an extremely wide range of manifestations. This makes diagnosis considerably difficult. Cutaneous spots and dermal neurofibromas represent a cosmetic problem. Cutaneous and

plexiform neurofibromas can undergo malignant transformation. Neurofibrosarcomas and another malignant tumors are rare. The individuals with NF1 can develop pheochromocytomas, juvenile chronic myeloid leukaemia, rhabdomyosarcomas at an increased frequency compared to the general population. The clinical and genetic analysis of the NF genes has broadened our understanding of this disease. Our improved diagnosis and management of the affected individuals will change the clinical manifestation and will restrict the heavy complications.

## MATERIALS AND METHODS

The diagnostic criteria are two or more of the following (3):

- 1) six or more cafe-au-lait macules over 5 mm in greatest diameter in pre-pubertal individuals and over 15 mm in greatest diameter after puberty
- 2) two or more neurofibromas of any type or one plexiform neurofibroma
- 3) freckling in the axillary or inguinal regions
- 4) an optic pathway tumor
- 5) two or more Lisch nodules (iris hamartomas)

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- 6) a distinctive osseous lesion such as sphenoid wing dysplasia or thinning of the cortex of the long bones (with or without pseudoarthrosis).
- 7) a first-degree relative (parent, sibling or offspring with NF1 by the above criteria).

## CLINICAL REPORT

We describe patients from families with NF1 and sporadic cases who present with clinical heterogeneity involving rare symptoms (Figure 1 and Table 1).

### Family 1

The proband was the first in the family with neurofibromatosis. She came to our clinic at the age of 18 when the clinical feature was widely represented. Large cafe-au lait spots were designated at birth. Different symptoms were observed later - lentiginous freckle in the axillae, melanocytic nevi, multiple cutaneous neurofibromas located on the trunk. A spinal deformation was discovered at the age of 5 which progressively grew and turned into a big hunch (Figure 2a and 2b).

### Family 2

The proband is a 4-years old girl. She comes from a NF1-family with disease segregating in three generations. She presents with cafe-au lait spots, scoliosis, pelvic asymmetry, mild hemihypertrophy and clitoromegaly. In the area of labia majora there was a big fibroma. The child was operated on. The first operation was a cosmetic one. Her father has only cafe-au lait spots. Her paternal grandmother has NF1 - plexiform neurofibromas, multiple brown spots, cutaneous and subcutaneous neurofibromas. Later one of the fibromas transformed into a malignant fibrosarcoma with metastases in the lung and she died at 55.

### Family 3

The proband is a 10-year-old boy with NF1. He has multiple brownish spots and facial asymmetry at birth. A few years later neurofibromas appeared on the left eyelid and the left side of the lower lip. Now he can hardly lift his eyelid. There is no mental retardation. His father and his paternal aunts have only axillary freckling, but no other symptoms of the disease.

### Family 4

The proband is an 11-year-old girl with cafe-au lait spots at birth on the trunk and freckles in the axillae. At the age 8 she started having seizures. She came to us with mild scoliosis. Her mother has brownish spots on the trunk, facial

asymmetry, exophthalm of the left eye and dental anomalies (Figure 3a and 3b). A few years ago an extirpation of a big palatal fibroma was made. Her maternal grandmother and her grand-grandmother also have a dermal form of neurofibromatosis.

### Family 5

The proband is a 4-year old girl with cafe-au lait spots and optic glioma. A few months before the operation the right eye was extremely protruding. The child often began to stumble when walking. The optic glioma was detected on MRI and CT of the head. The girl was the first case with neurofibromatosis in the family (Figure 4a and 4b).

### Family 6

The proband is a woman with NF1. The cafe-au lait spots have been observed at birth. Neurofibromas appear during early childhood. Her state progressively aggravated and later she developed leiomyoma uteri, polycystic ovary and breast carcinoma (Figure 5).

