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Evaluation of Clinical Findings and NF1 Genetic Variants in Patients Diagnosed with Neurofibromatosis Type 1: a Single-center Experience

Nörofibromatozis Tip 1 Tanılı Hastalarda Klinik Bulgular ve NF1 Genetik Varyantlarının Değerlendirilmesi: Tek Merkez Deneyim

Ünal Akça[1] | Aslıhan Sanrı[2] | Emre Sanrı[3] | Elif Pekmezci Yazgı[4] | Gülfer Akça[3]

[1]Samsun University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Neurology, Samsun, Türkiye
[2]Samsun University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Genetics, Samsun, Türkiye
[3]Samsun University Faculty of Medicine, Department of Pediatrics, Samsun, Türkiye
[4]Samsun University Faculty of Medicine, Department of Child and Adolescent Psychiatry, Samsun, Türkiye

Sorumlu Yazar | Correspondence Author
Ünal Akça
drunalakca@gmail.com
Address for Correspondence: Division of Pediatric Neurology, Department of Pediatrics, Faculty of Medicine, Samsun University, Samsun, Türkiye.

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Evaluation of Clinical Findings and NF1 Genetic Variants in Patients Diagnosed with Neurofibromatosis Type 1: a Single-center Experience

ABSTRACT

Objective: Neurofibromatosis type 1 is a common neurocutaneous syndrome with multisystemic involvement that facilitates tumor formation. The aim of this study was to evaluate the demographic and clinical characteristics as well as genetic results of pediatric patients diagnosed with neurofibromatosis type 1.

Material and Method: This retrospective, cross-sectional descriptive study included 23 patients. Main disease criteria, clinical features, and genetic results obtained using next-generation sequencing and multiple-ligation probe amplification techniques were recorded. Information on zygosity, mutation types, variant positions, American College of Medical Genetics classification, and inheritance models were analyzed.

Results: Café-au-lait spots were present in all patients. Inguinal/axillary freckling was the second most common finding seen in 60.9% of patients. Lisch nodules were observed in patients older than six years, whereas choroidal abnormalities were common in younger patients. Optic glioma was found in 13% of patients and cutaneous neurofibromas in 21.7% of patients, which is lower than that observed in adult patients. Focal signal intensity image was more common in patients with cognitive impairment (Odds Ratio: 4.50, Confidence Interval 95% 0.659-30.715, *p=0.02*). Epilepsy was diagnosed in two patients and treated with a single drug. Macrocephaly (30.4%) was the most common cranial deformity. Missense mutations (43.5%) were the most common, while one frameshift novel mutation (c.6771del. K2257Nfs*8) was identified.

Conclusion: The emergence of new genetic technologies and advances in health care may facilitate earlier diagnosis of neurofibromatosis and the prediction and treatment of complications that may develop.

Keywords: FASI, Neurofibromatosis, Rasopathy, Variant.

ÖZET

Amaç: Nörofibromatozis tip 1, tümör oluşumunu kolaylaştıran multisistemik tutulumu olan yaygın bir nörokutanöz sendromdur. Bu çalışmanın amacı, nörofibromatozis tip 1 tanısı alan çocuk hastaların demografik ve klinik özelliklerinin yanı sıra genetik sonuçlarını da değerlendirmektir.

Gereç ve Yöntem: Bu retrospektif, kesitsel tanımlayıcı çalışmaya 23 hasta dahil edildi. Hastalık ana kriterleri, klinik özellikleri, yeni nesil dizileme ve çoklu ligasyona bağlı prob amplifikasyon teknikleri kullanılarak elde edilen genetik sonuçları kaydedildi. Zigosite, mutasyon tipleri, varyant pozisyonları, Amerikan Tıbbi Genetik Kurulu sınıflandırması ve kalıtım modellerine ilişkin bilgiler analiz edildi.

