DOI: 10.20514/2226-6704-2021-12-2-93-103 УДК 616.833-006.38.03

Р.Н. Мустафин

ФГБУЗ «Башкирский государственный медицинский университет»,
Уфа, Россия

КЛИНИЧЕСКИЕ МАСКИ НЕЙРОФИБРОМАТОЗА 1-ГО ТИПА

R.N. Mustafin

Bashkir State Medical University, Ufa, Russia

Clinical Masks of Neurofibromatosis Type 1

Резюме

Нейрофиброматоз 1-го типа является самым распространенным аутосомно-доминантным опухолевым синдромом, встречающимся с частотой 1 на 3000 населения. Особенностью клинических проявлений болезни является постепенное появление признаков и выраженный клинический полиморфизм от стертых и атипичных форм до тяжелых классических проявлений. В данном обзоре рассмотрены заболевания, симптомы которых значительно схожи с нейрофиброматозом 1-го типа, в связи с чем важным методом для дифференциальной диагностики является молекулярная диагностика болезни. Поскольку 10% случаев заболевания обусловлены крупными делециями локуса 17q11.2, помимо секвенирования гена *NF1* необходимо проведение зависимой от лигирования мультиплексной амплификации зонда. В большинстве случаев начальными проявлениями нейрофиброматоза 1-го типа являются множественные пигментные пятна, которые на протяжении многих лет могут быть единственными внешними признаками болезни. В связи с этим могут быть ошибочно установлены диагнозы, для которых характерны данные пигментные изменения: синдромы Блума, LEOPARD, Карнея, Костелло, Коудена, Легиуса, Ниймеген, Нунан, Пейтца-Егерса, Сильвера-Рассела, кардио-фацио-кожный синдром. Обнаружение подкожных нейрофибром может стать основанием для неверной диагностики схожих по клинике синдромов Легиуса и множественной эндокринной неоплазии. Кроме того, множественные липомы являются специфическими проявлениями липоматозов Маделунга или Деркума, семейного ангиолипоматоза, этиология которых считается неизвестной. Сделано предположение, что эти заболевания являются атипичными формами нейрофиброматоза 1-го типа, поскольку ряд авторов описали идентификацию мутаций в гене *NF1* у пациентов со множественным липоматозом. Поэтому важное значение имеет широкое внедрение в клиническую практику возможности молекулярно-генетической идентификации болезни для выявления случаев нейрофиброматоза 1-го типа, не соответствующих принятым NIH (National Institute of Health) критериям диагностики. Наиболее перспективно создание панели с исследованием всех генов, мутации в которых могут вызывать схожие с нейрофиброматозом 1-го типа проявления. Ранняя диагностика заболевания необходима для своевременного начала лечения и предотвращения тяжелых проявлений, поскольку в клиническую практику внедряются эффективные методы противоопухолевой терапии, такие как ингибиторы митоген-активируемой киназы.

Ключевые слова: *ген NF1, дифференциальная диагностика, липоматоз, мутации, нейрофиброматоз 1-го типа, секвенирование*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 25.08.2021 г.
Принята к публикации 24.12.2021 г.

Для цитирования: Мустафин Р.Н. КЛИНИЧЕСКИЕ МАСКИ НЕЙРОФИБРОМАТОЗА 1-ГО ТИПА. Архивъ внутренней медицины. 2022; 12(2): 93-103. DOI: 10.20514/2226-6704-2021-12-2-93-103

*Контакты: Рустам Наилевич Мустафин, e-mail: ruji79@mail.ru
*Contacts: Rustam N. Mustafin, e-mail: ruji79@mail.ru
ORCID ID: https://orcid.org/0000-0002-4091-382X

Abstract

Neurofibromatosis type 1 is the most common autosomal dominant tumor syndrome. The prevalence of the disease is 1 in 3000 people. Neurofibromatosis type 1 is characterized by the gradual appearance of signs of the disease and pronounced clinical polymorphism from erased and atypical forms to severe classical manifestations. The review is devoted to the consideration of diseases, the manifestations of which are significantly similar to neurofibromatosis type 1, and therefore, molecular diagnosis of the disease is an important method for differential diagnosis. To make a diagnosis of neurofibromatosis type 1, it is necessary to find mutations in the *NF1* gene using sequencing. In 10% of cases, neurofibromatosis type 1 is caused by large deletions of the 17q11.2 locus, therefore, multiplex ligation-dependent probe amplification is also necessary. Typically, the initial manifestations of neurofibromatosis type 1 are multiple café-au-lait spots, which may be the only external signs of the disease for many years. Therefore, patients with neurofibromatosis type 1 may be mistakenly diagnosed with diseases for which these pigmentary changes are characteristic: Bloom, LEOPARD, Carney, Costello, Cowden, Legius, Nijmegen, Noonan, Peitz-Jägers, Silver-Russell, cardio-facio-cutaneous syndromes. The detection of subcutaneous tumors can become the basis for an incorrect diagnosis of the clinically similar Legius syndrome and multiple endocrine neoplasia. In addition, multiple lipomas are specific manifestations of Madelung or Dercum lipomatosis, familial angiolipomatosis, the etiology of which is considered unknown. Therefore, I assume that these diseases are atypical forms of neurofibromatosis type 1, since a number of authors have described the identification of mutations in *NF1* gene in patients with multiple lipomatosis. Therefore, it is important to widely introduce into clinical practice the possibility of molecular genetic identification of the disease in order to identify cases of neurofibromatosis type 1 that do not meet the diagnostic criteria adopted by the NIH. It is promising to create a panel for the study of all genes, mutations in which can cause manifestations similar to neurofibromatosis. Early diagnosis of the disease is necessary for timely initiation of treatment and prevention of severe manifestations, since effective methods of antitumor therapy of neurofibromatosis type 1, such as inhibitors of mitogen-activated kinase, are being introduced into clinical practice.

Key words: *NF1 gene, differential diagnosis, lipomatosis, mutations, neurofibromatosis type 1, sequencing*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 25.08.2021

Accepted for publication on 24.12.2021

For citation: Mustafin R.N. Clinical Masks of Neurofibromatosis Type 1. The Russian Archives of Internal Medicine. 2022; 12(2): 93-103. DOI: 10.20514/2226-6704-2021-12-2-93-103

AMP — adenosine monophosphate; NF1 — neurofibromatosis type 1

Introduction

Neurofibromatosis type 1 (NF1) is the most common hereditary tumor syndrome with autosomal dominant inheritance pattern. The global average incidence of NF1 is 1 per 3,000 people [1]. NF1 is caused by germline heterozygous mutations in the *NF1* gene, which is located at 17q11.2 and includes 280,000 bp and 57 exons. Mature mRNA of this gene is 11,000 bp long and is translated into the tumor suppressor protein neurofibromin [2]. The *NF1* gene is characterized by increased mutability, therefore, 50% of NF1 cases are sporadic due to *de novo* mutations in the germ cells of parents [3].

Neurofibromin regulates RAS-cyclic AMP (cyclic adenosine monophosphate) pathway, MAPK/ERK kinase cascade, adenylate cyclase and cytoskeletal assembly. The main domain of this protein is GRD (GAP (GTP-ase activating protein) related domain) that converts GTP-bound RAS oncogenes into GDP-bound (inactivated) forms [4]. The pathogenesis of NF1 is caused by the effect of neurofibromin deficiency (due to *NF1* mutations) on the hyperactivation of RAS oncogenes that increase AKT (RAC-alpha serine/threonine-protein kinase)/mTOR (mammalian target of rapamycin) and RAF (rapidly accelerated fibrosarcoma)/MEK (mitogen-activated protein kinase) signaling. As a result, the risk of developing tumors increases [2].

