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## SHORT REPORT

# Identification of three clinical neurofibromatosis 1 subtypes: Latent class analysis of a series of 1351 patients

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## Abstract

**Background** Neurofibromatosis 1 (NF1) is one of the most common inherited disorders characterized by mutations in the tumour suppressor gene *NF1*. Its clinical manifestations are highly variable and unpredictable. A specific *NF1* mutation does not predict the severity or complications of the disease.

**Objective** The objective of this study was to build an empirical classification scheme without any *a priori* hypotheses to identify the underlying NF1 subtypes that best explain the observed heterogeneity.

**Methods** We performed latent class analysis (LCA) of 1351 consecutive NF1 patients aged >17 years seen between 2002 and 2014. Data and phenotypic features were collected prospectively on a standardized form.

**Results** The median age was 36.8 (17–81) years. A three-class model showed the best fit: 706 (52%) belonged to the LC1 'Cutaneous neurofibromas' class having preferentially cutaneous neurofibromas (99%), plexiform neurofibromas (63%) and blue-red macules (29%); 593 (44%) belonged to the LC2 'Subcutaneous neurofibromas' class characterized by the presence of at least 10 subcutaneous neurofibromas (21%) and a familial form (77%) and 52 (4%) belonged to the LC3 'Dysmorphic phenotype' class characterized by dysmorphic features (78%) and learning difficulties (87%). Patients in LC1 had a higher likelihood of developing scoliosis (RR = 1.7, 95% confidence interval (CI) [1.2–2.4]). Patients in LC2 were more likely to be men (RR = 1.4, 95% CI [1.1–1.7]). Patients in LC3 were at higher risk of having an optic pathway glioma (RR = 4.8, 95% CI [1.9–11.8]) and epilepsy (RR = 4.5, 95% CI [1.8–11.6]).

**Conclusion** Our findings invite the performance of a larger cohort study to test whether the various latent classes reflect different underlying genetic modifiers of these phenotypic traits.

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## Conflict of interest

The authors have declared that no conflict of interest exists.

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## Introduction

Neurofibromatosis 1 (NF1) is an autosomal dominant genetic disease caused by mutations in the tumour suppressor gene *NF1* located at 17q11.2.<sup>1</sup> It is one of the most common inherited disorders affecting 1 in 2500–3000 individuals.<sup>2</sup> NF1 is a multisystem

genetic disease that is principally associated with cutaneous, neurologic, ophthalmologic and orthopedic manifestations; some of which are progressive and lead to significant morbidity or mortality.<sup>3</sup> Peripheral nerve sheath tumours are the hallmark of the disease. Individuals with NF1 are also susceptible to a variety of other

benign and malignant tumours. Clinical features also include multiple café-au-lait macules on the skin, axillary and inguinal freckling, benign hamartomas of the iris (Lisch nodules), learning disabilities and scoliosis.

Among individuals with NF1, the clinical manifestations are highly variable and unpredictable. Over 1400 different pathogenic *NF1* mutations have been described. However, a specific *NF1* mutation does not predict the severity or complications of the disease. Indeed, no straightforward genotype–phenotype correlations have been identified for patients with intragenic *NF1* mutations which represent over 90% of all NF1 cases,<sup>4–6</sup> with a few reported exceptions.<sup>7–9</sup> Multiple factors are responsible for the complexity of the NF1 phenotype such as variable expressivity, pleiotropy, stochastic events, epigenetic phenomena, and genetic modifiers.<sup>10</sup> The lack of a straightforward genotype–phenotype correlation in NF1 has important clinical consequences; most important of which is the inability to predict the prognosis regarding disease severity even among family members sharing an identical *NF1* mutation. An ability to classify NF1 patients based on common phenotypic features could help in optimizing their surveillance.

Given the heterogeneity of NF1, we hypothesized that the underlying subclasses could be individualized. The objective of this study was to build an empirical classification scheme without any *a priori* hypotheses to identify the underlying NF1 subtypes that best explain the observed heterogeneity. To achieve these goals, we used latent class analysis (LCA) using an approach from a dermatological perspective.

## Methods

Patients aged 17 years or older were prospectively enrolled between 2002 and 2014 in our NF-network database as described previously.<sup>5,11–13</sup> Only patients with a confirmed NF1 diagnosis according to the National Institutes of Health criteria were included. Data and phenotypic features were collected prospectively on a standardized form. LCA is a multivariate regression model that describes the relationships between a set of observed dependent variables ('latent class (LC) indicators'; here, the clinical features of NF1) and an unobserved categorical latent variable. For our study, we chose 7 indicators: cutaneous neurofibromas,  $\geq 10$  subcutaneous neurofibromas, plexiform neurofibromas, blue-red macules, dysmorphic features (defined as a broad neck, broad nasal bridge, hypertelorism, down slanted palpebral fissures and a coarse, sometimes fleshy facial appearance<sup>14–17</sup>), familial NF1 and learning difficulties.