Bulgular: Café-au-lait lekeleri tüm hastalarda mevcuttu. Kasık/aksiller çillenme, hastaların %60,9'unda görülen ikinci en yaygın bulguydu. Lisch nodülleri altı yaşından büyük hastalarda gözlenirken, koroidal anormallikler daha küçük hastalarda yaygındı. Optik gliom hastaların %13'ünde, kutanöz nörofibromlar ise hastaların %21,7'sinde tespit edilmiş olup bu oran yetişkin hastalarda gözlenenden daha düşüktür. Bilişsel bozukluğu olan hastalarda fokal sinyal yoğunluğu görüntüsü daha yaygındı (Odds Ratio: 4.50, %95 Güven Aralığı 0.659-30.715, *p=0.02*). İki hastada epilepsi tanısı konmuş ve tek bir ilaçla tedavi edilmiştir. Makrosefali (%30,4) en sık görülen kraniyal deformite idi. Missense mutasyonlar (%43,5) en sık görülürken, bir çerçeve kayması yeni mutasyon (c.6771del. K2257Nfs*8) tanımlanmıştır.

Sonuç: Yeni genetik teknolojilerin ortaya çıkması ve sağlık hizmetlerindeki ilerlemeler nörofibromatozisin daha erken tanı almasını ve gelişebilecek komplikasyonların öngörülmesini ve tedavisini kolaylaştırabilir.

Anahtar Sözcükler: FASI, Nörofibromatozis, Rasopati, Varyant.

Introduction

Neurofibromatosis type 1 (NF1) is a common autosomal dominant neurocutaneous disorder with variable expression and complete penetrance. The prevalence is approximately 1 in 3,000 (1). In 95% of cases, at least two of the diagnostic criteria described by the National Institute of Health (NIH) in 1988 must be met (2). The diagnostic criteria include the presence of six or more café-au-lait spots (CALM) larger than 5 mm before puberty and larger than 15 mm after puberty, axillary or inguinal freckling, and the presence of two or more neurofibromas. Additionally, the presence of plexiform neurofibromas, optic gliomas, two or more lisch nodules, and bone findings such as sphenoid dysplasia, thinning of the long bone cortex, and the presence of NF1 in first-degree relatives are indicative of the condition (3). In 2021, Legius et al. revised diagnostic criteria due to its similarity with neurocutaneous disorders such as Legius syndrome, constitutional mismatch repair deficiency (CMMRD) syndrome. They highlighted the importance of clinical and heterozygous pathogenic variants, such as dystrophic scoliosis, choroidal anomalies, and focal signal intensity image (FASI), in the context of these disorders (4).

In some cases, learning disabilities, various skeletal anomalies, attention deficit and hyperactivity disorders, congenital heart diseases, malignant peripheral nerve sheath tumors, and hematologic malignancies have been identified as potential contributing factors (5). By the age of eight years, the major criteria of the disease are clear in patients (6). Although NF1 is a classic monogenic disorder in adulthood, clinical symptoms may vary within families (7,8). The etiology of this phenotypic variability remains poorly understood. Modifier genes, epigenetic variation, and environmental factors are believed to be involved (4,6).

Neurofibromatosis type 1 is the result of a defect in the functioning of the neurofibromin gene, which is located on the long arm of chromosome 17 (17q11.2) (9). The gene in fact functions as a GTPase catalyst and a negative regulator of the RAS/MAPK signaling pathway. A consequence of the loss of function in the neurofibromin gene is the hyperactivation of cell growth, proliferation, and differentiation, which in turn gives rise to the formation of abnormal structures (10). To date, the Human Gene Mismatch Database (HGMD) has cataloged over 3,000 pathogenic variants associated with NF1. Half of the identified genetic variants are familial, while the remaining half are de novo (11,12). Most reported mutations (93%) are small mutations, including missense, nonsense, insertion, deletion, and splicing mutations. The remaining 2% were intragenic, and 5% were large deletions involving NF1 and neighboring genes. These mutations can be identified by multiple ligation-dependent probe amplification (MLPA) (7). Patients with microdeletions are more likely to present with somatic overgrowth, malignant tumors, and dysmorphic features (13). This study aims to describe the clinical symptoms observed in patients with a NF1 genetic diagnosis and to analyze the genetic results.

