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A Systematic Literature Review of Neurofibromatosis Type 1

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ABSTRACT

Background: Neurofibromatosis type 1 is an autosomal disease caused by a mutation on chromosome 17, resulting in several clinical manifestations outlined in the diagnostic criteria and affecting other organ systems. ***Objective:*** This research aims to review the correlation between genetic mutations and the clinical presentations of NF1. ***Method:*** A total of 829 studies were identified through e-databases and filtered using PRISMA. ***Results:*** The selected studies yielded several key findings. Nine studies identified point mutations, and four noted microdeletions. Diagnostic NF1 features were confirmed in 12 studies, with frequent additional involvement, including neurological (10), cognitive/behavioral (12), dysmorphic features (8), cardiovascular (7), ocular (6), and endocrine (4). Frameshift and nonsense mutations were associated with spine and bone deformities; missense and nonsense mutations with cardiovascular anomalies. Deletions were associated with broader symptoms, especially ocular anomalies, dysmorphic traits, and intellectual disability. ***Conclusion:*** Overall, this research highlights NF1's clinical and mutation diversity, with clinical characteristics ranging from the symptoms outlined in the diagnostic criteria to other organ abnormalities, and its relationship to specific mutation types.

Keywords: NF1; neurofibromatosis type 1; genetic; gene mutation; gene deletion; genotype; phenotype

INTRODUCTION

Neurofibromatosis type 1 (NF1) is the most common neurocutaneous tumor syndrome that affects approximately 1:3000 patients of all ages and genders [23]. The U.S. Department of Health and Human Services National Cancer Institute has stated that about 100,00 Americans are affected by NF1. It is an autosomal-dominant, heterozygous disorder caused by a mutation in the neurofibromin gene on chromosome 17 [23]. The disease is characterized by skin markings known as cafe-au-lait macules (CALMs), several central and peripheral nervous system tumors, such as neurofibromas, Lisch nodules, and optic pathway glioma, and bony lesions, including sphenoid bone dysplasia and thinning of long bones [10]. Other common neurological manifestations reported in children with NF1 include learning difficulties, autism, and ADHD [14].

Many tumor types can occur in patients with NF1; therefore, each tumor requires its own specific treatment. For instance, surgery has been considered difficult for removing plexiform neurofibromas (PNF) due to their infiltration into other body structures and their high risk of recurrence. However, further studies have shown that biological agents such as MEK inhibitors have been proven effective in shrinking inoperable PNFs [10]. Surgical resections are usually done to alleviate pain and inflammation in cutaneous neurofibromas and for severe vision loss and disfiguring proptosis in optic pathway gliomas. Due to PNFs evolving into malignant peripheral nerve sheath tumors, patients with NF1 have a reduced life expectancy of 10-15 years [14]. Furthermore, although NF1 is an autosomal disease, many cases are reported to be sporadic or de novo, where a study shows that most de novo mutations arise from the male germ line with advanced paternal age, indicating an increased risk of the disease [9].

Neurofibromatosis type 1 is still a widely researched disease with no fixed cure due to its genetic nature and numerous tumors. Studies have shown that genetic factors and mutations play a big role in the severity and phenotypes of the disease. Given that specific mutations can result in the appearance of certain symptoms, this review explores the different mutations of the NF1 gene and their correlation with the tumor manifestations of the disease.

METHODS

Study Selection

This review collected studies from e-databases, including Google Scholar, Sage Journals, Scopus, ScienceDirect, and PubMed, using keywords specified in the inclusion criteria. Moreover, studies were filtered using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart [20], which included the inclusion and exclusion criteria. This was done by filtering studies based on the relevance of the title, keywords, abstract, and the overall content of the study.

Inclusion and Exclusion Criteria

The following criteria were used to select studies and remove irrelevant ones: (1) cohort studies, (2) studies that included patients with NF1, (3) studies regarding NF1, NF1 genetic mutations, NF1 genotype, and phenotype. This review used the following as the exclusion criteria: (1) studies that have no relevance to NF1 genotype and phenotype, (2) studies not published in English, (3) studies that are not in full text, and (4) studies published outside of 2019-2024.

Data Extraction

General information from each selected study, including the authors, publication date, and population, was extracted. Furthermore, specific information regarding NF1 clinical presentations and mutations was also collected. Additionally, the percentage of patients presenting with a specific symptom and mutation was also obtained.