NF1 is characterized by complete penetrance by the age of five [5], when specific signs of the disease develop. These include café-au-lait macules (CALM), freckles, Lisch nodules, neurofibromas, optic nerve gliomas, and specific skeletal anomalies (sphenoid wing dysplasia, thinning of cortical bone, congenital pseudarthrosis). Diagnosis of NF1 is clinically confirmed by the presence of two of these signs or one sign in the case of first-degree blood relatives with NF1. These criteria are established by the National Institutes of Health (NIH) [1].

Specific features of NF1 include the development of new symptoms with age, as well as a pronounced variability of clinical presentations even in patients with an identical mutation and in members of the same family [1, 2, 6, 7], with the exception of monozygotic twins who have coinciding manifestations of NF1 even in the development of malignant neoplasms [8]. CALM are detected in 98% of NF1 patients [9], specific cutaneous or subcutaneous neurofibromas in 95%, plexiform neurofibromas

in 50% [10], spinal neurofibromas in 35%, and optic nerve gliomas in 18% [9]. NF1 patients are characterized by high risk of malignant neoplasms (MNs), especially of aggressive type such as MPNST (malignant peripheral nerve sheath tumor), that develops in 13% of patients, most often degenerating from plexiform neurofibromas [11]. Moreover, on average, in 10% of cases, somatic mutations in the *NF1* gene in individuals without NF1 cause sporadic MNs that are resistant to standard pharmacotherapy [4].

Differential diagnosis of pigment spots in neurofibromatosis type 1

CALM are detected in 3% of healthy newborns [12]. Since the average incidence of NF1 is 0.033% [1], CALM in most cases are not associated with a germline mutation in the *NF1* gene, which can lead to a wrong diagnosis of NF1 in children. There are a number of diseases with clinical signs similar to NF1, for which CALM are a typical symptoms or may develop in some patients. For the purposes of differential diagnosis, hereditary tumor syndromes with similar signs have to be considered above all. Clinical signs of NF1 are similar to those of neurofibromatosis type 2, patients with NF2 also develop CALM, however, in smaller size and numbers (Figure 1). This disease is caused by mutations in the *NF2* gene (that encodes schwannomin and is located at 22q12.2) [13]. The clinical presentation in Legius syndrome (NF1-like syndrome) is also very similar to that of NF1: multiple CALM or freckling, macrocephaly, facial dysmorphism, cognitive and behavioral disorders. This disease develops due to the mutations in the *SPRED1* gene that includes 7 exons and is localized at 15q3.2. The gene product (like neurofibromin) works as a negative regulator of RAS-MAPK signaling pathways [14].

In addition to NF1 and neurofibromatosis type 2, multiple CALM were described in cases of other RASopathies: Noonan syndrome (mutations in the *PTPN11* tyrosine phosphatase gene, localization 12q24.3), Costello syndrome (mutations in *HRAS* oncogene localized at 11p15.5), cardiofaciocutaneous syndrome (mutations in *BRAF* genes (encodes BRAF oncogene, locus 7q34)), *MAP2K1* (encodes mitogen-activated protein kinase, locus 15q22.31), *MAP2K2* (locus 19p13.3), *KRAS* (encodes KRAS oncogene, locus 12p12.1) [12]. RASopathies include LEOPARD syndrome (Lentigines, Electrocardiographic conduction abnormalities, Ocular hypertelorism, Pulmonic stenosis, Abnormal genitalia, Retardation of growth, Deafnes) when multiple lentigines (brown spots) on the face (Figure 2) are caused by mutations in the *PTPN11* (protein-tyrosine phosphatase non-receptor 11) gene. More than 65% of patients with LEOPARD syndrome have major missense mutations in the *PTPN11* gene — Tyr272Cys and Thr468Met. Like in NF1, the signs of LEOPARD syndrome also include skeletal anomalies, neuroblastomas, and hemoblastoses [15].

CALM and sun-sensitive butterfly-shaped facial rash are typical for Bloom's tumor syndrome that is caused by mutations in the *BLM* gene (locus 15q26.1), whose product has helicase activity [16]. Multiple CALM are also found in patients with other hereditary tumor syndromes: Fanconi anemia (affected *FANCA* gene (Fanconi anemia complementation group, locus 16q24.3)),

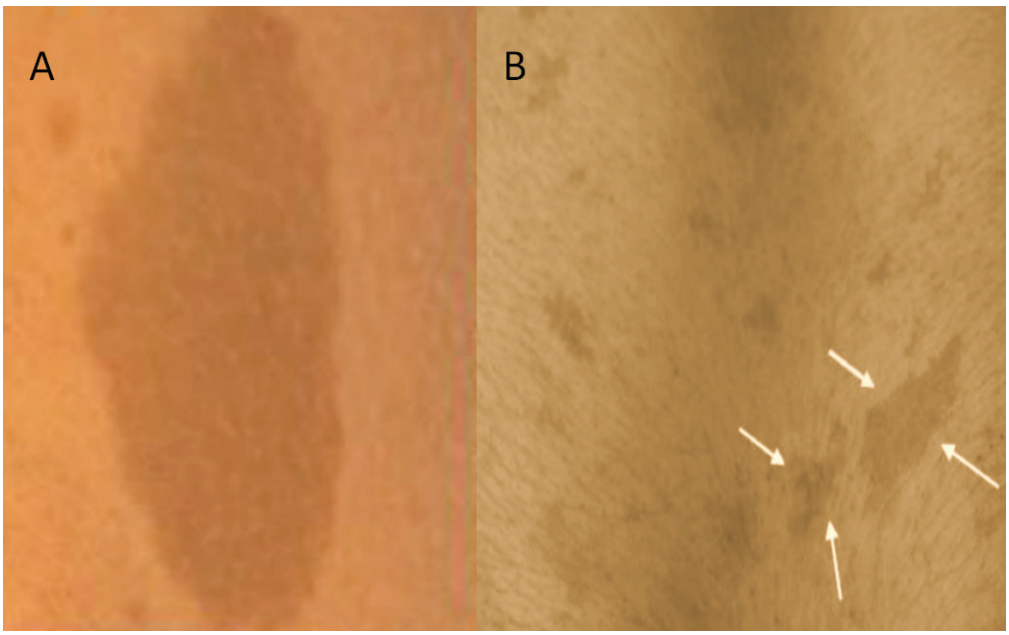

Figure 1. *Comparative characteristics of café-au-lait spots in neurofibromatosis type 1 (A) and neurofibromatosis type 2 (B) [13]*