Material and Method

This study evaluated 23 patients who were admitted to the pediatric neurology outpatient clinic of the Samsun University Pediatrics Department between June 2022 and June 2024 with NF1 clinical findings and whose NF1 gene pathological variants were detected by the pediatric genetic department. Initially, sequence analysis of the NF1 gene was performed for all patients. Genomic DNA was extracted from peripheral blood samples, and all exons of the NF1 gene, including exon-intron boundaries, were analyzed using next-generation sequencing (NGS). The obtained sequences were aligned to the reference genome (GRCh37/hg19), and variants were interpreted in accordance with the American College of Medical Genetics and Genomics (ACMG) guidelines.

For patients in whom no clinically significant variant was identified through sequencing, multiplex ligation-dependent probe amplification (MLPA) was conducted to detect potential deletions or duplications in the NF1 gene. MLPA was performed according to the manufacturer's protocol and results were compared to normal controls for interpretation. The inclusion criteria were as follows: the patients were required to be between the ages of 0 and 18 years and to be a patient whose NF1 diagnosis was confirmed by MLPA and NGS genetic tests. Patients with a clinical diagnosis of NF1 according to NIH (4) diagnostic criteria but without genetic testing were excluded from the study.

Patients were monitored on a regular basis by pediatricians, pediatric neurologists, and child psychiatrists. The patients were examined for any concomitant endocrinological, orthopedic, cardiological, cognitive, and neurological complications. The demographic findings, including age, gender, consanguineous marriage, the presence of NF1 in the family, physical examination findings, abdominal ultrasonography, brain magnetic resonance imaging, echocardiography results, cognitive and psychiatric tests, and treatments received, were analyzed in the patient file records. Genetic results were classified according to zygosity, mutation types, variant positions, ACMG classification, and inheritance types. All data were analyzed retrospectively.

The study was conducted in accordance with the ethical standards of the Samsun University Faculty of Medicine Ethics Committee, which approved the study on 26/06/2024 (decision number 2024/12/6). Prior to participation, informed consent was obtained from the legal guardians of all patients.

Statistical Analysis

The analyses were conducted using IBM SPSS Statistics 25.0. Numerical variables were expressed as mean ± standard deviation, while categorical variables were expressed as number and percentage. Tests were used to ascertain whether a relationship existed between the categorical variables and whether there were any significant differences between the demographic and clinical findings of the patients. The significance level was set at $p<0.05$.

Results

Demographic Characteristics

A total of 23 patients participated in the study, with 13 males (56.5%) and 10 females (43.5%). The mean age of the patients at the time of enrollment was 6.4 years (ranging from 1 to 14 years). 47.8% of the patients were less than six years old. 10 patients (43.5%) had no first-degree relatives with neurofibromatosis type 1.

Clinical Findings

All patients exhibited a minimum of six CALMs spots. Axillary or inguinal freckling was identified in 60.9% of patients. Upon examination of ocular involvement, 30.4% of patients exhibited Lisch nodules, while 13% demonstrated choroidal abnormalities. The mean age of patients with Lisch nodules was 11.5 years (range: 10-14 years), and the mean age of patients with choroidal abnormalities on optical coherence tomography was 3.6 years (range: 3-5 years). None of the patients exhibited severe visual loss or blindness. The frequency of NF1 findings is presented in Table I.