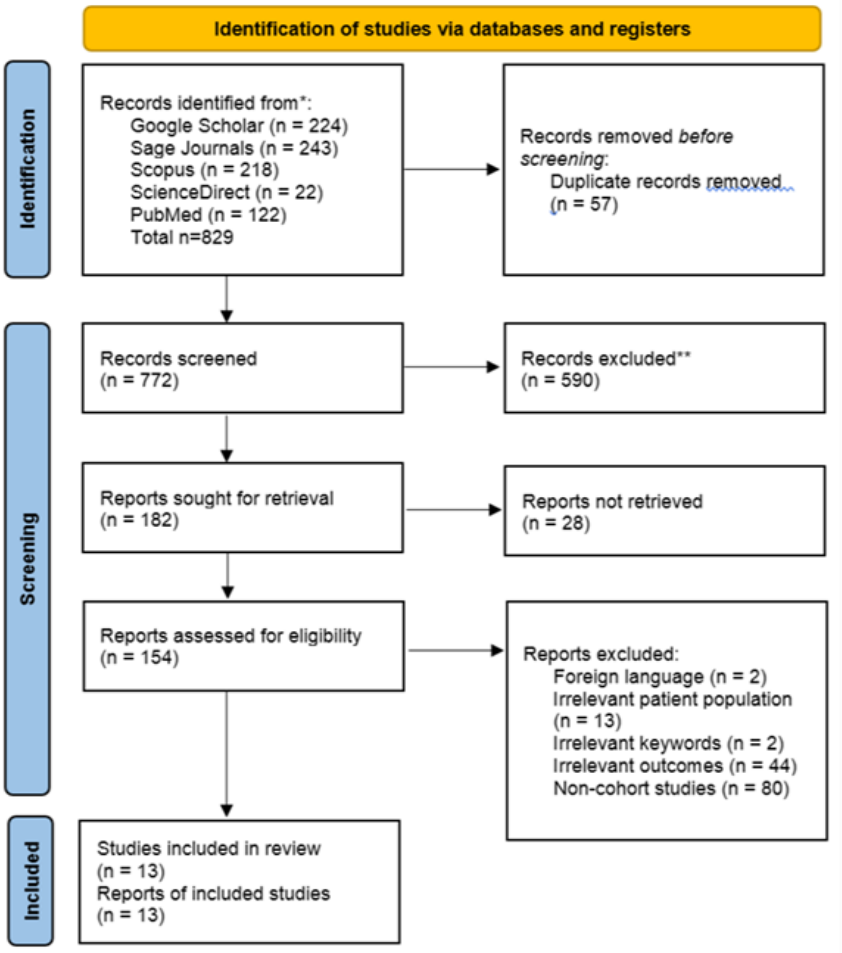

FIGURE 1: PRISMA Flow Diagram.

RESULTS

Characteristics of Selected Studies

A total of 13 studies were selected, where clinical presentations and the genetic mutations were described. All were cohort studies published from 2019 to 2024, with NF1 patients as their population sample. Furthermore, only one study by Alfurayh et al. focused on pediatric patients, while the rest had a mix of both pediatric and adult patients. Additionally, NF1 patients of sporadic and familial origin were both considered in this review.

Clinical Presentation

Neurofibromas are classified as cutaneous, subcutaneous, or general, where general encompasses both cutaneous (CNF) and subcutaneous (SNF), or in studies where none were mentioned. The general classification is totaled to 33.6%, whereas CNFs and SNFs are 60.0% and 56.2% respectively, indicating there is a slightly higher prevalence of CNFs. PNFs compile to a total of 25.0%, presenting a lower prevalence compared to NFs. MPNSTs, although identified by a few studies, present a total of 7.8%. OPGs total to 17.9%, a percentage a little lower than PNFs. CALMs present the most common presentation than PNFs. CALMs present the most common presentation with a total percentage of 95.0%. Freckling has a similar percentage to SNFs, with a percentage of 55.1%. Lisch nodules were mentioned by most studies, presenting a total of 36.9%.

Musculoskeletal anomalies were identified by almost all the studies, with a few mentioning specific presentations. Scoliosis was most frequently reported by the included studies, accounting for 27.4%. However, kyphoscoliosis was not mentioned as often as scoliosis but has a higher prevalence, at 36.4%. Similarly, scoliosis, osteoporosis, and osteopenia combined to a total of 24.1%, and patients with short stature accounted for 20.0%. The remaining presentations have a total percentage of 10-17%, with sphenoid wing dysplasia, pes cavus, pectus excavatum, and tall stature mentioned in about half of the studies.

Facial dysmorphism has the highest prevalence of patients with dysmorphic features, with a total of 64.4%. Macrocephaly follows in second with a total percentage of 40.7%. Hypertelorism, coarse facial appearance, and large hands and feet present with a total of 12.1%, and a broad fleshy nose, flat forehead, and deep front hairline present with 4.4%. Although only 2.4% of participants had sparse hair and low-set ears, these features were reported by a few studies.

Although hypertension was present in almost half of the studies, it accounted for only 3.9% of the total. On the other hand, aortic and mitral valve insufficiency and aortic stenosis were identified in only one study, but accounted for 13.0% overall. Coarctation of the aorta and hypertrophic cardiomyopathy account for about 11%, and the other cardiac presentations account for a total of 3-5%.

Focal areas of signal intensities (FASI) were found to have the highest prevalence compared to other neuropsychiatry presentations, along with anxiety, presenting a total of 69.1% and 61.9% respectively, and despite only being mentioned by 1-2 studies. UBOs were mentioned in three studies and presented with a percentage of 52.0%. Furthermore, sleep problems, depression, global developmental delays, and global developmental delays were identified by a few studies, yet they present a total of 34-42%. Epilepsy, headache, and learning disabilities were described by about half of the selected studies, yet epilepsy and headache present a total of 9.75% and 13.9% respectively, while learning disabilities present with 30.9%. ASD presents with the lowest prevalence in patients, with a total of 2.1% despite being identified in five studies. The remaining neuropsychiatric presentations account for 7-13% of the total.

About half of the included studies described the presence of ocular abnormalities, with decreased vision, strabismus, visual impairment, and visual disturbance having a higher prevalence, with a percentage of 21-34% compared to the remaining ocular abnormalities listed on Table 1, where they present with a percentage of 2-8%. Endocrine anomalies were reported by only a few studies, accounting for 3-5% of cases. Other non-nervous system oncological presentations were mentioned by only one study, which included breast cancer, prostate cancer, and gastrointestinal tumors, where they presented with a total of 16.5%, 4.7%, and 10.6% respectively.