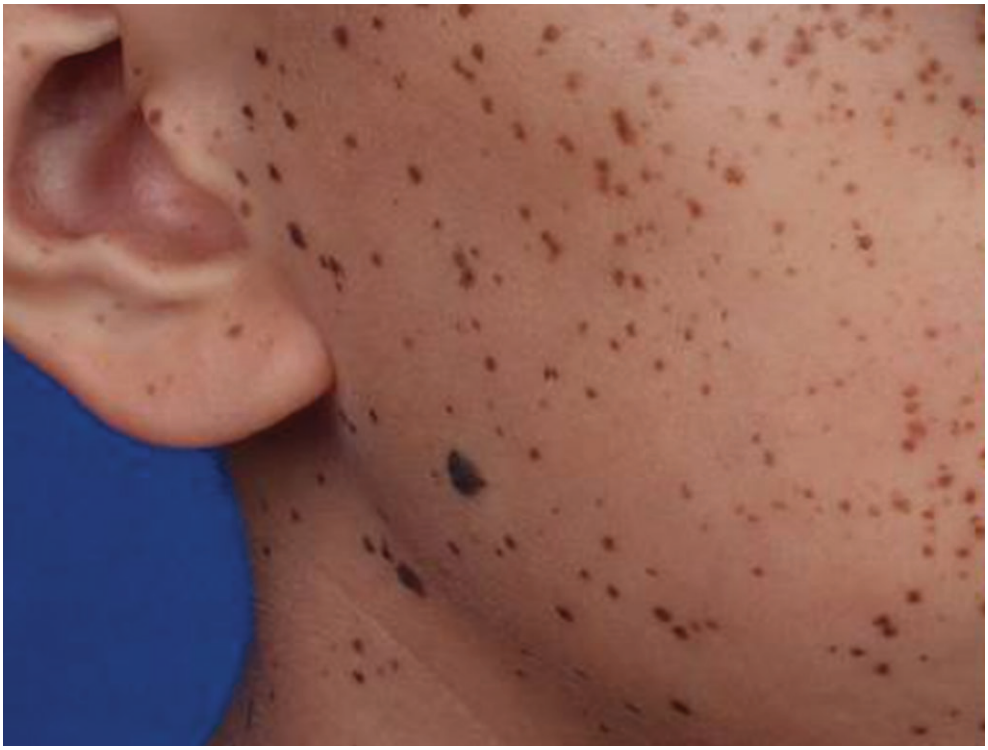

Figure 2. *Typical brown pigmented spots on the face in LEOPARD syndrome [15]*

Nijmegen syndrome (*NBN* gene (Nijmegen breakage syndrome, 8q21.3)) [17], Lynch syndrome (*MSH2* (mutS homolog 2, 2p21); *MSH6, MLH1, PMS2* genes) [18], Cowden syndrome (*PTEN* gene, 10q23.31) [19], Peutz-Jeghers syndrome (*STK11* gene encodes tumor suppressive serine-threonine kinase 11, locus 19p13.3) [16], Gorlin-Goltz syndrome (*PTCH1* gene, 9q22.32) [20]. CALM are also detected in 84% of cases of ataxia-telangiectasia (Louis-Bar syndrome), which is caused by mutations in the *ATM* gene (localization 11q22.3) that encodes serine-threonine protein kinase [21]. In cases of tuberous sclerosis, CALM are also detected in addition to typical depigmented spots [20]. Tuberous sclerosis is caused by mutations in tumor suppressor genes *TSC1* (localization 9q34) or *TSC2* (16p13.3) and its incidence is 1:6000 people [22].

Multiple CALM are typical signs of McCune-Albright-Braytsev syndrome (caused by a mutation in the *GNAS* gene (Guanine Nucleotide binding protein, Alpha Stimulating activity polypeptide, localization 20q13.32) [12]), Silver-Russell syndrome (caused by hypermethylation of the *H19* gene (11p15.5, tumor suppressor long non-coding RNA) [23], Carney syndrome (*PRKAR1A* gene, protein kinase cAMP-dependent type 1 regulatory subunit, 17q24.2) [20]. A familial case of the development of multiple CALM was described; the lesion was caused by a germline mutation in the *MAP2K2* gene that encodes mitogen-activated protein kinase involved in neurofibromin regulatory pathways [24]. Mutations in the *MAP2K2* gene are typical for Costello syndrome [12]. However, in the case described by the authors, CALM was the only sign of the disease [24]. CALM can also be found in patients with Marfan syndrome (fibrillin-1 gene, *FBN1*, 15q21), Gaucher's disease (glucosylceramidase beta gene, *GBA*, 1q22) and Hunter disease (iduronate sulfatase gene, *IDS*, Xq28) [16]. Since sporadic skin or subcutaneous tumors that can be confused with neurofibromas and lead to the diagnosis of NF1 cannot be excluded in any individuals with the diseases described above, a differential diagnosis is required, which is based on molecular genetic identification of a germline mutation in DNA isolated from blood WBC.

Differential diagnosis of tumors in neurofibromatosis type 1

Tumors that are similar to NF1 both in appearance and in pathogenesis develop in cases of type 2 neurofibromatosis. They can include NF1-like cutaneous neurofibromas, nodular schwannomas from peripheral nerves, and specific plaques (irregular, pigmented lesions circumscribed from the surrounding skin (Figure 3)). A characteristic difference between neurofibromatosis type 2 and NF1 is the development of schwannomas of acoustic nerves [25]. In tuberous sclerosis, facial angiofibromas (many reddish papules in the area of the chin, cheeks, nose, and nasolabial folds), gingival fibromas, subungual fibromas, and shagreen plaques on the skin

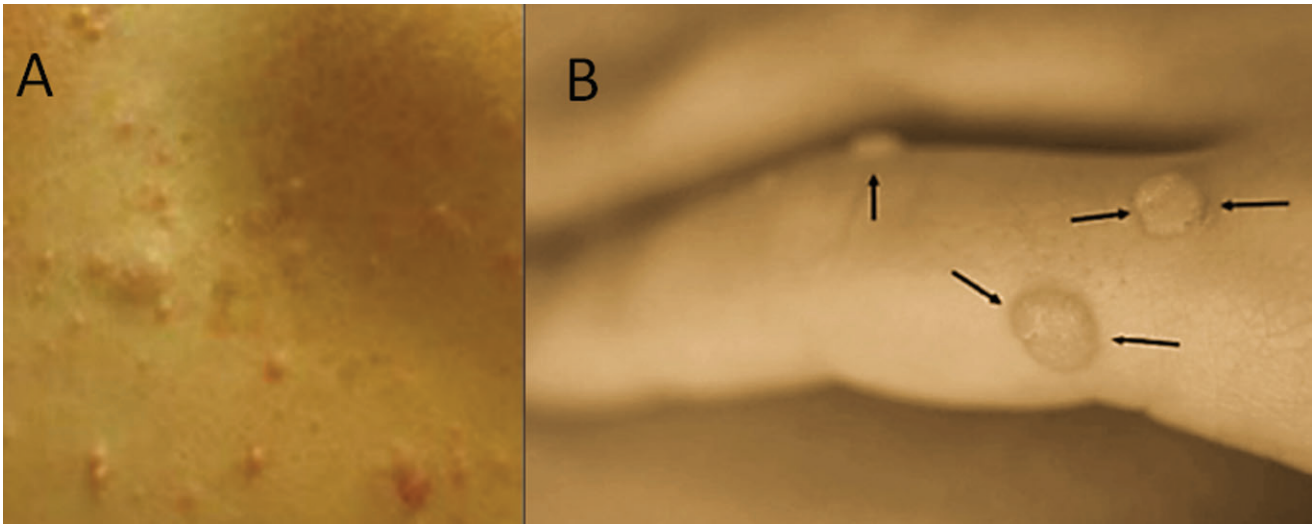

Figure 3. *Cutaneous neurofibromas in neurofibromatosis type 1 (A) [12] and classic cutaneous plaques in neurofibromatosis type 2 (B) [13]*

can also be confused with signs of NF1 [26]. In addition to CALM, Carney syndrome is characterized by pigmented tumors on the skin that may resemble pigmented neurofibromas [20]. In cases of Legius syndrome, multiple lipomas develop that are similar to subcutaneous neurofibromas [14].

NF1 types with subcutaneous neurofibromas depending on the location of the lesion may resemble the clinical presentation of different lipomatoses. In patients with Madelung's disease, lipomas are typically located on the lower body, legs and neck (proximal form), thighs, hands and knee joints (distal form), forearms, lower body, thighs and lower legs (central form) [27]. Like NF1, Madelung's disease can be also accompanied with polyneuropathy [28, 29] and cognitive impairment [30]. Multiple painful subcutaneous lipomas are also typical for Dercum's disease, which was described as early as 1892 and has an autosomal dominant pattern of inheritance, similar to NF1. This disease is subdivided into diffuse, generalized nodular, localized nodular, and periarticular types [31].

