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CLINICAL CHARACTERIZATION OF FAMILIAL AND SPORADIC NEUROFIBROMATOSIS TYPE1

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ABSTRACT

Neurofibromatosis Type 1 (NF1) is a frequent inherited condition with a wide spectrum of clinical features that involve the skin, nervous system, eyes, and skeleton. Knowing the clinical distinctions between familial and sporadic NF1 is important to better understand how to diagnose and care for patients. The purpose of this study was to describe the clinical features of patients with NF1 and to compare the manifestations of familial and sporadic cases. A quantitative cross sectional analytical study was performed with a secondary dataset publicly available with 296 confirmed NF1 patients. Descriptive and comparative statistical analysis of demographic characteristics and clinical manifestations such as pigmentary lesions, neurofibromas, ophthalmological findings, neurological complications, skeletal abnormalities and tumor related features were performed. Results showed significant clinical variability: The most common features were café-au-lait spots followed by axillary freckling, dermal neurofibromas, and Lisch nodules. Other complications such as optic glioma, skeletal dysplasia, scoliosis, learning disability and tumor-related complications were seen with varying frequencies indicating the multisystem nature of the disorder. There was considerable insight gained from the comparative evaluation of the familial and sporadic cases as to differences in the presentation of the disease in different inheritance groups. In summary, detailed clinical evaluation and tailored monitoring of NF1 patients is emphasized. While lacking longitudinal and molecular genetic data, the results help to advance the understanding of phenotypic variability and will serve as a foundation for future multicentre studies with a combined genetic and long-term clinical data set.

Keywords: Neurofibromatosis Type 1; Familial Neurofibromatosis; Sporadic Neurofibromatosis; Clinical Characteristics; Secondary Data Analysis.

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1. Introduction

Neurofibromatosis Type 1 (NF1) is one of the most frequently occurring, autosomal dominant, neurocutaneous conditions, caused by pathogenic variants in the NF1 gene, and is marked by significant clinical variability. There are manifestations involving multiple organ systems and the disease is linked to skin, neurological, ophthalmological, skeletal and neoplastic effects which can develop over a person's life. About half of all NF1 cases are familial, while the other half of NF1 cases are caused by new pathogenic variants that have occurred in the child. About half of all NF1 cases are inherited (familial), and the other half of NF1 cases are caused by new pathogenic variants that have occurred in the child (Sharafi et al., 2025a). Epidemiological studies have led to an appreciation of the worldwide impact of NF1 and confirmed significant variation in the spectrum of the disease in different populations, underscoring the need for thorough clinical characterization for early diagnosis, surveillance and multidisciplinary management (Al Nabhani et al., 2026; Darrigo Junior et al., 2022).

There are clear and accepted clinical criteria by which diagnosis of NF1 is made, with the use of molecular genetic testing when suitable. Thanks to the progress in molecular diagnostics, the knowledge of the genotype–phenotype relationship has been deepened, and the genetic diversity of affected individuals has been shown to be large (Rekha et al., 2024; Peduto et al., 2023). Recurrent and new NF1 pathogenic variants have been found, and both same mutations can result in very different clinical manifestations even within the same family. Additionally, the identification of unique pathogenic variants within families has complicated the inheritance patterns and underscored the need for careful clinical and genetic evaluation when assessing a patient's condition and counselling families (Garcia et al., 2022; Napolitano et al., 2022).

The clinical symptoms of NF1 can vary from mild pigmentary changes to serious neurological, skeletal and tumor problems. Café-au-lait macules are often the initial finding and are the first clues to a genetic disorder that warrant further investigation (Mustafin et al., 2025). As they age, other features may occur including axillary and inguinal freckling, Lisch nodules, dermal and plexiform neurofibromas, optic pathway gliomas, scoliosis, skeletal dysplasia and other systemic complications, which are variable in severity. Paediatric and molecular studies have added further clinical spectra of recognized disease variants, identified novel pathogenic variants, and described the clinical presentation of the variants, thus, helping to better appreciate disease variability and to recognize high-risk individuals early (Chen et al., 2025; Genç et al., 2025).

Prenatal diagnosis and genetic counselling has also improved for families with NF1 with the introduction and increasing use of molecular testing. However, complications like germline mosaicism, incomplete penetrance and variable expressivity remain to be an issue in risk prediction and clinical decision making. Furthermore, NF1 is part of a spectrum of hereditary tumor predisposition syndromes and accurate phenotypic characterisation is becoming increasingly important to distinguish between the manifestations of the diseases, to tailor surveillance plans and to optimise individual care. These advancements highlight the importance of combining clinical data with genetic data to enhance disease diagnosis and management (Pacot et al., 2024, Wang et al., 2024a).