Types of Genetic Mutations

Table 2 describes the different types of genetic mutations present in NF1 patients. The nonsense mutation has the highest prevalence (30.3%), followed by stop-gain (28.5%) and frameshift (27.1%). Even though missense and splicing were mentioned in more than half of the included studies, like nonsense and frameshift, they accounted for only about half the percentage of the latter, 16.0% and 12.1%, respectively. Other mutation types were identified by a few studies, accounting for 1-4% of total mutations. Studies that described microdeletions identified type-1 as the most common, with a frequency of 16.9%, followed by type-2 (5.3%), atypical (4.9%), and type-3 (4.1%).

Genotype-Phenotype Correlation

Genotype-phenotype correlations were explained in six of the selected studies, as listed in Table 3. Neurofibromas were observed in four studies, each of which identified different types of mutations. Study 3 described patients with a stop-gain mutation as associated with NF, while Study 8 identified nonsense and in-frame mutations; Study 10, deletions; and Study 11, type-1 and atypical microdeletions. PNFs were described in 2 studies: Study 3 associated them with stop-gain, while Study 11 associated them with type-1. MPSNTs were observed only in Study 11, mainly in patients with type-1 microdeletion. OPGs were primarily associated with frameshift mutations and atypical microdeletions, as reported in Studies 8 and 11. CALMs were present in almost all mutation types mentioned in Table 3 and identified in three studies. Freckling was described differently across three studies: Study 8 associated it mainly with frameshifts and splicing, Study 10 with deletions, and Study 11 with type-1 and atypical microdeletions. Lisch nodules were also reported in different studies, each identifying distinct mutations, mainly stop-gain mutations, deletions, and type-1 microdeletions.

Bone abnormalities were reported in Studies 2, 3, and 8, associating the presentation with nonsense, frameshift, and splicing, respectively. Additionally, spine deformities were observed in Studies 2, 8, and 11, where they were identified mostly in patients with frameshift and nonsense in-frame, and type-1 microdeletions, respectively. Dysmorphic features were described in Studies 8 and 11, with the former reporting them in patients with deletions and the latter identifying type-1 microdeletion as the most common. Cardiorespiratory anomalies were mainly associated with missense mutations, as noted in two studies. Neurological abnormalities were identified by only one study, observing epilepsy in patients with nonsense and headache in all types of mutations mentioned in the table above. Two studies observed psychiatric abnormalities, both associating them with deletions. Ocular abnormalities were reported in one study, which associated them with deletion.

TABLE 1: General Characteristics of Selected Studies.

No.	Reference	Title	Country of study	Study design	Study population
1	Alfurayh et al., 2023	Phenotype and Genotype of Saudi Pediatric Patients with Neurofibromatosis Type 1: A Seven-Year Multicenter Experience from Saudi Arabia	Saudi Arabia	Cohort	160 Saudi NF1 pediatric patients consisting of 81 males and 79 females with a mean age of 8.08 years collected from January 2016 to September 2022.
2	Napolitano et al., 2022	Genotype-Phenotype Correlations in Neurofibromatosis Type 1: Identification of Novel and Recurrent NF1 Gene Variants and Correlations with Neurocognitive Phenotype	Italy	Cohort	85 NF1 adult patients consisting of 47 females and 38 males collected from January 2013 to December 2020.
3	Scala et al., 2021	Genotype-Phenotype Correlations in Neurofibromatosis Type 1: A Single-Center Cohort Study	Italy	Cohort	583 patients of different ancestries with at least one NIH criterion for NF1 diagnosis consisting 309 males and 275 females with an age range of 1 to 73 years collected from 2009 to 2020.
4	Garzon et al., 2024	Expanding the phenotype of neurofibromatosis type 1 microdeletion syndrome	United States of America	Cohort	57 patients with NF1 microdeletion syndrome consisting of 36 females and 21 males with an age range of 1 month to 51.4 years collected from 1994 to 2024.
5	Tang et al., 2022	Assessment of Rare Genetic Variants to Identify Candidate Modifier Genes Underlying Neurological Manifestations in Neurofibromatosis 1 Patients	China	Cohort	13 NF1 patients with neurological manifestations and 457 healthy controls.
6	Pacot et al., 2021	Severe Phenotype in Patients with Large Deletions of NF1	France	Cohort	126 NF1 patients consisting of 51 males and 75 females with an age range of 4 months and 69 years old.
7	Rekha A et al., 2024	Clinical and Molecular Profile of Neurofibromatosis Type 1 Patients Using Revised Diagnostic Criteria - A Retrospective Cohort Study	India	Cohort	42 genetically confirmed cases of NF1 from 2014 to 2021 consisting of 19 males and 23 females with an age range of 1 to 48 years.
8	Gjorgjievska et al., 2023	Mutational Spectrum and Genotype-phenotype Correlations in Neurofibromatosis Type 1 Patients from North Macedonia: Identification of Ten Novel NF1 Pathogenic Variants	North Macedonia	Cohort	30 NF1 patients are collected in nine years.
9	Kehrer-Sawatzki et al., 2020	Clinical characterization of children and adolescents with NF1 microdeletions	Germany	Cohort	30 patients with NF1 microdeletions consisting of 18 males and 12 females with an age range of 1 to 15 years, and a control group of 30 age-matched children and adolescents with intragenic NF1 mutations.
10	Kang et al., 2019	Phenotype categorization of neurofibromatosis type I and correlation to NF1 mutation types	South Korea	Cohort	427 Korean patients with NF1 consisting of 223 females and 204 males with an age range of 0.2 to 67.6 years.
11	Buki et al., 2021	Genotype-Phenotype Associations in Patients with Type-1, Type-2, and Atypical NF1 Microdeletions	Hungary	Cohort	17 patients with large NF1 deletions consisting of 7 females and 10 males with a mean age of 12.9 years, and a control group of 33 intragenic NF1 patients.
12	Sorrentino et al., 2021	Epilepsy in NF1: Epidemiologic, genetic, and clinical features. a monocentric retrospective study in a cohort of 784 patients	Italy	Cohort	784 NF1 patients consisting of 371 females and 413 males with a clinical diagnosis or suspicion of NF1 before 13 years of age.
13	Pinna et al., 2019	Prevalence, type, and molecular spectrum of nf1 mutations in patients with neurofibromatosis type 1 and congenital heart disease	Italy	Cohort	493 patients with a molecularly confirmed diagnosis of NF1 consisting of 217 males and 276 females with an age range of four months to 64 years. Among these 493 patients, 62 patients had congenital heart disease (CHD).