### Family 7

The proband is a young man affected with signs symptoms typical for neurofibromatosis - cafe-au lait spots, cutaneous neurofibromas, facial asymmetry, spinal neurofibromas in association with severe scoliosis and mild mental retardation. CT and MRI discovered C1-C2 dumbbell tumor - neurofibroma, compressing the spinal cord (Fig. 6a and 6b).

### Family 8

The proband is a 11-year-old girl with sporadic NF1. She presents with multiple cafe au lait spots, diffuse hyperpigmentation, short stature, mild macrocephaly, scoliosis, neurofibroma with overlying hyperpigmentation and hypertrichosis. At 1,5 year she developed nephrotic syndrome with unknown etiology and was successfully treated with corticosteroids. At age 10 she was operated for scoliosis (Th2-Th10).

### Family 9

The proband is a 10-year-old girl with sporadic NF1. She came to us with cafe au lait spots, hyperpigmentation, macrocephaly, learning disability, speech impediment, mild scoliosis, severe myopia. By laryngoscopy undertaken during tonsillectomy a fibroma of the larynx was observed.

## DISCUSSION

NF1 gene spans over 350 kb of genomic DNA in chromosomal region 17q11.2 and encodes

an mRNA of 11-13kb containing at least 59 exons. NF1 is widely expressed in a variety of human tissues. Four alternatively spliced NF1 transcripts have been identified. Three of these transcript isoforms (9br, 23a, 48a) show differential expression to some extent in various tissues, while the fourth isoform (2.9kb in length) remains to be examined (4). NF1 is a tumor suppressor gene, which encodes a GTPase-activating product - neurofibromin. The neurofibromin acts as regulator of biological activity of p21-RAS oncoproteins. Therefore the neurofibromin represents a negative regulator of cell growth and acts on a recessive manner in the cell.

NF1 is transmitted in a pattern consistent with autosomal dominant inheritance. Penetrance appears to be close to 100% but the expression is extremely variable with some patients manifesting only minor phenotypic characteristics. We observed variable expression among the members of one and the same family. This wide variability in clinical pictures can not be explained with the presence of different mutations. This may be due to variations in other genes interfering with neurofibromin functions. Some authors suggest that functions of the three embedded genes (EVI2A, EVI2B and OMGP) and their relationship with NF1 may participate in the modification of NF1 function (5). Besides the search for homologous loci in the human genome has shown that NF1 related with loci on chromosomes 2, 12, 14, 15, 20, 21 and 22 (6, 7). Expression of NF1 gene was found in many human tissues, including brain, kidney, WBC, skin fibroblasts, spleen, lung, muscle and in some tumors (neuroblastoma, melanoma, thymoma, neurofibroma, breast cancer) (4). Most observed mutations in NF1 patients are point mutations, but some cases are reviewed with large deletions of the gene. A strong genotype/phenotype correlation has been not established. A large number of neurofibromas have been reported as a specific sign of NF1 patients with deletions over 700kb, suggesting that deletion of an unknown gene in the NF1 region may affect tumor initiation or development (8). Skeletal deformities have been found in a very small number of patients. In the literature 5 patients with constitutional chromosomal rearrangements identified by cytogenetic methods have been reported. (8, 9, 10, 11, 12, 13).

At present no medical treatment is available to prevent or reverse the characteristic lesions of NF1. Critical to the management of youngsters with NF1 is the

testing of intellectual and cognitive skills, as well as evaluating general coordination, speech and language development, vision and hearing, with prompt referrals for special assistance appropriate to deficits that are found. Problems as school performance difficulties and speech impediments are the most important to warrant vigorous intervention. The genetic counselling is very important especially in familial cases, the including of affected individuals in habilitative programs will help them for their social adaptation. The supplying of prenatal diagnosis in reproductive age will have a great social and economical effect.