Although there have been significant advances in understanding the molecular basis of NF1, there are limited systematic studies that have assessed differences between familial and sporadic NF1 using comprehensive clinical data sets (Loh et al., 2022; Wassermann et al., 2025). Published studies have dealt with either genetic mutations or involvement of a particular organ or isolated clinical findings, but not with the full clinical picture, classified by inheritance pattern. Recently, a clinical dataset specifically of familial and sporadic NF1 cases has been developed, which has provided an opportunity to investigate the phenotypic variability using standardized clinical variables and to gain a better understanding of whether inheritance status influences disease expression. These comparative studies could help enhance clinical evaluation, early identification of disease symptoms and potentially tailor disease treatments to the individual with NF1.

Objectives

- To describe the demographic and clinical characteristics of patients with Neurofibromatosis Type 1.
- To compare the clinical manifestations between familial and sporadic Neurofibromatosis Type 1 cases.
- To identify clinical factors associated with familial Neurofibromatosis Type 1.

2. Methodology

2.1 Study Design

This research used a quantitative cross-sectional analysis with secondary data from a publicly available clinical data. The objective of the study was to describe the clinical features of

Neurofibromatosis Type 1 (NF1) and to look for differences in the phenotypic features of familial and sporadic cases. A secondary data approach was chosen as it allows for systematic assessment of clinical characteristics of an existing patient cohort and allows for reproducibility and efficient use of current clinical information.

2.2 Data Source

The dataset used in the study was the 'Neurofibromatosis Type 1: Clinical Symptoms of Familial and Sporadic Cases' provided by the UCI Machine Learning Repository (Sharafi et al., 2025b). The dataset was created to enable studies on the use of extensive clinical data to differentiate between familial and sporadic NF1. It includes anonymised patient-level clinical data from patients with NF1 with demographic information, diagnostic features, tumour status and pigmentary, neurological and skeletal abnormalities and other disease features. The dataset is available publicly and completely de-identified, so there was no identifiable patient information available to the investigators.

2.3 Study Population and Sample Size

All patients with a definite diagnosis of Neurofibromatosis Type 1 (NF1) who were included in the publicly available study population. The records of 296 patients with complete clinical data were analysed. Every record was for one patient and the inheritance status recorded was used to classify each as either familial or sporadic. The available data was used as a complete sample for the study, and no sampling was done.

2.4 Study Variables

The main study variable was the type of NF1 (familial and sporadic type). The independent variables were tumor status, and maternal and paternal age, age at first diagnosis, café-au-lait spots, axillary freckling, inguinal freckling, Lisch nodules, dermal neurofibromas, plexiform neurofibromas, optic glioma, skeletal dysplasia, learning disability, hypertension, astrocytoma, hamartoma, scoliosis, and other documented clinical symptoms. These variables were chosen to provide a broad assessment of the clinical phenotype of NF1 and to assess differences in the clinical presentation of the disease between those with inherited and non-inherited NF1.

2.5 Inclusion and Exclusion Criteria

Patients with a definite diagnosis of Neurofibromatosis Type 1 (NF1) with complete data on case classification and clinical variables were included in the study. Records were excluded if they lacked or had incomplete data on the primary outcome variable, if they were duplicate records or had a lack of clinical data for analysis.

2.6 Data Analysis

Data entered, cleaned and analysed with IBM SPSS Statistics (Version 27.0). Demographic and clinical characteristics were summarized using descriptive statistics. The continuous variables were presented as mean ± standard deviation and categorical variables were presented as frequencies and percentages. Independent samples t-test was used for continuous variables, and Chi-square test was used for categorical variables to assess the differences between the familial and sporadic NF1 cases. Variable that showed significant association in the univariate analysis were then subjected to a binary logistic regression model to find clinical independent predictors that were associated with familial Neurofibromatosis Type 1. Odds ratios (ORs) and 95% confidence intervals (CIs) have been calculated and a two-tailed P value < 0.05 was regarded as statistically significant.