Table I. Neurofibromatosis type 1 Clinical Characteristics of Participants and Mean Age at Diagnosis.

	n	%	Mean age (years)
Female/Male	10/13		
6 CALMs	23/23	100	6.4
Freckling	14/23	60.9	7.9
Lisch nodule	7/23	30.4	11.6
Choroidal abnormalities	4/23	17.4	3.7
Cutaneous neurofibromas	5/23	21.7	8.8
Optic glioma	3/23	13.0	9.7
Sphenoid wing dysplasia	3/23	13.0	5.7
Long bone dysplasia	1/23	4.3	14.0
Epilepsy	2/23	8.7	8.6
Short stature	11/23	47.8	7.5
Macrocephaly	7/23	30.4	5.3
Scoliosis	6/23	26.0	8.2
Focal areas of high signal intensity	8/23	34.8	7.9
Attention deficit hyperactivity disorder	6/23	26.1	7.2
Pulmonary artery stenosis	2/23	8.7	12.5

Three patients presented with optic gliomas. All had pre-chiasmatic localization and did not receive chemotherapy due to the absence of visual acuity impairment. None exhibited proptosis, pupillary dysfunction, or optic atrophy. Two patients with optic gliomas had precocious puberty. The prevalence of cutaneous neurofibroma was 21.7%. The majority were located on the back and trunk. None had peripheral nerve sheath tumors, glomus tumors, or stromal tumors.

Scoliosis was observed in 26.1% of cases. Sphenoid wing dysplasia was observed in 13% of cases, with two patients exhibiting grade 1 and one patient exhibiting grade 2 dysplasia. Additionally, anterolateral curvature of the tibia was identified in a 14-year-old male patient.

The analysis of neurological anomalies revealed that learning retardation was present in 60.9% of

Table II. Comprehensive Clinical Characteristics of Patients

Patient	CALMs	Freckling	Ocular features	Tumors	Bone abnormalities	Short stature	Neurological abnormalities	Family history of NF1	FASI	Other lesions
1	+					+		+		Growth retardation
2	+	+	LN	CN	S		LD	+	+	ADHD
3	+		CA					+		Frontal bossing, hemangioma
4	+		CA		SWD			+		Dysmorphic face
5	+	+	LN	OG	SWD		LD	+	+	Dysmorphic face, premature puberty
6	+	+	LN			+	LD			
7	+	+	LN			+		+		Growth retardation
8	+			OG	S	+	LD		+	Macrocephaly, downward and slanting eyes, ADHD
9	+							+		
10	+	+		CN			LD			Macrocephaly
11	+	+					LD	+		Macrocephaly
12	+					+	LD		+	Macrocephaly, ADHD
13	+	+				+	LD, E		+	Brachycephaly, epilepsy, downward and slanting eyes, ADHD
14	+	+	CA							
15	+			CN			LD	+		Speech delay, ADHD
16	+	+				+	LD			Short stature, pectus excavatum, speech impairment, delayed walking.
17	+	+	LN	OG	S	+	LD		+	Pectus excavatum, scoliosis, hypertelorism, strabismus, premature puberty
18	+	+	CA		S	+	LD			Speech retardation, scoliosis, pectus excavatum, pes planus, ADHD
19	+	+			S, SWD	+		+	+	Polydactyly, dysmorphic face, epicanthus, tele canthus, depressed nasal root
20	+	+	LN				LD	+		Depressed nasal root, pulmonary artery stenosis, hypertelorism
21	+									Macrocephaly,
22	+			CN				+		Macrocephaly, speech retardation,
23	+	+	LN	CN	LBD, S	+	LD, E	+	+	Macrocephaly, pulmonary artery stenosis

LN: lisch Nodule, CA: Choroidal abnormalities, CN: Cutaneous neurofibromas, OG: Optic glioma, LBD: Long bone dysplasia's: sphenoid wing dysplasia, S: scoliosis, LD: learning disabilities, E: epilepsy, ADHD: Attention deficit hyperactivity disorder, FASI: Focal areas of high signal intensity

the participants, while no patient exhibited severe intellectual disability. Four patients were undergoing language therapy for speech retardation. Epilepsy was diagnosed in two patients. Both patients were monitored for seizures and remained seizure-free following single valproate treatment. FASI imaging was identified in 34.8% of patients undergoing neuroimaging. Six patients were followed up in the pediatric psychiatry clinic with a diagnosis of ADHD. Two patients were receiving risperidone, and two patients were receiving stimulant support.