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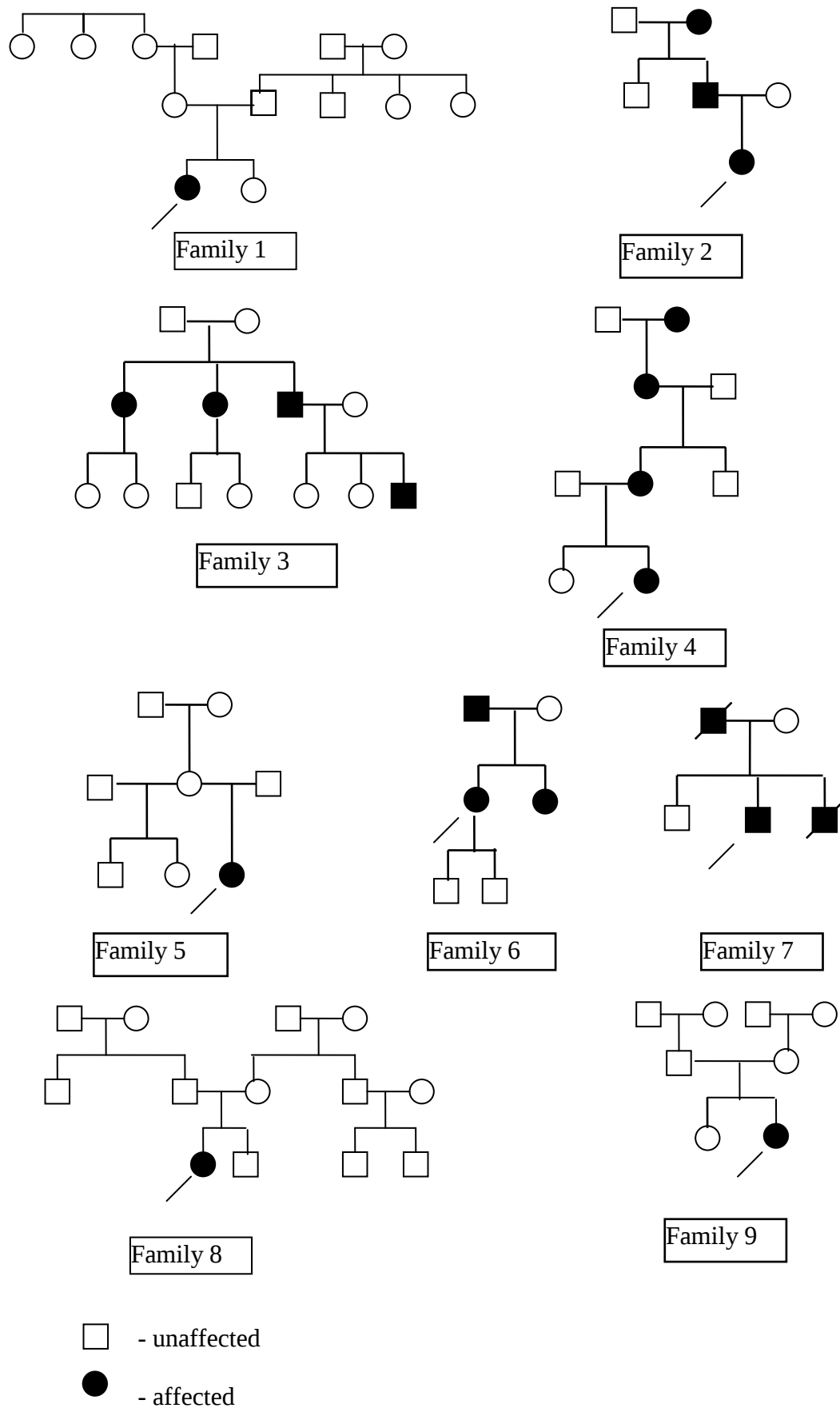
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**Table 1.** Clinical findings in the patients