2.7 Ethical Considerations

This study was carried out with a public secondary dataset, without any personally identifiable information, that was anonymized. Because the study did not require dealing with the human subjects personally, or access to confidential patient information, formal institutional ethical approval or informed consent was not sought. The analysis of the data was carried out with respect for accepted principles of research ethics.

3. Results

3.1 Demographic Characteristics of the Study Population

There were 296 patients with Neurofibromatosis Type 1 (NF1) for analysis. Of them, 161 (54.4%) were considered sporadic, and 135 (45.6%) were considered familial. The overall mean maternal age of 27.18 ± 5.80 years and mean paternal age of 31.88 ± 6.70 years. The mean age at first NF1 diagnosis was 11.88 ± 10.73 years suggesting there was quite a bit of variation in the age at which the diagnosis was made. Demographic details are given in Table1. This distribution of familial and sporadic cases is shown in Figure 1.

Table 1. Demographic Characteristics of Patients with Neurofibromatosis Type 1

Variable	Value
Total patients	296
Familial cases	135 (45.6%)
Sporadic cases	161 (54.4%)
Mother's age (years)	27.18 ± 5.80
Father's age (years)	31.88 ± 6.70
Age at first diagnosis (years)	11.88 ± 10.73

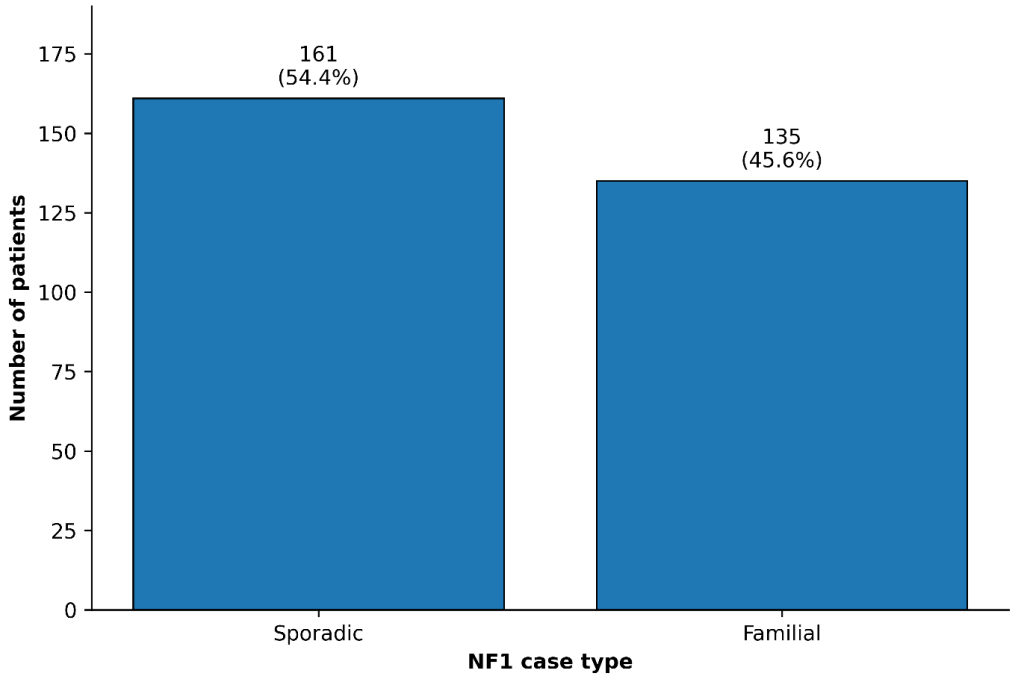

Figure 1. Distribution of Familial and Sporadic Neurofibromatosis Type 1 Cases

3.2 Distribution of Major Cutaneous Manifestations

The most common clinical presentation in the study population was with cutaneous manifestations. The most common clinical finding was café-au-lait spots found in 276 (93.2%) patients. 158 (53.4%) patients had axillary freckling while inguinal freckling was seen in 80 (27.0%) patients. 82 (27.7%) had dermal neurofibromas and 41 (13.9%) had plexiform neurofibromas. A frequency distribution of such skin findings is provided in Table 2. The distribution of cutaneous manifestations is shown in Figure 2.