In addition to Dercum's disease, a number of authors describe familial angiolipomatosis with an autosomal dominant inheritance with no accurate identification of the genetic causes of this disease. It is assumed that they are based on NF1 [32, 33]. It can be assumed that Madelung's and Dercum's diseases are also atypical forms of NF1. This is evidenced by information on the role of mast cells in the development of angiolipomas in Dercum's disease [34] and familial angiolipomatosis [35], since mast cells are also important in the development of neurofibromas [36].

Other hereditary tumor syndromes can also cause multiple lipomas. Familial multiple lipomatosis (FML) with the incidence of 1:50,000 people [37] may be caused by atypical hereditary retinoblastoma. A family was described with a splice site mutation in the *RB1* gene (encodes the tumor suppressor protein RB, locus 13q14.2) accompanied by the development of many lipomas with incomplete penetrance in regard to retinoblastoma [38]. FML is also found in cases of multiple endocrine neoplasia with loss of heterozygosity of the *MEN1* gene (locus 11q13.1, encodes the tumor suppressor protein menin) in some tumors [39]. A recent publication describes a case of genetically confirmed Cowden syndrome (mutation c.195C>A (p.Y65*) in the *PTEN* gene) with multiple CALM and subcutaneous lipomas. Immunohistochemical results revealed no loss of heterozygosity for the *PTEN* gene in tumors [19].

Therefore, since the genetic basis of a number of lipomatoses has not yet been established, but an autosomal dominant type of inheritance was determined, it can be assumed that they are one of the types of NF1 and other hereditary tumor syndromes. To confirm this assumption, mutations in the *NF1* gene and other tumor suppressor genes in all patients with multiple lipomas should be searched for. At the same time, there are cases when no mutations in the *NF1* gene are found with a typical NF1 clinical presentation with CALM, freckles, neurofibromas, and Lisch nodules [40], as well as cases of familial lipomatosis with an autosomal dominant type of inheritance and with the absence of mutations in *NF1, SPRED1,* and *PTEN* genes [41]. This suggests the need to develop a full panel of molecular genetic tests for differential diagnosis of various diseases with signs similar to NF1. Table 1 includes the characteristics of all the abovementioned diseases with a clinical presentation characterized by the presence of CALM and/or tumor syndrome. To develop a differential diagnostic panel for NF1, molecular genetic testing of genes is required that can be affected by mutations causing these diseases (Table 1).

Table 1. *Neurofibromatosis type 1 differential diagnoses*

Disease (mutated gene, localization)	Pigmented cutaneous manifestations (difference from NF1*)	Tumors and tumor-like formations (difference from NF1)
Familial angiolipomatosis (unknown)	not typical	multiple lipomas (histologically angiolipomas)
Ataxia-telangiectasia (*ATM*, 11q22.3)	CALM**	leukemias, carcinomas
Bloom's syndrome (*BLM,* 15q26.1)	CALM, a rash on the face of the "butterfly" type	leukemias
Gorlin-Golts syndrome (*PTCH1,* 9q22.32)	CALM	basal cell skin cancer, medulloblastoma
Gaucher disease (*GBA,* 1q22)	CALM	not typical
Dercum disease (unknown)	not typical	multiple painful lipomas (histologically angiofibrolipomas)
Cardio-facio-cutaneous syndrome (*BRAF*-7q34, *MAP2K1*-15q22.31, *MAP2K2*-19p13.3, *KRAS*-12p12.1)	multiple CALM	not typical
Carney syndrome (*PRKAR1A*, 17q24.2)	CALM on the face	pigmented skin tumors, heart myxomas, pituitary adenomas
Costello syndrome (*HRAS,* 11p15.5)	multiple CALM	skin papillomas
Cowden syndrome (*PTEN,* 10q23.31)	CALM	skin trichilemmomas (on the face and ears), thyroid and breast cancer, endometrial cancer, hamartomas, intestinal polyps, multiple lipomas
Lynch Syndrome (*MSH2,* 2p21)	multiple CALM	colon cancer, endometrial and ovarian cancer
Legius syndrome (*SPRED1*, 15q3.2)	multiple CALM or freckles	multiple lipomas (histologically lipomas)
Madelung disease (unknown)	not typical	multiple subcutaneous lipomas with specific localization (not neurofibromas histologically)
McCune-Albright-Braitse syndrome (*GNAS*, 20q13.32)	large CALM	not typical
Marfan syndrome (*FBN1*, 15q21)	CALM	not typical
Multiple endocrine neoplasia (*MEN1,* 11q13.1)	not typical	multiple lipomas (lipomas histologically)
Neurofibromatosis type 2 (*NF2,* 22q11.2)	CALM (fewer and smaller spots)	NF1-like cutaneous neurofibromas (fewer), nodular schwannomas (from large nerve trunks), plaques (pigmented)
Nijmegen syndrome (*NBN*, 8q21.3)	multiple CALM	rhabdomyosarcoma, lymphoma, leukemias
Noonan syndrome (*PTPN11*, 12q24.3)	multiple CALM	neuroblastoma, leukemias
Peutz-Jeghers syndrome (*STK11*, 19p13.3)	CALM, pigmented spots on the lips and oral mucosa	polyps and hamartomas of the gastrointestinal tract, colon cancer, pancreas cancer, breast and ovary cancer
Hereditary retinoblastoma (*RB1,* 13q14.2)	not typical	multiple lipomas (histologically lipomas), retinoblastoma (retina malignant tumor)
Silver-Russell syndrome (*H19,* 11p15.5)	multiple CALM	not typical
Tuberous sclerosis (*TSC1*-9q34, *TSC2*-16p13.3)	depigmentation spots along with CALM	angiofibromas (localized on the face), fibromas (located on the gums and under the nails), internal organs hamartomas
Fanconi anemia (*FANCA,* 16q24.3)	CALM multiple CALM	squamous cell carcinoma, leukemias, Wilms' tumor and brain tumors
Hunter syndrome (*IDS,* Xq28)	CALM CALM	not typical
LEOPARD**** syndrome (*PTPN11,* 12q24.3)	multiple lentigines	neuroblastoma (malignant tumor, unlike benign neurofibromas)

Note: NF1* — neurofibromatosis type 1; CALM — café-au-lait macules, LEOPARD**** — Lentigines, Electrocardiographic conduction abnormalities, Ocular hypertelorism, Pulmonic stenosis, Abnormal genitalia, Retardation of growth, Deafnes)

Identification of atypical forms of neurofibromatosis type 1

Results of histological examinations of subcutaneous tumors in NF1 revealed the presence of atypical signs of the disease in the form of liponeurofibromas. For example, analysis of 130 neoplasm samples from various NF1 patients demonstrated that the microscopic pattern in 24.6% of cases can be described as liponeurofibromas. These changes are most often found in patients of advanced age and in female patients. At the same time, intratumoral fat deposits differ in morphology and size in comparison with subcutaneous tissue during light microscopy [42]. Histological results also demonstrated atypical neurofibromas consisting of cells with hyperchromic nuclei, with a large number of recurrent chromosomal aberrations including deletion of the 9p21.3 locus that includes *CDKN2A/B* genes. It should be noted that 9p21.3 deletion is a specific sign of MPNST, therefore, these atypical neurofibromas [11] are characterized by frequent malignant transformation [43].