TABLE 2: Clinical Presentation of Selected Studies.

Clinical presentations		Study 1	Study 2	Study 3	Study 4	Study 5	Study 6	Study 7	Study 8	Study 9	Study 10	Study 11	Study 12	Study 13	Total
Nervous System Tumors	Cutaneous NF	-	-	-	-	-	71/114	-	-	32/46	228/416	1/17	-	112/152	444/745 (60.0%)
	Subcutaneous NF	-	-	-	-	-	53/94	-	-	25/48	-	8/17	-	82/140	168/299 (56.2%)
	Neurofibromas (general)	33/160	70/85	137/583	41/56	-	-	26/42	20/48	-	-	-	-	-	327/974 (33.6%)
	Plexiform neurofibromas	31/160	11/85	76/583	25/57	-	17/75	11/42		16/30	138/315	2/17	-	55/197	402/1609 (25.0%)
	MPNSTS	-	-	-	3/57	-	4/48	-	-	20/30	2/247	2/17	-	-	31/399 (7.8%)
	Optic Pathway Glioma	29/160	10/85	94/583	10/57	-	9/80	1/42	7/48	3/29	21/324	4/17	143/412	37/221	368/2058 (17.9%)
Pigmentation Anomalies	Cafe au lait macules	133/160	-	552/583	-	-	115/126	41/42	37/48	-	416/420	17/17	-	337/338	1648/1734 (95.0%)
	Freckling	44/160	-	280/583	-	-	31/123	20/42	16/48	-	272/388	13/17	-	256/329	932/1690 (55.1%)
	Lisch nodules	54/160	-	89/583	24/50	-	40/77	21/42	2/48	-	214/ 284	4/17	-	112/256	560/1517 (36.9%)
Musculoskeletal Abnormalities	Scoliosis	17/160	64/85	89/583	21/57	-	52/107	-	5/48	16/30	93/327	7/17	-	90/330	454/1659 (27.4%)
	Kyphoscoliosis	27/160 (as a whole)		-	-	-		4/42	4/48 (classified as bone lesions)	-	-	16/17 (as a whole)	-	-	167/459 (36.4%)
	Sphenoid wing dysplasia		-	15/583	-	-		1/42		-	-		-	-	115/957 (12.0%)
	Long bone dysplasia		-	13/583	-	-		-		-	-		-	19/304	131/1219 (10.7%)
	Congenital bone bowing		-		-	-		-		-	-		-	-	154/915 (16.8%)
	Pseudoarthritis		-	55/583	-	-		-		-	-		-	-	154/915 (16.8%)
	Rib cage/pectus deformities		-		-	-		-		-	-		-	-	154/915 (16.8%)

	Joint hypermobility		-		6/46	-		-		-	-			-	-	160/961 (16.6%)
	Joint hyperflexibility		-		-	-		-		-	-			-	-	154/915 (16.8%)
	Pes cavus		-		-	-		-	3/48	6/29	-			-	-	159/944 (16.8%)
	Pectus excavatum		-	10/583	-	-		-	-	6/29	-	7/17		-	-	102/896 (11.4%)
	Osteoporosis			-	-	-		-	-	-	-	-		-	-	85/352 (24.1%)
	Osteopenia			-	-	-		-	-	-	-	-		-	-	85/352 (24.1%)
	Foot deformities		6/85	-	-	-	-	-	-	-	-	-		-	-	33/245 (13.5%)
	Tall stature			-	3/55	-	3/77	-	-	-	-	7/17		-	-	46/394 (11.7%)
	Short stature	24/160		-	-	-	29/79	-	-	-	52/414	-		-	64/207	192/962 (20.0%)
	Facial dysmorphism	-	-	-	38/56	-	-	-	-	-	-	9/17		-	-	47/73 (64.4%)
	Macrocephaly	-	-	-	21/53	-	1/77	-	-	-	167/314	9/17		-	35/129	233/573 (40.7%)
	Sparse hair	-	-	-	-	-	-	1/42	-	-	-	-		-	-	1/42 (2.4%)
Dysmorphic features	Low set ears	-	-	-	-	-	-	1/42	-	mentioned	-	-		-	-	1/42 (2.4%)
	Bilateral clinodactyly	-	-	-	-	-	-	1/42	-	-	-	-		-	-	1/42 (2.4%)
	Hexadactyly	-	-	-	-	-	-		5/48	-	-	-		-	-	7/90 (7.8%)
	Hypertelorism	-	-	-	-	-	-	2/42 (as a whole)	2/48	mentioned	-	9/17		-	-	13/107 (12.1%)
	Broad fleshy nose	-	-	-	-	-	-			mentioned	-	-		-	-	4/90 (4.4%)