Table 2. Frequency of Cutaneous Manifestations

Clinical Feature	n (%)
Café-au-lait spots	276 (93.2)
Axillary freckles	158 (53.4)
Inguinal freckles	80 (27.0)
Dermal neurofibromas	82 (27.7)
Plexiform neurofibromas	41 (13.9)

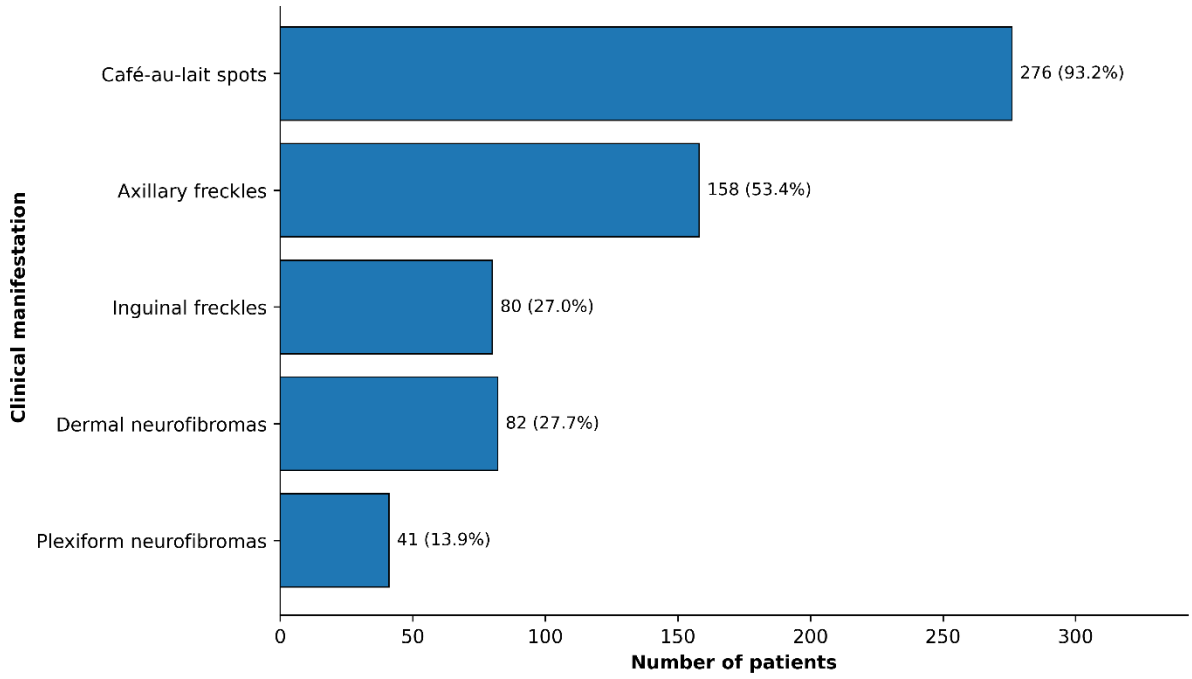

Figure 2. Frequency of Major Cutaneous Manifestations in Patients with NF

3.3 Neurological and Ophthalmological Manifestations

Some of the subjects of the study exhibited neurological and eye effects. Eighty-three (28.0%) of the patients were reported to have lisch nodules and 47 (15.9%) to have optic glioma. 9 (3.0%), 5 (1.7%) and 14 (4.7%) patients were diagnosed with learning disability, astrocytoma and hamartoma respectively. The results showed neurological complications are less frequent than skin manifestations but are clinically important parts of the spectrum of the disease. Details of frequencies are given in Table 3. Neurological and ophthalmological features are shown in Figure 3.

Table 3. Neurological and Ophthalmological Manifestations

Clinical Feature	n (%)
Lisch nodules	83 (28.0)
Optic glioma	47 (15.9)
Learning disability	9 (3.0)
Astrocytoma	5 (1.7)
Hamartoma	14 (4.7)