Due to the possibility of detection the mutations in the *NF1* gene, clinical signs of NF1 that do not meet the NIH diagnostic criteria are described. NF1 patients with multiple lipomas are described [44, 45]. In 2021, sequencing of the *NF1* gene in two patients from the same family with lipomatosis and CALM revealed the missense mutation c.3445A>G (p.Met1149Val) [46]. Earlier in 2020, missense mutations leading to the replacement of methionine in position 1149 of neurofibromin (p.Met1149) were described in 62 NF1 patients with mild clinical course of the disease, mainly with CALM and with no visible plexiform neurofibromas and gliomas [47]. In 2019, 135 NF1 patients from 103 unrelated families were described; they had identical three-nucleotide deletion of c.2970_2972del resulting in methionine depletion in neurofibromin (p.Met992del). All patients are characterized by atypical clinical presentation with no cutaneous, subcutaneous, or spinal neurofibromas, as well as optic nerve gliomas. However, 38.8% of patients had cognitive impairments, and 4.8% had brain tumors not related to optic nerves [1]. In 2019, Trevisson E. et al. identified the missense mutation c.3112A>G (p.Arg1038Gly) in 7 NF1 patients with CALM as the only sign of the disease [48].

In 2009, Upadhyaya M. et al., while examining NF1 patients with spinal plexiform neurofibromas, determined the association of missense and splicing mutations in the *NF1* gene in patients with scarce clinical signs of the disease that did not meet the NIH diagnostic criteria [49]. In 2015, Pinna V. et al. examined 786 NF1 patients and found among them 6 unrelated patients with identical missense mutation c.5425C>T (p.Arg1809Cys) with a mild course of the disease with characteristic CALM and freckling, but with no skin or plexiform neurofibromas, no Lisch nodules, skeletal anomalies, or gliomas of optic nerves [50]. There were cases of NF1 with inapparent clinical signs with no visible skin or plexiform neurofibromas, with a three nucleotide deletion in exon 17 of the NF1 gene (c.2970-2972 delAAT) that results in the loss of one amino acid, methionine (p.Met991) in neurofibromin [5]. A missense mutation with an arginine amino acid substitution in an identical position (p.Arg1809) in 136 patients with NF1 causes one typical feature of NF1 such as only multiple CALMs, with no visible skin or plexiform neurofibromas. These patients were characterized by Noonan-like syndrome (25%); they also had increased risk of developing pulmonary artery stenosis and short stature [3]. It is noteworthy that multiple pigmented spots, short stature, and pulmonary artery stenosis are also specific for LEOPARD syndrome [51].

Genophenotypic correlations in NF1 were also determined for microdeletions of the 17q11.2 locus together with the *NF1* gene and its flanking neighboring genes that are detected in 10% of all NF1 patients. These patients have more pronounced signs of the disease with cognitive deficiency and facial dysmorphism [7], as well as early manifestation of tumors [52]. The 3 most common types of microdeletions are the following: type 1 as 1.4 megabases in size, flanked proximally by NF1-REPa and distally by NF1-REP-c; type 2 as 1.2 megabases in size, with deletion of *NF1*, *SUZ12* and *SUZ12P* genes; type 3 as 1.0 megabases in size, with breakpoint regions in paralogous areas in the middle of NF1-REP-b and distally of NF1-REP-c [53]. Type 1 is detected in 70–80% of cases, type 2 in 10–23%, and type 3 in 1–4%. The reason is non-allelic homologous recombination (NAHR) between low copy repeats during meiosis (types 1 and 3) or mitosis (type 2) [7]. More severe manifestations of NF1 with extended deletions of the entire *NF1* gene with neighboring loci [53] may indicate the impact of the loss of genes located in the area of the microdeletion on the pathogenesis of NF1. In particular, in cases of type 1 microdeletion, the *HCA66* gene is lost, which has a protein product that interacts with the tumor suppressor Apaf-1 (apoptic protease activating factor-1). Therefore, when *HCA66* is inactivated, cells become less susceptible to apoptosis, which contributes to the exacerbation of the tumor syndrome in NF1 [54].

Current diagnostic approaches and management of neurofibromatosis type 1

Since the clinical manifestations of NF1 may not meet the criteria established by NIH, one of the most important methods of diagnosing this disease is the molecular genetic test for the mutation that should be performed in all suspected cases. Since the disease is caused by germline heterozygous mutations in the *NF1* gene, DNA isolated from peripheral blood WBC is used to find said mutations. Subsequently, the detection of intragenic mutations is carried out using next-generation sequencing with Integrative genomics viewer software [55] and

confirmation of results via Sanger sequencing [56]. Since 10% of NF1 cases are caused by microdeletions at the 17q11.2 locus [7], multiplex ligation-dependent probe amplification (MLPA) is used to detect them with analysis of results by means of Coffalyser MLPA analysis software [57].

The identification of mutations in the *NF1* gene is important for the development of treatment for NF1 patients, since, in cases of nonsense mutations (up to 20% of all types of changes in NF1 [58]), the technique of terminating the translation of premature termination codons in the reading frame can be used. To this end, pseudouridylation, inhibition of nonsense-mediated mRNA decay, and suppressor tRNAs are used [59]. Management of cystic fibrosis with aminoglycosides demonstrated that the use of gentamicin in low doses in cases of nonsense mutations in the CFTR gene (formation of a stop codon at amino acid residues 542 and 553 of protein product) contributes to the translation of a protein of normal length in the amount of 25–35% of normal. This effect is associated with closely related mismatch of aminoacyl-tRNA with a premature termination codon [60]: deoxystreptamine ring of aminoglycosides connected to several amino sugars connects to the decoding center of the ribosome (acts as a proofreader for attaching only related aminoacyl-tRNAs to the peptidyl transferase center of ribosome). The effectiveness of gentamicin in restoring normal protein expression in the presence of a premature termination codon was proven in experiments on mice regarding the Duchenne muscular dystrophy, nephrogenic diabetes insipidus, hemophilia, retinal degeneration, *APC*-mediated colon cancer, Hurler syndrome. Other antibiotics that cause translational termination of premature termination codons include negamycin (binds to the small ribosomal subunit), spiramycin, josamycin, and tylosin. Suppression of translation of premature termination codons in mammalian cells without affecting translation termination in normal termination codons is caused by PTC124, known as ataluren. This agent demonstrated its effectiveness in restoring the translation of normal proteins in models of various monogenic diseases [59]. Antitumor activity is also demonstrated by tetracycline group antibiotics that inhibit protein synthesis in tumor mitochondria, thus causing a cytotoxic effect. Further, the analysis of a culture of MPNST cells from an NF1 patient demonstrated that doxycycline in combination with photodynamic effect caused by 5-aminolevulinic acid had a pronounced cytotoxic effect on tumor cells [61]. The suppression of translation of premature termination codons has been shown to be effective against tumor suppressor genes in other hereditary tumor syndromes [59], however, no such studies were conducted for NF1. However, in cases of deep intron mutations in the *NF1* gene that cause insertions of latent exons in mRNA, experimental studies on fibroblast and lymphocyte lines demonstrated the effectiveness of antisense oligomers in the restoration of normal splicing. These molecules specifically bind to new 5' splice sites required for insertion of latent exons and suppress them, preventing the formation of mutant mRNA [58, 62].