	Flat forehead	-	-	-	-	-	-			mentioned	-	-	-	-	4/90 (4.4%)
	Deep front hairline	-	-	-	-	-	-			-	-	-	-	-	4/90 (4.4%)
	Broad neck	-	-	-	-	-	-			mentioned	-	1/27	-	-	5/117 (4.3%)
	Coarse facial appearance	-	-	-	-	-	-			-	-	9/17	-	-	13/107 (12.1%)
	Large hands and feet	-	-	-	-	-	-			-	-	9/17	-	-	13/107 (12.1%)
Cardiorespiratory abnormalities	Hypertension	-	24/85	7/583	3/57	-	-	-	-	-	24/342	-	-	16/310	50/1292 (3.9%)
	Aortic and mitral valve insufficiency	-		-		-	-	-	-	-	-	-	-	-	53/409 (13.0%)
	Moya Moya disease	-		15/583		-	-	-	-	-	4/288	-	-	-	68/1077 (6.3%)
	Coarctation of aorta	-		-		-	-	-	-	-		-	-	-	48/409 (11.7%)
	Aortic stenosis	-		-		-	-	-	-	-		-	-	-	53/409 (13.0%)
	Pulmonic stenosis	-	-	3/583		-	2/39	-	-		5/203 (as a whole)	-	-	23/493	51/1400 (3.6%)
	Ventricular septal defect	-	-	-	-	-		-	-	9/18		-	-	2/493	40/835 (4.8%)
	Atrial septal defect	-	-	-		-		-	-			-	-	2/493	40/835 (4.8%)
	Hypertrophic cardiomyopathy	-	-	-		-		-	-			-	-	-	38/342 (11.1%)
	Valvolopathies	-	-	3/583		-	-	-	-	-	-	-	-	9/86	41/993 (4.1%)
	Arrhythmia	-	-			-		-	-	-	8/290	-	-	-	35/994 (3.5%)
	Mitral valve anomalies	-	-	-		-		-	-	-	5/203 (as a whole)	-	-	14/493	43/817 (5.3%)

Neurological abnormalities	Seizures	-	-	-	-	-	60/78 (as a whole)	5/42	-	-	4/395	-	-	-	69/515 (13.4%)
	Epilepsy	27/160	-	27/583	-	2/13		-	8/48	-	-	-	37/784	-	161/1666 (9.7%)
	Headache	27/160	-	27/583	-	1/13		-	4/48	-	-	1/17	114/784	-	234/1683 (13.9%)
	Unidentified bright objects	-	15/85	-	-	-	35/62	-	-	-	-	-	217/366	-	267/513 (52.0%)
	Focal areas of signal intensity	-	-	-		-	-	-	-	-	216/323	13/17	-	-	289/418 (69.1%)
Psychiatric abnormalities	Cognitive impairment	15/160	-	-	-	-	-	-	-	-	-	-	-	-	15/160 (9.4%)
	Learning disability	-	-	-	-	1/13	-	-	16/48	-	38/386	10/17	124/784	85/281	458/1481 (30.9%)
	Intellectual disability	-	-	12/583	20/48	2/13	74/102	-		-	-	-		32/288	82/1082 (7.6%)
	Developmental disability	-	-		-	-		-	-	-	-	-	126/784	-	212/1469 (14.4%)
	Developmental delays	-	-	-	39/49	2/13	-	2/42	-	-	-	-	-	-	43/104 (41.3%)
	ADHD	-	-	12/583	23/42	3/13	-	-	-	15/17	27/383	2/17	-	-	82/1055 (7.8%)
	Autism Spectrum Disorder	-	-		5/46	4/13	-	-	-	mentioned	1/385	-	-	-	22/1027 (2.1%)
	Depression	-	-	-	15/40	-	-	-	-	-	-	-	-	-	15/40 (37.5%)
	Anxiety	-	-	-	26/42	-	-	-	-	-	-	-	-	-	26/42 (61.9%)
	Language developmental delay	-	-	-	-	3/13	-	-	-	-	-	-	-	-	3/13 (23.1%)
	Global developmental delay	-	-	-		-	-	2/42	-	28/30	-	-	-	-	30/72 (41.7%)
	Sleep problems	-	-	-	21/57	3/13	-	-	-	-	-	-	-	-	24/70 (34.3%)

Ocular abnormalities	Visual impairment	35/160	-	-	-	-	-	-	-	-	-	-	-	-	35/160 (21.9%)
	Visual loss	13/160	-	-	-	-	-	-	-	-	-	-	-	-	13/160 (8.1%)
	Colomba	-	-	4/583	-	-	-	-	-	-	-	-	-	-	4/583 (0.7%)
	Glaucoma	-	-		-	-	-	-		-	-	-	-	-	4/583 (0.7%)
	Decreased vision	-	-	-	31/50	-	-	-	3/48	-	-	-	--	-	34/98 (34.7%)
	Strabismus	-	-	-	19/50	-	-	-	-	-	-	2/17	-	-	21/67 (31.3%)
	Ptosis	-	-	-	-	-	-	-	1/48	-	-	-	-	-	1/48 (2.1%)
	Myopia	-	-	-	-	-	-	3/42	-	-	-	-	-	-	3/42 (7.1%)
	Visual disturbance	-	-	-	-	-	-	-	-	-	-	4/17	-	-	4/17 (23.5%)
Endocrine anomalies	Precocious puberty	4/160	-	31/583	-	-	-	-	3/48	-	-	-	-	-	7/208 (3.4%)
	Obesity	-	4/85		-	-	-	-	-	-	-	-	-	-	4/85 (4.7%)
	Hypercholesterol	-	-		-	-	-	-	-	-	-			-	31/583 (5.3%)
	Overweight	-	-		-	-	-	-	-	-	-	-	-	-	31/583 (5.3%)
	Hypothyroidism	-	-		-	-	-	-	-	-	-	-	-	-	31/583 (5.3%)
Non-nervous system oncological manifestation	Breast cancer	-	14/85	-	-	-	-	-	-	-	-	-	-	-	14/85 (16.5%)
	Hematopoietic malignancies	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Rhabdomyosarcoma of the bladder	-	-	-	-	-	-	-	-	-	-		-	-	-