The frequency of learning disabilities was found to be statistically significantly higher in patients with FASI images (odds ratio: 4.50, CI 95 %0.659-30.715, *p=0.02*). Macrocephaly was observed in 30.4% of the patients. One patient exhibited brachycephaly,

Table III. Evaluation of the Neurofibromatosis Type 1 Variant Mutations of the Participants

Patient	Age	Gender	Zygosity	Mutation	Protein	Mutation Type	Variant Position	ACMG Classification	References	Inheritance
1*	8	M	Heterozygous	c.7415del	p. P2472Lfs*17	Frameshift	Exon 50	Pathogenic	Reported	Paternal
2*	12	M	Heterozygous	c.2530C>T	p. L844F	Missense	Exon 21	Pathogenic	Reported	Maternal
3*	3	M	Heterozygous	c.4247C>T	p. P1416L	Missense	Exon 32	Likely Pathogenic	Reported	Maternal
4*	3	F	Heterozygous	c.1A>G	p. M1V	Missense	Exon 1	Pathogenic	Reported	Paternal
5**	12	M	Heterozygous			Deletion	Exon 24	Pathogenic	Reported	Maternal
6*	10	M	Heterozygous	c.1466A>G	p. Y489C	Missense	Exon 13	Pathogenic	Reported	De novo
7*	12	F	Heterozygous	c.2T>G	p.M1R	Missense	Exon 1	Pathogenic	Reported	Maternal
8*	7	F	Heterozygous	c.6771delA	p. K2257Nfs*8	Frameshift	Exon 45	Likely Pathogenic	Novel	De novo
9*	1	M	Heterozygous	c.2511G>A	p.W837*	Nonsense	Exon 21	Pathogenic	Reported	Maternal
10*	7	M	Heterozygous	c.5305C>T	p.R1769*	Nonsense	Exon 38	Pathogenic	Reported	De novo
11*	1	M	Heterozygous	c.62T>C	p. L21P	Missense	Exon2	VUS	Reported	Maternal
12*	4	F	Heterozygous	c.1466A>G	p. Y489C	Missense	Exon 13	Pathogenic	Reported	De novo
13**	3	M	Heterozygous	c.3709-2A>G		Splice Acceptor		Pathogenic	Reported	De novo
14**	5	M	Heterozygous	c.7458-1G>C		Splice Acceptor		Pathogenic	Reported	De novo
15*	8	M	Heterozygous	c.1882dup	p. Y628Lfs*6	Frameshift	Exon 17	Pathogenic	Reported	Maternal
16*	8	F	Heterozygous	c.3461A>T	p. N1154I	Missense	Exon 26	Likely Pathogenic	Reported	De novo
17*	10	F	Heterozygous	c.3834C>G	p. N1278K	Missense	Exon 28	Pathogenic	Reported	De novo
18**	4	M	Heterozygous			Deletion	Whole gene	Pathogenic	Reported	De novo
19**	2	M	Heterozygous			Deletion	Whole gene	Pathogenic	Reported	Maternal
20*	11	F	Heterozygous	c.7415del	p. P2472Lfs*17	Frameshift	Exon 50	Pathogenic	Reported	Paternal
21*	1	F	Heterozygous	c.4243A>T	p. N1415Y	Missense	Exon 32	Pathogenic	Reported	De novo
22*	3	F	Heterozygous	c.186del	p.L62*6	Frameshift	Exon 29	Pathogenic	Reported	Maternal
23*	14	M	Heterozygous	c.501del	p.C167Qfs*10	Frameshift	Exon 31	Pathogenic	Reported	Maternal

*Next-generation sequencing (NGS), ** Multiple ligation dependent probe amplification (MLPA)
ACMG: The American College of Medical Genetics and Genomics, F: female, M: male; VUS: Variant of Uncertain Significance

and one patient demonstrated frontal bossing. Pulmonary artery stenosis was identified in two patients. The comprehensive clinical findings of the patients are presented in Table II.