Currently, the only agent approved by the FDA (Food and Drug Administration) for the targeted therapy of NF1 is the ATP-independent inhibitor of mitogen-activated protein kinase (MEK) selumetinib [63]. This agent is recommended at a dose of 25 mg per 1 m^2 of body surface area. Back in 2016, the results of treatment of 24 NF1 pediatric patients with selumetinib were published. There were rare side effects in the form of acne, asymptomatically increased level of creatine kinase, and lesions of the gastrointestinal tract (GIT). After a course of treatment with 28-day cycles, 71% of children demonstrated a decrease in the size of neurofibromas [64]. The effectiveness of selumetinib in combination therapy with LDN-193189 (inhibitor of BMP2 receptor of type 1) was proven in vitro on MPNST (NF1-/-) cell line, while the isolated use of LDN-193189 gave no proper antiproliferative effect. Based on the results obtained, it is expected that selumetinib can be used in the complex chemotherapy of MPNST [65]. In 2020, Baldo F. et al. examined 17 children with plexiform neurofibromas during one year of treatment with selumetinib and observed a decrease in size (more than 20% of volume) of tumors in 16 out of 17 patients with NF1 [66]. In 2020, Santo V.E. et al described the effectiveness of selumetinib in the management of plexiform neurofibromas in 18 out of 19 patients with NF1 (95%) during the first 60–90 days of treatment [67]. In 2020, Gross A.M. et al., in a phase 2 open-label clinical trial of selumetinib on a continuous schedule (28-day cycles) in children with NF1, described a persistent decrease in the size of inoperable neurofibromas in 70% of patients (35 of 44) [68]. Selumetinib has been shown to be effective in the management of brain tumors in cases of NF1: in 36% (9 of 25) of patients with grade 1 pilocytic astrocytoma and in 40% (10 of 25) of patients with low-grade glioma [69]. Treatment with selumetinib (12 cycles) in 24 NF1 patients with spinal neurofibromas demonstrated 75% efficacy [70].

Gene therapy may become a promising technique for NF1management. The insertion of a full-length normal *NF1* gene using recombinant adeno-associated virus (rAAV) containing an expression cassette to replace mutant alleles and to restore neurofibromin function is difficult due to the large size of cDNA (8500 bp). Therefore, the use of truncated variants of *NF1* gene that retain functional domains is more favourable [58]. A panel of AAV vectors was used in vitro on MPNST cell lines and human Schwann cell lines to restore the Ras-GTPase activity of neurofibromin. As a result, significant restoration of the ability to suppress RAS oncogenes using neurofibromin domain was determined [71]. Partial restoration of their normal tumor suppressive function was demonstrated on cell lines of neurofibromas, upon

transfection of isolated domains GRD, CSRD, LRD, CTD of the *NF1* gene into their genomes. These recombinant transgene sequences can be designed to encode truncated functional proteins that can be easily packaged into viral vectors [72].

Conclusion

Neurofibromatosis type 1 is the most common hereditary tumor syndrome. A number of authors have described atypical manifestations of NF1, including those with multiple lipomas, as well as those that do not meet NIH criteria. Since no genetic etiology was established for a number of familial lipomatoses, it was suggested that they may be atypical signs of NF1 and other hereditary tumor syndromes. It is evidenced by the data of the results of the papers by different authors, presented in this review. To confirm this assumption, a standardized panel should be developed to search for mutations in tumor suppressor genes that are involved in diseases characterized by the development of multiple lipomas and/or CALM. Modern medicine requires wide implementation of methods available for patients for molecular genetic confirmation of NF1 diagnosis into clinical practice. It will allow early identification of the disease and the use of effective treatment methods with mitogen-activated protein kinase inhibitors.

Список литературы/ References:

1. Koczkowska M., Callens T., Gomes A. et al. Expanding the clinical phenotype of individuals with a 3-bp in-frame deletion of the NF1 gene (c.2970_2972del): and update of genotype-phenotype correlation. Genet Med. 2019; 21(4): 867-876. doi: 10.1038/s41436-018-0326-8.
2. Barrea C., Vaessen S., Bulk S. et al. Phenotype-Genotype Correlation in Children with Neurofibromatosis Type 1. Neuropediatrics. 2018; 49(3): 180-184. doi: 10.1055/s-0037-1620239.
3. Rojnueangnit K., Xie J., Gomes A. et al. High Incidence of Noonan Syndrome Features Including Short Stature and Pulmonic Stenosis in Patients carrying NF1 Missense Mutations Affecting p.Arg1809: Genotype-Phenotype Correlation. Hum Mutat. 2015; 36(11): 1052-63. doi: 10.1002/humu.22832.
4. Ratner N., Miller S.J. A RASopathy gene commonly mutated in cancer: the neurofibromatosis type 1 tumour suppressor. Nat Rev Cancer. 2015; 15(5): 290-301. doi: 10.1038/nrc3911.
5. Upadhyaya M., Huson S.M., Davies M. et al. An absence of cutaneous neurofibromas associated with a 3-bp inframe deletion in exon 17 of the NF1 gene (c.2970-2972 delAAT): evidence of a clinically significant NF1 genotype-phenotype correlation. The American Journal of Human Genetics. 2007; 80: 140–151. doi: 10.1086/510781.
6. Quintans B., Pardo J., Campos B. et al. Neurofibromatosis without Neurofibromas: Confirmation of a Genotype-Phenotype Correlation and Implications for Genetic Testing. Case Rep Neurol 2011;3(1):86-90. doi: 10.1159/000327557.
7. Buki G., Zsigmond A., Czako M. et al. Genotype-Phenotype Associations in Patients with Type-1, Type-2, and Atypical NF1 Microdeletions. Front. Genet. 2021; 12: 673025. doi: 10.3389/fgene.2021.673025.
8. Galbiati M., Lettieri A., Micalizzi C. et al. Natural history of acute lymphoblastic leukemia in neurofibromatosis type 1 monozygotic twins. Leukemia. 2013; 27(8): 1778-81. doi: 10.1038/leu.2013.55.
9. Tabata M.M., Li S., Knight P. et al. Phenotypic heterogeneity of neurofibromatosis type 1 in a large international registry. J Cl Insight 2020; 5(16): e136262. doi: 10.1172/jci.insight.136262.
10. Yu Y., Choi K., Wu J. et al. NF1 patient missense variants predict a role for ATM in modifying neurofibroma initiation. Acta Neuropathol 2020; 139(1): 157-174. doi: 10.1007/s00401-019-02086-w.
11. Beert E., Brems H., Daniels B. et al. Atypical neurofibromas in neurofibromatosis type 1 are premalignant tumors. Genes Chromosomes Cancer. 2011; 50(12): 1021-32. doi: 10.1002/gcc.20921.
12. Lalor L., Davies O.M., Basel D. et al. Café au lait spots: When and how to pursue their genetic origins. Clin. Dermatol. 2020; 38: 421-431. doi: 10.1016/j.clindermatol.2020.03.005.
13. Ruggieri M., Pratico A.D., Serra A. et al. Childhood neurofibromatosis type 2 (NF2) and related disorders: from bench to bedside and biologically targeted therapies. Acta Otorhinolaryngol. Ital. 2016; 36(5): 345-367. doi: 10.14639/0392-100X-1093.
14. Sumner K., Crockett D.K., Muram T. et al. The SPRED1 Variants Repository for Legius Syndrome. G3 (Bethasda). 2011; 1(6): 451-6. doi: 10.1534/ g3.111.000687.
15. Yue X., Zhao X., Dai Y. et al. Leopard syndrome: the potential cardiac defect underlying skin phenotypes. Hereditas. 2021; 158(1): 34. doi: 10.1186/s41065-021-00199-5.
16. Karalis A., Tischkowitz M., Millington G.W.M. Dermatological manifestations of inherited cancer syndromes in children. Br. J. Dermatol. 2011; 164: 245-256. doi: 10.1111/j.1365-2133.2010.10100.x.
17. Kuhlen M., Borkhardt A. Cancer susceptibility syndromes in children in the area of broad clinical use of massive parallel sequencing. Eur. J. Pediatr. 2015; 174(8): 987-97. doi: 10.1007/s00431-015-2565-x.
18. Baris H.N., Barnes-Kedar I., Toledano H. et al. Constitutional Mismatch Repair Deficiency in Israel: High Proportion of Founder Mutations in MMR Genes and Consanguinity. Pediatr. Blood Cancer. 2016; 63(3): 418-27. doi: 10.1002/pbc.25818.
19. Yotsumoto Y., Harada A., Tsugawa J. et al. Infantile macrocephaly and multiple subcutaneous lipomas diagnosed with PTEN hamartoma tumor syndrome: A case report. Mol. Clin. Oncol. 2020; 12: 329-335. doi: 10.3892/mco.2020.1988.
20. Dos Santos A.C.E., Heck B., Camargo B.D., et al. Prevalence of Café-au-Lait Spots in children with solid tumors. Genet. Mol. Biol. 2016; 39: 232-8. doi: 10.1590/1678-4685-GMB-2015-0024.
21. Greenberger S., Berkun Y., Ben-Zeev B. et al. Dermatologic manifestations of ataxia-telangiectasia syndrome. J. Am. Acad. Dermatol. 2013; 68: 932-6. doi: 10.1016/j.jaad.2012.12.950.
22. Ehninger D., Silva A. Rapamycin for treating Tuberous Sclerosis and Autism Spectrum Disorders. Trends Mol Med. 2011; 17: 78-87.
23. Luk H.M., Yeung K.S., Wong W.L. et al. Silver-Russell syndrome in Hong Kong. Hong Kong Med. J. 2016; 22: 526-33. doi: 10.12809/hkmj154750.
24. Takenouchi T., Shimizu A., Torii C. et al. Multiple café au lait spots in familial patients with MAP2K2 mutation. Am. J. Med. Genet. 2014; 164A: 392-6.
25. Bettegowda C., Upadhayaya M., Evans D.G. et al. Genotype-Phenotype Correlations in Neurofibromatosis and Their Potential Clinical use. Neurology 2021; 10.1212/WNL. 0000000000012436.
26. Portocarrero L.K.L., Quental K.N., Samorano L.P. et al. Tuberous sclerosis complex: review based on new diagnostic criteria. An. Bras. Dermatol. 2018; 93: 323-331. doi: 10.1590/abd1806-4841.20186972.