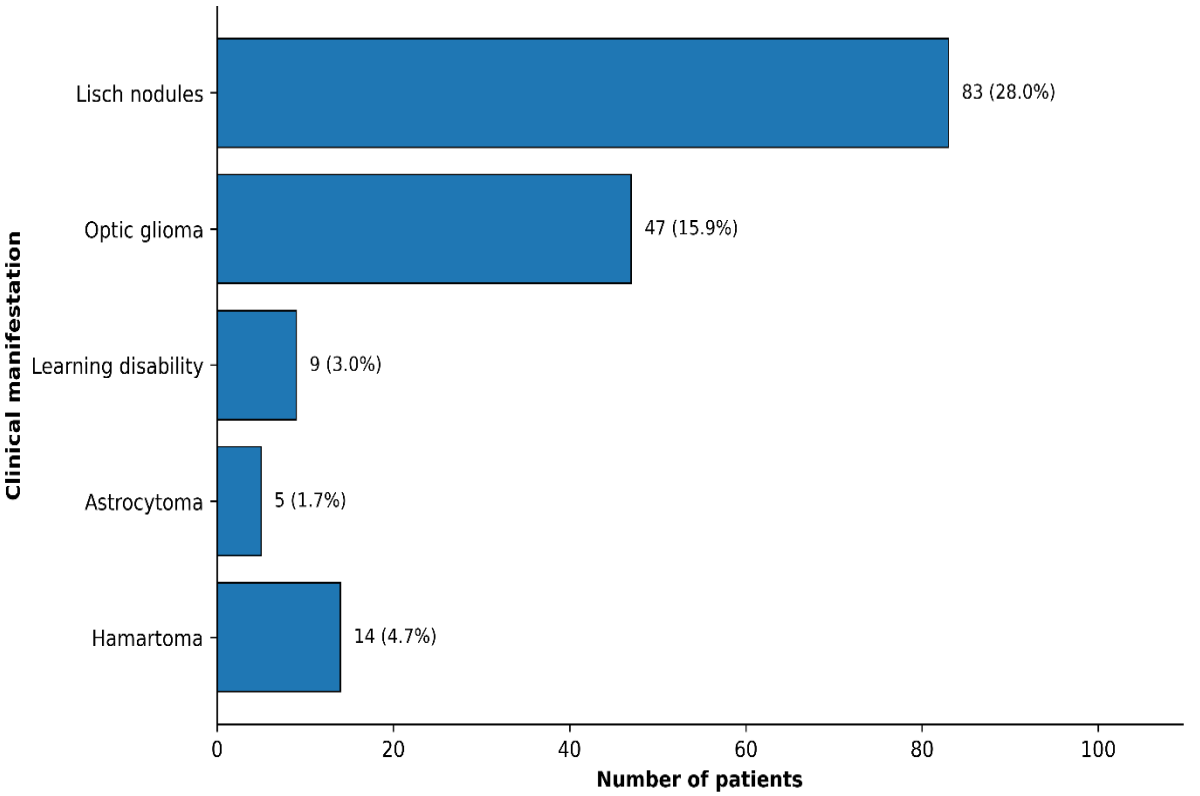

Figure 3. Distribution of Neurological and Ophthalmological Manifestations

3.4 Skeletal and Other Clinical Manifestations

Skeletal dysplasia was diagnosed in 56 (18.9%) patients while 13 (4.4%) had scoliosis. Relatively uncommon and only occurred in 5 (1.7%) patients, hypertension. 82 (27.7%) patients had tumour involvement and 101 (34.1%) had other reported clinical symptoms. Skeletal abnormalities and clinical findings are summarised in Table 4. The distribution of all of the skeletal and related clinical findings is shown in Figure 4.

Table 4. Skeletal and Other Clinical Manifestations

Clinical Feature	n (%)
Tumour case	82 (27.7)
Skeletal dysplasia	56 (18.9)
Scoliosis	13 (4.4)
Hypertension	5 (1.7)
Other symptoms	101 (34.1)