Genetic testing revealed that all patients exhibited heterozygous inheritance. A novel frameshift mutation was identified in one patient, who was subsequently classified as likely pathogenic according to ACMG. The remaining mutations were distributed as follows: 43.5% were missense, 26.1% were frameshift, 13% were deletions, 8.7% were nonsense, and 8.7% were splice acceptors. The mutations identified in this study are presented in Table III.

Discussion

Neurofibromatosis type 1 (NF1) is a multisystemic neurocutaneous disorder characterized by pigmentary changes, benign peripheral nervous system gliomas (also known as neurofibromas) and an increased risk of malignant tumors, as well as learning difficulties. The most prominent features are multiple café-au-lait spots and associated cutaneous neurofibromas. Neurofibromatosis type 1 is an autosomal dominant disease caused by pathogenic variants in the NF1 gene. The diagnostic criteria are met in the first year of life, with almost all patients fulfilling the criteria by the age of eight years (1,2).

CALMs are uniform hyperpigmented macules that typically manifest in the first year after birth and increase in size and number during early childhood. It has been reported that the probability of a CALM not reaching six in the first five years is low in individuals who are subsequently diagnosed with NF (14). In the present case series, more than six café-au-lait macules were observed in all patients, including those aged one year.

Inguinal and axillary freckles are defined as hyperpigmented macules in the form of clusters, which are typically smaller in size compared to CALMs, particularly in the fold areas. They are less

frequently observed in individuals younger than three years of age (15). In our study, the presence of freckles was observed in 60% of patients, with a mean age of 7.9 years. The mean age of patients without freckles was 3.7 years, which is consistent with the findings in the literature.

Ocular involvement represents the most significant finding associated with NF1, following the identification of cutaneous manifestations. Lisch nodules and choroidal anomalies, discernible through optical coherence tomography (OCT), are incorporated into the diagnostic criteria for NF1. The incidence of these anomalies is less than 10% in children under the age of six and 90% in adults (16). In our study, the incidence was 34.8%, with the youngest age of detection being eight years.

Choroidal anomalies are defined as clusters of melanocytes, which can be identified using OCT. In comparison to Lisch nodules, these anomalies are more prevalent in younger age groups and in pediatric cases (17). The mean age of the patients included in our study was 3.6 years, and it is postulated that this conclusion was reached due to the inability to perform the examination in younger patients. It is hypothesized that this will prove to be a more sensitive indicator of NF1 in younger patients with CALMs.

Individuals with NF1 are at an increased risk of developing both benign and malignant tumors over the course of their lifetime. The incidence of cancer is higher in those with NF1 than in the general population (18). Cutaneous neurofibromas are the most common intradermal benign tumors. They tend to occur just before puberty (19). They were observed in 21.7% of our patients, with a mean age at presentation of 9 years. Malignant transformation is not expected. Optic gliomas are low-grade pilocytic astrocytoma and occur in all visual pathways. In a study comprising 562 NF1 patients, the overall prevalence was determined to be 9.3%. Most localizations were prechiasmatic, with optic tract involvement representing the most common visual impairment (20). In our study, the prevalence of optic glioma was found to be 13%, with all cases exhibiting prechiasmatic involvement.

MPNSTs are characterized by severe pain, progressive hardening and rapid growth, arising from pre-existing plexiform or atypical neurofibromas. Differential diagnosis from benign cutaneous neurofibromas can be made by positron emission tomography. It typically develops in young adults (21). Our cohort did not include any individuals with MPNSTs, as the oldest participant was only 14 years old.