27. Батюшин М.М., Пасечник А.В., Садовничая Н.А. Множественный липоматоз (болезнь Маделунга) и поражение почек. Два клинических случая. Нефрология. 2013; 17(5): 89-95. DOI: 10.24884/1561-6274-2013-17-5-89-95.
Batyushin M.M., Pasechnik A.V., Sadovnichaya N.A. Multiple lipomatosis (Madelung's disease) and kidney injury. Two clinical cases. Nephrologiya. 2013; 17(5): 89-95. DOI: 10.24884/1561-6274-2013-17-5-89-95 [In Russian].
28. Sawyer S.L., Ng A.C-H., Innes A.M. et al. Homozygous mutations in MFN2 cause multiple symmetric lipomatosis associated with neuropathy. Hum. Mol. Genet. 2015; 24(18): 5109-14. doi: 10.1093/hmg/ddv229.
29. Liu Q., Lyu H., Xu B. et al. Madelung Disease Epidemiology and Clinical Characteristics: a Systemic Review. Aesthetic Plast Surg. 2021; 45(3): 977-986.
30. Hasbani G.E., Assaker R., Nithsoontorn S. et al. Madelung's Disease Leading to Presenile Dementia in a Non-alcoholic Patient. Med. Arch. 2019; 73(4): 285-287. doi: 10.5455/medarh.2019.73.285-287.
31. Hansson E., Svensson H., Brorson H. Review of Dercum's disease and proposal of diagnostic criteria, diagnostic methods, classification and management. Orphanet J Rare Dis. 2012; 7: 23. doi: 10.1186/1750-1172-7-23.
32. Maheshwari S., Arora E.L. Exploring a Tumor Spectrum in Patient with Familial Angiolipmatosis. Asian J. Neurosurg. 2019; 14(3): 886-889. doi: 10.4103/ajns.AJNS_295_17.
33. Garib G., Siegal G.P., Andea A.A. Autosomal-dominant familial angiolipomatosis. Cutis. 2015; 95: E26–29.
34. Beltran K., Herbst K.L. Differentiating lipedema and Dercum's disease. Int. J. Obes. (Lond). 2017; 41: 240–245. doi: 10.1038/ijo.2016.205.
35. Herbst K.L., Feingold K.R., Anawalt B. et al. Subcutaneous Adipose Tissue Diseases: Dercum Disease, Lipedema, Familial Multiple Lipomatosis, and Madelung Disease. 2019. Endotext (Internet). PMID: 31895524. Bookshelf ID: NBK552156.
36. Wei C.J., Gu S.C., Ren J.Y. et al. The impact of host immune cells on the development of neurofibromatosis type 1: The abnormal immune system provides an immune microenvironment for tumorigenesis. Neurooncol. Adv. 2019; 1(1): vdz037. doi: 10.1093/noajnl/vdz037.
37. Ware R., Mane A., Saini S. et al. Familial multiple lipomatosis — a rare syndrome diagnosed on FNAC. International Journal of Medical Science and Public Health. 2016; 5: 367–369.
38. Genuardi M., Klutz M., Devriendt K. et al. Multiple lipomas linked to an RB1 gene mutation in a large pedigree with low penetrance retinoblastoma. Eur J Hum Genet. 2001; 9: 690–694. doi: 10.1038/sj.ejhg.5200694.
39. Morelli A., Falchetti A., Weinstein L. et al. RFLP analysis of human chromosome 11 region q13 in multiple symmetric lipomatosis and multiple endocrine neoplasia type 1-associated lipomas. Biochem Biophys Res. Commun. 1995; 207:363-368. doi: 10.1006/bbrc.1995.1196.
40. Oktenli C., Gul D., Deveci M.S. et al. Unusual features in a patient with neurofibromatosis type 1: multiple subcutaneous lipomas, a juvenile polyp in ascending colon, congenital intrahepatic portosystemic venous shunt, and horseshoe kidney. Am. J. Med. Genet. A. 2004; 127: 298–301. doi: 10.1002/ajmg.a.30008.
41. Lee C.H., Spence R.A.J., Upadhyaya M., et al. Familial multiple lipomatosis with clear autosomal dominant inheritance and onset in early adolescence. B.M.J. Case Rep. 2011; 2011: bcr1020103395. doi: 10.1136/bcr.10.2010.3395.
42. Lee S., Bak H., Ahn S.K. Liponeurofibroma: Clinicopathological features and histogenesis. J Dermatol. 2018; 45(4): 416-424. doi: 10.1111/1346-8138.14238.
43. Miettinen M.M., Antonescu C.R., Fletcher C.D.M. et al. Histopathologic evaluation of atypical neurofibromatous tumors and their transformation into malignant peripheral nerve sheath tumor in patients with neurofibromatosis 1 — a consensus overview. Hum Pathol 2017; 67: 1-10. doi: 10.1016/j.humpath.2017.05.010.
44. Miraglia E., Fino P., Lopez T. et al. Multiple lipomas in a patient with Neurofibromatosis Type 1. G Ital Dermatol Venereol. 2019; 154(6): 734-735. doi: 10.23736/S0392-0488.18.05869-8.
45. Miraglia E., Calvieri S., Giustini S. Lipomas in neurofibromatosis type 1: a single-institution experience. G Ital Dermatol Venereol. 2020; 155(3): 375-376. doi: 10.23736/S0392-0488.18.06044-3.
46. Ramirez E., Morris S.M., Turner T.N., et al. Familial Lipomas Without Classic Neurofibromatosis-1 Caused by a Missense Germline NF1 Mutation. Neurol Genet 2021; 7(3): e582. doi: 10.1212/NXG.0000000000000582.
47. Koczkowska M., Callens T., Chen Y. et al. Clincal spectrum of individuals with pathogenic NF1 missense variants affecting p.Met1149, p.Arg1276, and p.Lys1423: genotype-phenotype study in neurofibromatosis type 1. Hum Mutat 2020; 41(1): 299-315. doi: 10.1002/humu.23929.
48. Trevisson E., Morbidoni V., Forzan M. et al. The Arg1038Gly missense variant in the NF1 gene causes a mild phenotype without neurofibromas. Mol Genet Genomic Med 2019; 7(5): e616. doi: 10.1002/mgg3.616.
49. Upadhyaya M., Spurlock G., Kluwe L. et al. The spectrum of somatic and germline NF1 mutations in NF1 patients with spinal neurofibromas. Neurogenetics 2009; 10(3): 251-63. doi: 10.1007/s10048-009-0178-0.
50. Pinna V., Lanari V., Daniele P. et al. p.Arg1809Cys substitution in neurofibromin is associated with a distinctive NF1 phenotype without neurofibromas. Eur J Hum Genet 2015; 23: 1068-1071. doi: 10.1038/ejhg.2014.243.
51. Rahal N., Sadi A., Cohen-Barak E. et al. LEOPARD syndrome: A report of a case with a novel PTPN11 mutation. JAAD Case Rep 2021; 11: 57-59. doi: 10.1016/j.jdcr.2021.03.022.
52. Kang E., Kim Y.M., Seo G.H. et al. Phenotype categorization of neurofibromatosis type 1 and correlation to NF1 mutation types. J Hum Genet. 2020; 65(2): 79-89. doi: 10.1038/s10038-019-0695-0.
53. Pasmant E., Sabbagh A., Masliah-Planchon J. et al. Role of noncoding RNA ANRIL in genesis of plexiform neurofibromas in neurofibromatosis type 1. J Natl Cancer Inst 2011; 103(22): 1713-22. doi: 10.1093/jnci/djr416.
54. Sharafi P., Ayter S. Possible modifier genes in the vatiration of neurofibromatosis type 1 clinical phenotypes. J Neurogenet 2018;32(2):65-77. doi: 10.1080/01677063.2018.1456538.
55. Robinson J.T. Integrative genomics viewer. Nat. Biotechnol. 2011; 29: 24-26. doi: 10.1038/nbt.1754.
56. Tsipi M., Poulou M., Fylaktou I. et al. Phenotypic expression of a spectrum of Neurofibromatosis Type 1 (NF1) mutations identifies through NGS and MLPA. J. Neurol. Sci. 2018; 395: 95-105. doi: 10.1016/j.jns.2018.10.006.
57. Coffa J., van den Berg J. Analysis of MLPA data using novel software coffalyser.NET by MRC-Holland. Modern Approaches To Quality Control. 2011; 125-150.