Prostate cancer	-	4/85	-	-	-	-	-	-	-	-	-	-	-	4/85 (4.7%)
Benign pheochromocytoma	-	-	-	-	-	-	-	-	-			-	-	-
Gastrointestinal tumors	-	9/85	-	-	-	-	-	-	-	-	-	-	-	9/85 (10.6%)
Endocrine tumors	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Skin cancer	-	-	-	-	-	-	-	-	-	-	-	-	-	-

TABLE 3: Types of Genetic Mutations of Selected Studies.

	Genetic mutation	Study 1	Study 2	Study 3	Study 4	Study 5	Study 6	Study 7	Study 8	Study 9	Study 10	Study 11	Study 12	Study 13	Total
	Missense	20/160	20/85	85/351	-	mentioned	-	-	1/25	-	-	-	64/784	113/493	303/1898 (16.0%)
	Splicing	12/160	16/85	49/351	-	mentioned	-	6/42	5/25	-	-	-	75/784	74/493	237/1940 (12.1%)
	Nonsense	30/160	19/85	-	-	-	-	15/42	12/25	-	98/427	-	279/784	158/493	611/2016 (30.3%)
	Frameshift	10/160	18/85	77/351	-	-	-	10/42	6/25	-	114/427	-		128/493	642/2367 (27.1%)
	Stop-gain	-	-	100/351	-	-	-	-	-	-	-	-	-	-	100/351 (28.5%)
	Start loss	-	3/85	1/351	-	mentioned	-	-	-	-	-	-	-	-	4/436 (0.9%)
	Duplication	-	2/85	2/351	-	-	-	-	-	-	-	-	-	-	4/436 (0.9%)
	In-frame	-	-	-	-	-	-	-	3/25	-	13/427	-	8/784	-	24/1236 (1.9%)
	Partial deletion	-	-	11/351	-	-	-	-	-	-	-	-	-	-	11/351 (3.1%)
	Intragenic deletion	-	-	13/351	-	-	-	-	-	-	-	-	-	-	13/351 (3.7%)
	Whole gene deletion	3/160	-	12/351	-	-	-	-	-	-	-	-	-	15/493	30/1004 (3.0%)
Microdeletion	Type 1	7/160	-	-	28/43	-	71/108	-	-	27/30	24/427	12/17	24/784	-	193/1142 (16.9%)
	Type 2		-	-	4/43	-	21/108	-	-	-		1/17		-	81/1539 (5.3%)
	Type 3		-	-	2/43	-	5/108	-	-	-		-		-	62/1522 (4.1%)
	Atypical		-	-	9/43	-		-	-	3/27		4/17		-	71/1458 (4.9%)

TABLE 4: Types of Genetic Mutations of Selected Studies.

Phenotype-genotype correlations		Study 1	Study 2	Study 3	Study 4	Study 5	Study 6	Study 7	Study 8	Study 9	Study 10	Study 11	Study 12	Study 13
Nervous System Tumors	Neurofibromas	-	-	Cutaneous neurofibroma and subcutaneous neurofibroma: Stop-gain	-	-	-	-	Equally affecting patients with nonsense and in-frame mutations, but is less frequent in frameshift mutations	-	Cutaneous neurofibroma: More frequent in deletions compared to splicing and missense	Cutaneous neurofibroma: less frequent, only present in one patient with type-1 deletion Subcutaneous neurofibroma: type-1 and atypical	-	-
	Plexiform neurofibromas	-	-	Stop-gain	-	-	-	-	-	-	-	Less frequent but present in patients with type-1 deletion	-	-
	MPNSTS	-	-	-	-	-	-	-	-	-	-	Less frequent but present in patients with type-1 deletion	-	-
	Optic Pathway Glioma	-	-		-	-	-	-	More frequent in frameshift mutations compared to splicing	-	-	More frequent in atypical deletions compared to type-1	-	-
Pigmentation Anomalies	Cafe au lait macules	-	-	-	-	-	-	-	Deletion, nonsense, frameshift, splicing, in-frame	-	Affecting all types of mutations	Type-1, type-2, and atypical	-	-
	Freckling	-	-	Stop-gain	-	-	-	-	Equally affecting patients with frameshift and splicing mutations, but is less frequent in nonsense mutations	-	More frequent in deletions compared to splicing and missense	Type-1 and atypical	-	-
	Lisch nodules	-	-	Stop-gain		-	-	-	Deletions	-	-	More frequent in type-1 deletions compared to type-2	-	-

Musculoskeletal abnormalities	Spine deformities	-	Frameshift and nonsense	Frameshift (as a whole)	-	-	-	-	In-frame	-	-	Type-1	-	-
	Pes cavus	-			-	-	-	-	Frameshift	-	-	-		-
	Pectus excavatum	-	Nonsense (as a whole)		-	-	-	-	More frequent in splicing mutations compared to nonsense (as a whole)	-	-	-	-	-
	Others	-			-	-	-	-		-	-	-	-	-
Dysmorphic features	Facial dysmorphism	-	-	-	-	-	-	-	Deletions (as a whole)	-	-	Type-1 and atypical	-	-
	Macrocephaly	-	-	-	-	-	-	-		-	-	More frequent in type-1 deletions compared to atypical	-	-
	Coarse facial appearance	-	-	-	-	-	-	-		-	-	Type-1 and type-2	-	-
	Large hands and feet	-	-	-	-	-	-	-		-	-	Type-1 and type-2	-	-
	Hexadactyly	-	-	-	-	-	-	-	Deletions	-	-	-	-	-
Cardiorespiratory abnormalities	CHD	-	Missense and nonsense (as a whole)	-	-	-	-	-	-	-	-	Type-1 and atypical (as a whole)	-	More frequent in missense mutations compared to nonsense and frameshift
	PVS	-		-	-	-	-	-	-	-	-		-	More frequent in missense mutations compared to frameshift