Bone abnormalities and short stature are also common findings associated with NF1. There is a high degree of clinical overlap between NF1 and other conditions, such as Legius syndrome, McCune Albright syndrome, Noonan syndrome, and CMMRD, which are associated with CALMs (22). Genetic investigations are becoming increasingly important in this context. The prevalence of scoliosis in individuals with NF1 has been reported to range from 10 to 25% (23). A reduction in birth weight and an increase in head circumference have been observed in infants born to mothers with NF1 (24). In our study, the prevalence of macrocephaly was found to be 30.1%, which is considerably higher than that observed in the general population.

Long bone dysplasia encompasses a range of conditions, including antero-tibial curvature, which may progress to medullary canal narrowing, cortical thickening and fractures (25). One of our patients exhibited this finding. Sphenoid wing dysplasia, which can lead to facial asymmetry, is another significant condition (26). It was identified in 13% of our patients. Short stature is a characteristic observed in patients with NF1. The underlying cause of this phenomenon is believed to be a significant reduction in the growth rate during puberty, particularly in males. It has been demonstrated that the impact of short stature is more pronounced, particularly in males with pronounced macrocephaly (27). In our patient cohort, no gender-based differences in short stature were identified.

Neurological abnormalities may manifest as cognitive impairments, learning difficulties and seizures. Although the risk of intellectual disability is slightly higher than the population average, a lower IQ level is a more realistic observation. Learning difficulties, attention deficits, speech disorders and impaired social skills are more prevalent (28). The series revealed a prevalence of learning disabilities in 65% of cases, with ADHD occurring in 30-40% of instances (29). The prevalence of these conditions

was found to be almost identical in our patient cohort. The incidence of seizures is twofold that observed in the general population. The number of cases exhibiting treatment resistance is low, and new-onset seizures may necessitate neuroimaging (30).

Pulmonary stenosis has the highest association with NF1 when congenital heart diseases are analyzed. A study of 493 patients revealed that 21 (4.2%) of them had both congenital heart disease and pulmonary stenosis (31). In the present study, pulmonary stenosis was identified in two patients. The patients in question were demonstrated to be more prone to exhibiting phenotypic characteristics associated with Noonan syndrome.

Neuroimaging features are summarized as increased brain volume and the presence of bright spots, which are associated with NF1. FASI is most frequently observed in the basal ganglia, cerebellum, and subcortical white matter in 40–95% of patients (32). It is hypothesized that this is associated with dysplastic glial proliferation and fluid increase, which are linked to vacuolar myelopathy. One of the most significant findings of our investigation is that learning disabilities and neurological complications are more prevalent in individuals with FASI. Similarly, two studies have demonstrated that patients with FASI exhibit lower IQ values and a higher prevalence of mental retardation (33,34).

In cases where a diagnosis is suspected, it has been deemed appropriate to either confirm the diagnosis or to perform targeted testing on the proband, rather than undertaking a comprehensive mutation range of the entire gene. It should be noted that a positive NF1 mutation test does not necessarily indicate the severity of the disorder or the potential for complications, with a few exceptions (12). Nevertheless, recent years have seen a proliferation of studies mapping nonsense mutations at specific codons in terms of their specificity in causing heart diseases, susceptibility to the Noonan phenotype, dysmorphic facial features or mental retardation (35-37). As genetic investigations become more prevalent, there is a corresponding increase in genotype-to-phenotype correlation studies.

Conclusion

Neurofibromatosis type 1 is a genetic disease with multisystemic involvement and an increased risk of malignancy. The necessity for genetic examinations in patients with CALM who do not meet the criteria for age-related NF1 is becoming increasingly apparent. The clinical, diagnostic, and predictive advances in healthcare facilitate the early recognition of disease complications and the planning of appropriate treatments. It is anticipated that the advent of new pharmaceuticals and a multidisciplinary approach to treatment will result in a significant reduction in the feared aspects of the disease, following the complete elucidation of the pathogenesis.

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