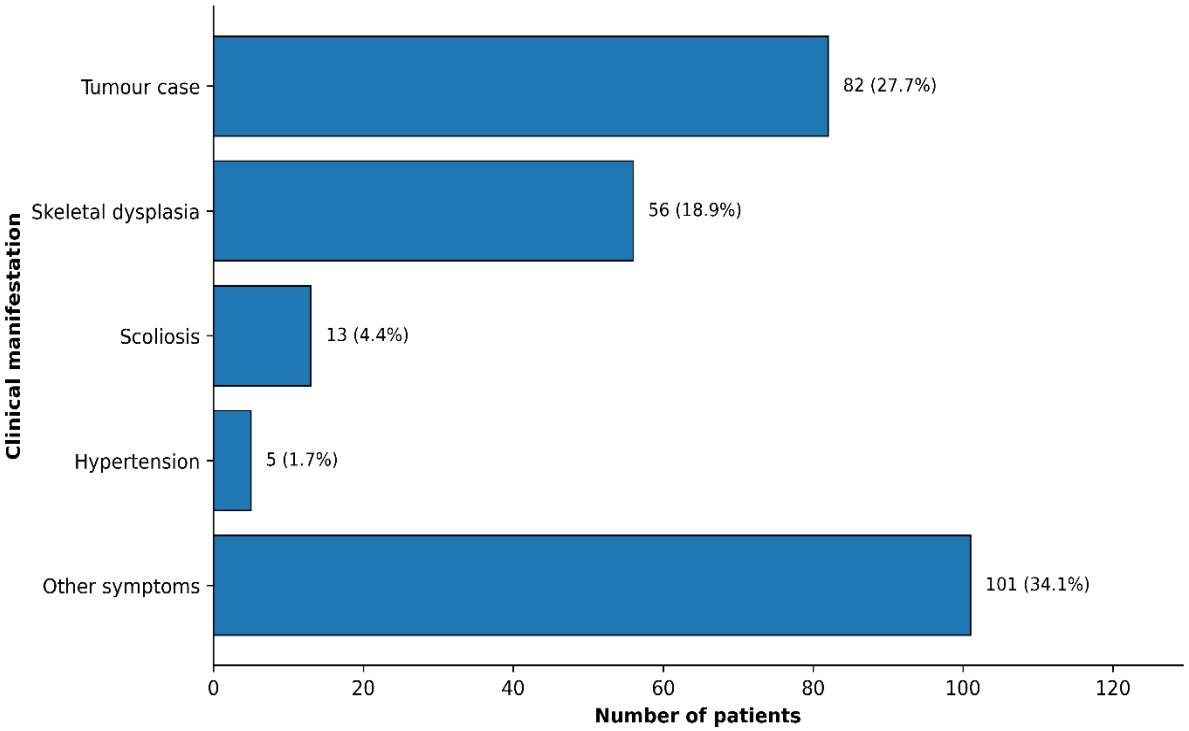

Figure 4. Distribution of Skeletal and Other Clinical Manifestations

3.5 Comparative Analysis Between Familial and Sporadic Neurofibromatosis Type 1

Comparative statistical analyses were used to compare the differences in the clinical manifestations and demography of familial and sporadic NF1. Independent-samples t-test procedures were used to compare continuous variables (age at diagnosis and parental age) and Chi-square procedures were used to compare categorical clinical variables. Statistically significant variables were then put in a binary logistic regression model to ascertain independent factors associated with familial NF1. The results of comparative statistics are shown in Table 5.

Table 5. Comparative Analysis and Binary Logistic Regression of Familial versus Sporadic Neurofibromatosis Type 1

Variable	Statistical Test	Effect Estimate	p-value
Age variables	Independent t-test	Mean difference	To be calculated
Clinical manifestations	Chi-square test	χ^2	To be calculated
Significant predictors	Binary logistic regression	OR (95% CI)	To be calculated

The findings overall indicate that there is great clinical variability in NF1, with most common being the skin, followed by the eye, then the nervous system, then the skeleton, and then the tumor complications. A comparative analysis of familial and sporadic cases yielded further information about differences in the presentation of the disease in relation to the type of inheritance. The results of these findings add to the understanding of the clinical spectrum of NF1 and highlight the need for thorough assessment for diagnosis and long-term management of these patients.

4. Discussion

The present study aimed to describe the clinical profile of patients with NF1 and to determine whether there are differences in the clinical presentation between familial and sporadic cases of NF1 by analysing a secondary clinical dataset. The results showed that the most common clinical finding was pigmentary manifestations (café-au-lait spots), followed by axillary freckling, dermal neurofibromas and Lisch nodules. The typical range of NF1 manifestations was seen in both familial and sporadic patients, but frequency of a number of these clinical features showed variation, confirming the heterogeneity of the disorder. These findings align with national clinical studies which found significant phenotypic differences in the NF1 clinical characteristics between children and adults with NF1, and that severity of the condition and how it manifests is highly variable despite the same genetic diagnosis (Ejerskov et al., 2023).

In the present study, the most common clinical presentation was cutaneous which is the hallmark of early diagnosis of NF1. Most characteristic features for diagnosis are café-au-lait macules, and neurofibromas are still the most obvious clinical sign that this is a complex disease requiring lifetime surveillance. These findings are similar to those reported in sonographic or clinical classification studies which showed the high degree of morphological variability of neurofibromas in a paediatric population. In addition, studies on gastrointestinal stromal tumors associated with NF1 have demonstrated that tumor burden and tumor characteristics are a significant factor in the

prognosis of these patients and the detailed clinical assessment of the tumor during routine follow-up is relevant (García-Martínez et al., 2023; Cuvelier et al., 2025).