Neurological abnormalities	Epilepsy	-	-	-	-	-	-	-	More frequent in nonsense mutations compared to splicing	-	-	-	-	-
	Headache	-	-	-	-	-	-	-	Equally affecting patients with splicing and in-frame mutations	-	-	-	-	-
	Unidentified bright objects	-	-	-	-	-	-	-		-	-	-	-	-
Psychiatric abnormalities	Learning disability	-	-	-	-	-	-	-	Deletions	-	Deletions	-	-	-
	Intellectual disability	-	-	-	-	-	-	-		-	-	-	-	-
Ocular abnormalities	Decreased vision	-	-	-	-	-	-	-	More frequent in deletions compared to splicing	-	-	-	-	-
	Ptosis	-	-	-	-	-	-	-	Deletions	-	-	-	-	-

DISCUSSION

Neurofibromatosis type 1 is a systemic disease caused by mutations or deletions of the neurofibromin protein. These genetic alterations and their clinical characteristics differ from patient to patient. Patients are diagnosed using the diagnostic criteria, which require fulfillment of one or two criteria. In addition to the diagnostic criteria's features, patients may exhibit multiple organ abnormalities and neurological manifestations. Each characteristic may be associated with specific genetic mutations, as reported by a couple of studies.

Nine of the thirteen studies focused primarily on patients with point mutations, in which nonsense, frameshift, missense, splicing, start-loss, and stop-gain mutations were identified. Nonsense mutations account for the highest percentage of patients (30.3%), followed by stop-gain (28.5%) and frameshift (27.1%). The mutational spectrum includes missense or nonsense mutations, which constitute a larger part of the spectrum, followed by small deletions, splicing substitutions, small insertions and deletions, and gross deletions [22]. Missense mutations are identified by almost half of the included studies, but they are present in only 16.0% of patients.

These studies also identified gene deletions, called microdeletions, which, when compared to point mutations, were found in a small number of patients, with Abramowicz et al. stating that about 5-7% of NF1 cases are associated with gene deletions. In four studies examining populations affected by NF1 microdeletions, type 1 microdeletions were observed in all cases, accounting for the highest percentage of patients with this mutation (16.9%). Type-2 microdeletion was present at a much lower percentage (5.3%), and atypical microdeletions were identified at a similar percentage (5.9%). Type-1 and atypical microdeletions were observed in almost half of the included studies, but the former were present with a higher percentage compared to the latter.

The presence of one or more diagnostic criteria is sufficient to confirm a diagnosis of NF1. Cafe-au-lait macules are often the first manifestations of NF1, described as uniform, light to dark brown, oval-shaped, and smooth-textured, with a high incidence in NF1 patients [16]. As they are the most common sign of NF1 [17], they are present in 95.0% of patients with this symptom. Additionally, CALMs are presented in almost all types of mutations, making them the most common symptom of NF1. Skinfold freckling, or Crowe sign, is most commonly seen in the armpits and may appear in the perineum and develops during puberty after CALMs and before neurofibromas, with about 70% of patients observed with this [3]. However, this presentation was observed in 55.1% of the total number of patients. They were mainly associated with frameshift, splicing, and deletions, specifically type-1 and atypical microdeletions.

Neurofibromas are another characteristic present in NF1 patients. They are soft, pea-size bumps that appear on the skin (cutaneous) or under the skin (subcutaneous) [17]. CNF is present in 60.0% of patients, slightly higher than in SNF (56.2%). In the study by Alfurayh et al., which focused on pediatric patients, cutaneous neurofibromas were found in fewer than 50% of the population, as expected, as these typically emerge during or after adolescence and tend to increase with age [18]. As neurofibromas grow with age, they can cause itching and tenderness and, in some cases, grow particularly large or in inconvenient places, causing cosmetic and other issues [17]. NF was mainly linked to different types of mutations, stop-gain, nonsense, in-frame, and type-1 and atypical microdeletions. Plexiform neurofibromas, another diagnostic criterion for NF1, are a rare subtype of neurofibroma that occurs in approximately 30–50% of patients with NF1 [13]. In the 11 studies identifying PNFs, they reported that these tumors occur in 25.0% of patients. These symptoms were identified with stop-gain and type-1 microdeletion.

Lisch nodules in the irises were identified in 9 studies, occurring in 36.9% of patients, mainly associated with stop-gain mutations and specifically with type 1 microdeletion. These are raised, tan-colored iris hamartomas, usually appearing after age 3, with a prevalence of 43% among those <12 years old and 57-75% among those ≤15 years old, while they are seen in >90% of adults [19]. Optic pathway glioma is another diagnostic criterion for NF1, reported in twelve studies, with a prevalence of 17.9% among patients. It is the most frequent central nervous system tumor in children, usually seen in 15-20% of patients [7], while it is rarely seen in adolescence or adulthood [6]. Furthermore, they were observed in patients mostly with frameshift and atypical microdeletions.