|                                                                                                                                                                                                | case 1 | case 2                                       | case 3          | case 4                   | case 5 | case 6 | case7                             | case 8 | case 9 |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------|----------------------------------------------|-----------------|--------------------------|--------|--------|-----------------------------------|--------|--------|
| <b>Pigmentation</b><br>- cafe au lait spots<br>- axillary freckling<br>- other freckling<br>-hyperpigmentation<br>(overlying neurofibroma)                                                     | +      | +,+f, +pgm<br>+f, +pgm<br>+f, +pgm           | +<br>+f         | +, +m, +mgm              | +      | +      | +, +f, +b                         | +      | +      |
| <b>Neurofibromas</b><br>- cutaneous<br>- deep<br>- diffuse<br>= orbital/ periorbital<br>= other craniofacial<br>=paraspinal/cervical<br>=paraspinal/ thoracic<br>=abdominal<br>=limb           | +      | +f, +pgm<br>+, +pgm<br>+<br><br>+pgm<br>+pgm | +<br><br>+<br>+ | +m, +mgm<br>+m<br><br>+m |        | +      | +, +b<br>+<br>+<br><br>+<br><br>+ | +      | +      |
| <b>Central nervous system tumors</b><br>- glioma<br>- other orbit tumor                                                                                                                        |        |                                              |                 |                          | +      |        |                                   |        |        |
| <b>Other benign tumors</b><br>- leiomyoma<br>- polycystic ovary<br>Malignancy<br>- breast cancer<br>- neurosarcoma<br>- lung                                                                   |        | +pgm<br>+pgm                                 |                 |                          |        | +      |                                   |        |        |
| <b>Ocular</b><br>- Lisch nodules<br>- ptosis                                                                                                                                                   |        | +pgm                                         | +               |                          | +      | +      |                                   | +      |        |
| <b>Skeletal</b><br>- short stature<br>- macrocephaly<br>- craniofacial dysplasia<br>- spine<br>=vertebral dysplasia<br>=scoliosis/<br>kyphoscoliosis<br>- pectus excavatum<br>- other skeletal | +      | +, +f<br>+                                   | +               | +m                       | +      |        | +                                 | +      | +      |
| <b>Neurologic</b><br>- seizures<br>- mental retardation<br>- learning disability<br>- speech impediment                                                                                        | +      |                                              | +               | +                        |        |        | +                                 |        | +      |

This table is a summary of the clinical symptoms included in our protocol: + - symptom found in proband; m - in the mother; f - in the father; pgm –

**Figure 1.** Pedigrees of the reported families. Families 1, 5, 8 and 9 with sporadic NF1; families 2, 3, 4, 6 and 7 represent familial cases.



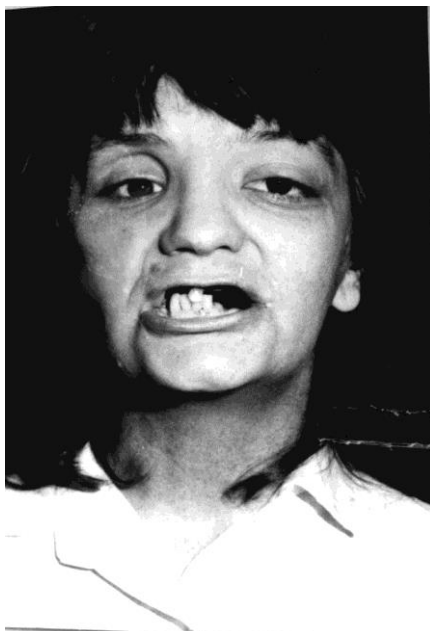
**Figure 2a and 2b.** Patient 1, a girl aged 18: a pectus and spinal deformity and a big hunch.