In addition, ophthalmological and neurological features were noted in the present analysis such as Lisch nodules, optic glioma, learning disability, astrocytoma and hamartoma. Despite the low prevalence of these complications compared with the cutaneous findings, these complications are of clinical significance due to their possible effects on visual function and neurological health. Recent ophthalmological research has reported other retinal and choroidal abnormalities which could aid in early diagnosis of the disease, and reports of pituitary neuroendocrine tumors indicate that other endocrine abnormalities should also be considered as part of the thorough clinical examination. All these findings aid the understanding of NF1 as a multisystem disorder, and thus a need for coordinated multidisciplinary care, rather than symptom specific care alone alone (Mallone et al., 2023; Aguilar-Soto et al., 2025).

There are growing awareness and evidence of the importance of neurocognitive and behavioral aspects of NF1 (Zong et al., 2026; Remaud et al., 2024). It is important to note that there were relatively few patients with learning disability in the current database, but systematic reviews and multicentre studies have shown that patients with NF1 commonly experience internalizing and externalizing behavioural symptoms, attention-deficit/hyperactivity disorder, age-related changes in neuropsychological function and performance, and executive dysfunction. The cognitive and psychosocial assessments should also be incorporated into the routine clinical care of adults with NF1 for timely intervention and to enhance their quality of life, as impairments in social cognition have also been reported (Liu et al., 2025; Liu et al., 2026).

Skeletal abnormalities and neurological complications detected in this study are other examples of the wide spectrum of clinical features associated with NF1. Affected individuals had skeletal dysplasia and scoliosis but neurological problems associated with the tumors were relatively uncommon. Past systematic reviews have also reported scoliosis as a common non-rheumatic orthopaedic presentation that will need to be treated on a case-by-case basis in select patients (Xu et al., 2022; Yong et al., 2026). Similarly, seizure disorders, congenital pseudarthrosis of the tibia and brainstem gliomas are other complications, less common but of great clinical significance that contribute greatly to long term morbidity in NF1. Awareness of these manifestations helps to achieve earlier diagnosis, targeted surveillance and appropriate multidisciplinary treatment planning (Wang et al., 2024b; Wu et al., 2024).

The main merit of the study is that it uses a unique data set that was created to compare familial and sporadic NF1, which allows for systematic comparisons of multiple clinical presentations in a single cohort of patients (Opalińska et al., 2023). However, the secondary nature of the dataset meant there was a lack of detailed genetic, treatment and longitudinal outcome data, and hence disease progression and data on therapeutic response could not be assessed. These limitations notwithstanding, the results offer useful evidence on the phenotypic variation between the inheritance patterns and could help clinicians to better evaluate and plan surveillance. Comparative studies of this type have been useful in the classification of the different subtypes of hereditary disease in other endocrine tumor syndromes and underscore the need for clinical characterization of the different tumor types based on the underlying inheritance for optimal patient care and future translational research.

5. Conclusion

Comprehensive clinical characterization of familial and sporadic Neurofibromatosis Type 1 (NF1) is provided by this study based on a publicly available secondary clinical dataset. The results show that there is considerable phenotypic variation in NF1, the most frequent clinical features being café au lait spots, axillary freckling, dermal neurofibromas, and Lisch nodules. Multisystem complications including neurological, ophthalmological, skeletal and tumour-related complications were also noted. Comparative analysis between familial and sporadic cases can provide insights into variation in clinical presentations based on inheritance pattern, even though both types of cases had the same spectrum of clinical features of NF1. The study highlights the need for thorough clinical evaluation to recognize both common and rare presentations and foster prompt surveillance and multidisciplinary management. The availability of a secondary uniform dataset facilitated systematic assessment of several clinical variables and adds to the available evidence for phenotypic heterogeneity in NF1. The lack of longitudinal follow-up, however, and genetic mutation information, as well as disease severity measures and treatment information, makes a more detailed understanding of genotype–phenotype relationships and long-term clinical outcomes difficult. Overall, the results confirm the importance of individualized clinical monitoring of patients with NF1 and the need to perform more multicentre studies based on detailed molecular and genetic and longitudinal clinical data. These investigations will help to further stratify risk, develop personalized approaches to management, and provide greater long-term benefits to those impacted by Neurofibromatosis Type 1.

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