58. Walker J.A., Upadhyaya M. Emerging therapeutic targeting for neurofibromatosis. Expert. Opin. Ther. Targets. 2018; 22(5): 419-437. doi: 10.1080/14728222.2018.1465931.
59. Keeling K.M., Xue X., Gunn G., et al. Therapeutics based on stop codon readthrough. Annu. Rev. Genomics. Hum. Genet. 2014; 15: 371-394. doi: 10.1146/annurev-genom-091212-153527.
60. Crawford D.K., Mullenders J., Pott J. et al. Targeting G542X CFTR nonsense alleles with ELX-02 restores CFTR function in human-derived intestinal organoid. J. Cyst. Fibros. 2021; 20(3): 436-442. doi: 10.1016/j.jcf.2021.01.009.
61. Lee M.J., Hung S.H., Huang M.C. et al. Doxycycline potentiates antitumor effect of 5-aminolevulinic acid-mediated photodynamic therapy in malignant peripheral nerve sheath tumor cells. PLoS One. 2017; 12(5): e0178493. doi: 10.1371/journal.pone.0178493.
62. Brosseau J.P., Liao C.P., Le L.Q. Translating current basic research into future therapies for neurofibromatosis type 1. Br. J. Cancer. 2020; 123: 178-186. doi: 10.1038/s41416-020-0903-x.
63. Galvin R., Watson A.L., Largaespada D.A. et al. Neurofibromatosis in the Era of Precision Medicine: Development of MEK Inhibitors and Recent Successes with Selumetinib. Curr. Oncol. Rep. 2021; 23(4): 45. doi: 10.1007/s11912-021-01032-y.
64. Dombi E., Baldwin A., Marcus L. et al. Activity of Selumetinib in Neurofibromatosis Type1-Related Plexiform Neurofibromas. N. Engl. J. Med. 2016; 375(26): 2550-2560. doi: 10.1056/NEJMoa1605943.
65. Ahsan S., Ge Y., Tainsky M.A. Combinatorial therapeutic targeting of BMP2 and MEK-ERK pathways in NF1-associated malignant peripheral nerve sheath tumors. Oncotarget. 2016; 7(35): 57171-57185. doi: 10.18632/oncotarget.11036.
66. Baldo F., Grasso A.G., Wiel L.C. et al. Selumetinib in the Treatment of Symptomatic Intractable Plexiform Neurofibromas in Neurofibromatosis Type 1: A Prospective Case Series with Emphasis on Side Effects. Paediatr. Drugs. 2020; 22(4): 417-423. doi: 10.1007/s40272-020-00399-y.
67. Santo V.E., Passos J., Nzwalo H. et al. Selumetinib for plexiform neurofibromas in neurofibromatosis type 1: a single-institution experience. J. Neurooncol. 2020; 147(2): 459-463. doi: 10.1007/s11060-020-03443-6.
68. Gross A.M., Wolters P.L., Dombi E. et al. Selubetinib in Children with Inoperable Plexiform Neurofibromas. N. Engl. J. Med. 2020; 382(15): 1430-1442. doi: 10.1056/NEJMoa1912735.
69. Fangusaro J., Onar-Thomas A., Poussaint T.Y. et al. Selumetinib in paediatric patients with BRAF-aberrant or neurofibromatosis type-1-associated recurrent, refractory, or progressive low-grade gliomas: a multicentre, phase 2 trial. Lancet Oncol. 2019; 20(7): 1011-1022. doi: 10.1016/S1470-2045(19)30277-3.
70. Jackson S., Baker E.H., Gross A.M. et al. The MEK inhibitor selumetinib reduces spinal neurofibroma burden in patients with NF1 and plexiform neurofibromas. Neurooncol. Adv. 2020; 2(1): vdaa095. doi: 10.1093/moajnl/vdaa095.
71. Bai R.Y., Esposito D., Tam A.J. et al. Feasibility of using NF1-GRD and AAV for gene replacement therapy in NF1-associated tumors. Gene Ther. 2019; 26(6): 277-286. doi: 10.1038/s41434-019-0080-9.
72. Cui X.W, Ren J.Y., Gu Y.H. et al. NF1, Neurofibromin and Gene Therapy: Prospects of Next-Generation Therapy. Curr. Gene Ther. 2020; 20(2): 100-108. doi: 10.2174/1566523220666200806111451.