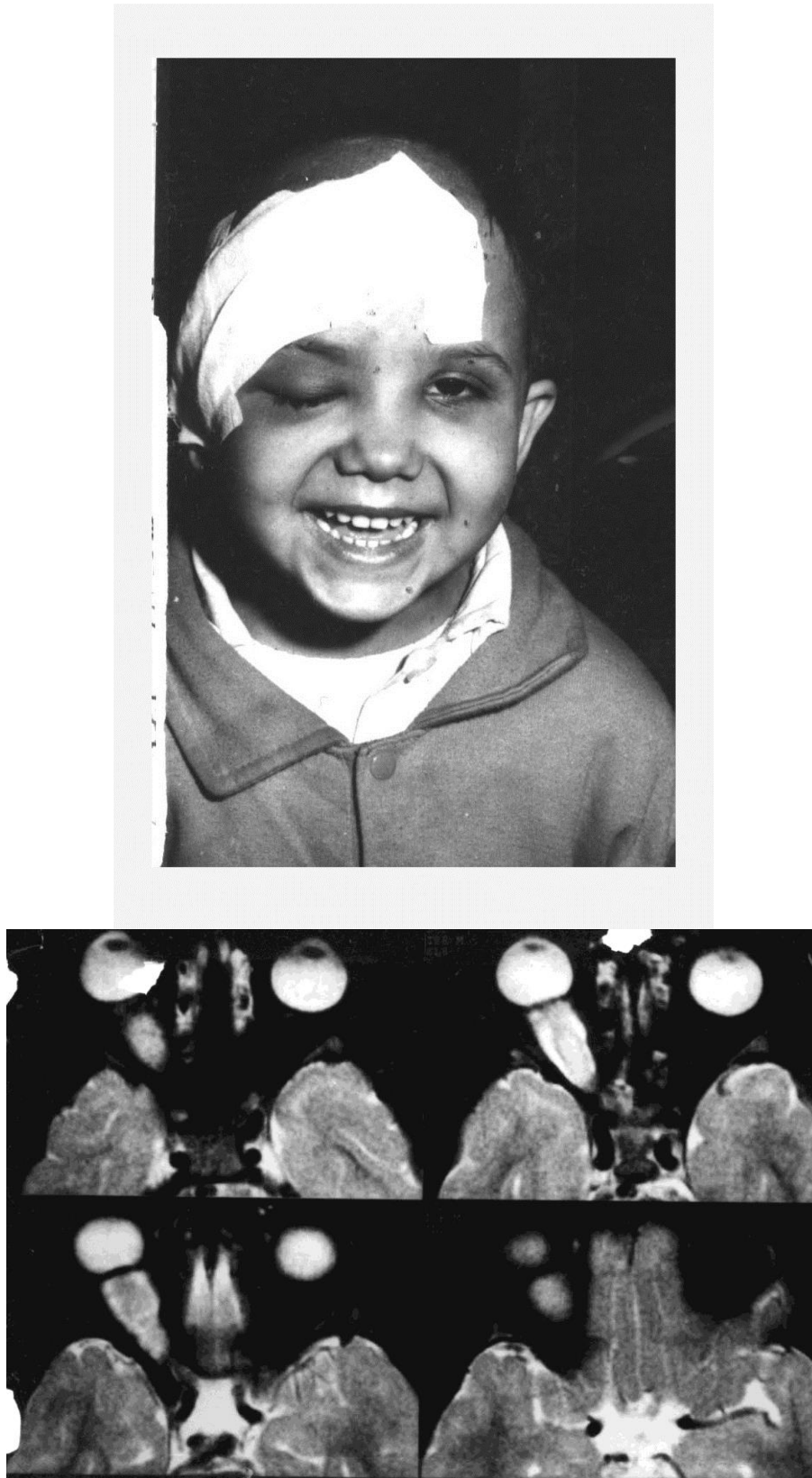
**Figure 3.** Patient 3, a boy aged 10: a neurofibromas on the left eyelid and of the lower lip.



**Figure 4a and 4b.** The mother of patient 4: facial asymmetry, exophthalm on the left eye, dental anomalies (a) and palatal defect after extirpation of a fibroma (b).



**Figure 5a and 5b.** Patient 5, a girl aged 4 with optic glioma: CT of the head (a) and after operation (b).



**Figure 6.** Patient 6, a woman with cafe-au lait spots, neurofibromas, leiomyoma uteri, polycystic ovary and breast carcinoma



**Figure 7a and 7b.** Patient 7, a man with NF1: facial asymmetry (a) and MR in the patrnal grandmother; mgm - in the