Skeletal anomalies are seen in up to 50% of patients [18], with the most common being scoliosis, sphenoid wing dysplasia, long-bone bowing, and pseudoarthritis. Compared with the results of this study, kyphoscoliosis (36.4%), scoliosis (27.4%), osteoporosis (24.1%), and osteopenia (24.1%) are the most common skeletal symptoms. Patients with nonsense, frameshift, and splicing mutations were mainly identified with these symptoms. Additionally, spine deformities, such as scoliosis, were mainly linked with frameshift, nonsense, in-frame, and type-1 microdeletions.

Dysmorphic features were observed by eight studies, with facial dysmorphism presenting with the highest total percentage of 64.4%. Facial dysmorphism was reported in Study 7, including sparse hair and low-set ears. Additionally, Study 9 described their patients as having hypertelorism, a broad, fleshy nose, a flat forehead, a deep front hairline, a broad neck, and low-set ears.

Furthermore, Study 11 noted a coarse facial appearance in their patients. They were mainly associated with patients with microdeletions, specifically in type-1 microdeletions.

Neuropsychiatric deficits were also found encompassing developmental delays, behavioral abnormalities, and psychiatric anomalies as well. Seizures leading to epilepsy were mainly described by Study 12, where they stated that these seizures can either be focal or generalized, and West Syndrome is also observed. In a review by Bernando et al. [5], epilepsy in NF1 patients is caused by low-grade gliomas, mesial temporal sclerosis, malformation of cortical development, dysembryonic neuroepithelial tumor, and cerebrovascular lesions. Moreover, the study observed that the overall prevalence was 5.4%, slightly lower in children at 3.7%. On the other hand, this study totalled a percentage of 13.4% for seizures and 9.7% for epilepsy. Headaches were identified in seven studies, totaling 13.9%, and Study 5 noted that its patients had migraines. The genotype correlations were identified in Study 8, in which epileptic patients were mostly observed to have nonsense mutations, whereas patients with headaches were associated with all types of the mentioned mutations. Other neurological anomalies include UBOs and FASI, which, despite being mentioned by only a few studies, present with high percentages of 69.1% and 52.0%, respectively.

Furthermore, Study 4 noted that these patients had special education services and individualized education plans. Additionally, the authors also noticed that some of their patients graduated from high school. Moreover, Study 9 also stated that patients had special needs inclusion schools, while others enrolled in secondary schools as regular pupils. This indicated that education levels and needs differ from patient to patient with NF1, with regard to their mental state.

Behavioral abnormalities such as ADHD and ASD were observed, where, despite being mentioned in about half of the included studies, they present with a small percentage of 7.8% and 2.1% of patients, respectively. Compared to the general child population, ADHD was more common in NF1 patients, while ASD in NF1 children had a similar prevalence to the general child population, with autism symptoms not reaching the clinically significant thresholds [15]. Psychiatric symptoms were only reported by Study 4, in which depression and anxiety were included, where patients with anxiety totaled 61.9% and depression to 37.5%. With NF1's unpredictable nature with its variability in severity of symptoms and medical complications, NF1 patients are at an increased risk for social and emotional difficulties, including anxiety, depression, low self-esteem and/or body image, social withdrawal, difficulty forming interpersonal relationships, behavioral problems, and school difficulties [8]. Furthermore, psychiatric symptoms were identified to be mainly associated with deletions.

Ocular manifestations other than OPG and Lisch nodules were also observed, with Study 8 associating them with deletions. OPG causes orbital compression of the optic nerve, which may result in proptosis, strabismus, papilledema, visual field defects, and reduced visual acuity [1]. Decreased vision was present in 34.7% of total patients compared to the other symptoms.

Cardiovascular abnormalities were identified in 7 of the 13 selected studies, including congenital heart disease and hypertension. Two studies identified missense mutations linked to this symptom. Hilal et al [12] state that 10-15% of NF1 patients have CHD. Hypertension is present in 3.9% of patients, even though it was reported in almost half of the selected studies. On the other hand, aortic and mitral valve insufficiency and aortic stenosis were identified in only one study, but together accounted for 13.0%, similar to what Hilal et al [12] reported. Pulmonary valve stenosis was 3.6%, much lower than in Hilal et al.'s [12] patients, where 50% had PVS.

According to a study by Alshahrani et al. [4], the prevalence of endocrine diseases in NF1 patients was estimated at 19.4%. In contrast, endocrine abnormalities in this study are totaled to have a lower percentage of 2-8%. Other cancers associated with NF1 found in this study were breast, prostate, and gastrointestinal cancers, where Reynolds mentioned similar symptoms as well.

The limitations of this research include the majority of studies reporting a retrospective data collection approach and a small sample size. Due to these two main limitations, some have reported missing or incomplete data, assessing rare variants in rare diseases is difficult, and establishing genotype-phenotype correlations is complex. For these reasons, this research could not establish a specific gene mutation for some diseases.

CONCLUSION

In conclusion, Neurofibromatosis type 1 is a disease caused by a mutation in the neurofibromin gene on chromosome 17q11.2, leading to a variety of clinical symptoms. The mutations affecting patients mainly include missense, splicing, nonsense, and frameshift mutations, with a few selected articles identifying stop-gain, start-loss, duplication, and in-frame mutations, as well as microdeletions. Clinical manifestations include NF1 diagnostic criteria and other organ system anomalies, including musculoskeletal, cardiorespiratory, neuropsychiatric, and ocular systems. Genotype-phenotype correlations were identified in a few of the selected articles, mainly by describing characteristics from the diagnostic criteria, including freckling, bone abnormalities, neurofibromas, and Lisch nodules.

This shows that genotype-phenotype correlations in NF1 patients remain limited, despite the numerous possible clinical manifestations.

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