## Statistics

**Identification of the underlying NF1 subtypes** The number of LC was determined iteratively, beginning with a two-class model and proceeding to test models with increasing numbers of classes reaching a six-class model. Goodness-of-fit statistics were used

to select the optimal model. We compared successive models based on the Bayesian information criterion which indicates the most parsimonious solution, considering the number of indicators. Patients with missing data were not included in the final analysis.

**Factors associated with the LC** We then used membership in an identified class as a surrogate variable to describe the pattern of characteristics. Associations between variables (sex, age, internal neurofibroma, Lisch nodules, optic pathway glioma, epilepsy, hypertension, scoliosis and malignancy) and membership in each class were quantified by the relative risk (RR) and 95% confidence interval (CI), using multinomial univariate logistic regression. The dependent variable was the LC. All comparisons were two-sided, and  $p < 0.05$  was considered significant. Post hoc comparisons were performed with Bonferroni's correction. LCA was conducted using LatentGold (LatentGold 4.5, Statistical Innovations, Belmont, MA). Other analyses were performed using the Stata Statistical software v11 (StataCorp 2003. Release 8.2. College Station, TX).

## Study approval

The study was approved by the local ethical committee and all participants gave their written informed consents.

## Results

A total of 1351 NF1 patients aged 17 years or older were included (636 men (41,1%)). The median age was 36.8 years (range 17–81 years). A three-class model showed the best fit, with the lowest Bayesian information criterion. Table 1 reports the probabilities of each of the 7 previously selected indicators being present in the three LC.

**Table 1** Parameters estimates for the three LC solution in 1,351 patients with NF1

|   | LC1<br>'Cutaneous<br>neurofibromas'<br>N = 706 | LC2<br>'Subcutaneous<br>neurofibromas'<br>N = 593 | LC3<br>'Dysmorphic<br>phenotype'<br>N = 52 |
|---|--|---|--|
| Probability of membership in each class | 0.52   | 0.44  | 0.038                                      |
| Conditional probabilities* of:          |  |   |  |
| Cutaneous NF                            | 0.99   | 0.69  | 0.56                                       |
| >10 Subcutaneous NF                     | 0.16   | 0.21  | 0.07                                       |
| Plexiform NF                            | 0.63   | 0.32  | 0.47                                       |
| Blue-red macules                        | 0.29   | 0.11  | 0.01                                       |
| Dysmorphic features                     | 0.08   | 0.00  | 0.78                                       |
| Learning difficulties                   | 0.54   | 0.40  | 0.87                                       |
| Familial NF1                            | 0.58   | 0.77  | 0.50                                       |

NF1, neurofibromatosis 1; NF, neurofibroma; LC, latent class.

\*Probability of each indicator among patients of this class.

Of the 1351 NF1 patients, 706 (52%) belonged to the LC1, 593 (44%) to the LC2, and 52 (4%) to LC3. LC1 was termed the ‘Cutaneous neurofibromas’ class as it consisted of patients having preferentially cutaneous neurofibromas (99%), plexiform neurofibromas (63%) and blue-red macules (29%). LC2 was termed the ‘Subcutaneous neurofibromas’ class characterized by the presence of at least 10 subcutaneous neurofibromas (21%) and a familial form (77%). LC3 was termed the ‘Dysmorphic phenotype’ class and was characterized by dysmorphic features (78%) and learning difficulties (87%).

Results of the multinomial univariate logistic regression are found in Table 2. Patients in LC1 had a higher likelihood of developing scoliosis (RR = 1.7, 95% CI [1.2–2.4]). Patients in LC2 were more likely to be men (RR = 1.4, 95% CI [1.1–1.7]). Patients in LC3 were at higher risk of having an optic pathway glioma (RR = 4.8, 95% CI [1.9–11.8]) and epilepsy (RR = 4.5, 95% CI [1.8–11.6]).

### Discussion

We hereby report an empirical classification of NF1 based on the LCA of clinical variables without any *a priori* hypotheses. Using our pre-selected variables, our results indicate the existence of three classes with distinct phenotypes. Our classification makes clinical sense, as it fits with typical clinical observations. The first class corresponds to the classical form of NF1 with an overall mild presentation and a high prevalence of cutaneous neurofibromas<sup>18</sup>; while the other two classes have more severe phenotypes. Blue-red macules represent unusual variants of cutaneous neurofibromas,<sup>19,20</sup> it is therefore not surprising to find them predominate in the ‘Cutaneous neurofibromas’ class. The LC2 probably

corresponds to the previously identified NF1 phenotype, coined the ‘at-risk’ phenotype. This phenotype consists of patients with at least 10 subcutaneous neurofibromas who are prone to internal neurofibromas specifically at risk for malignant transformation and axonal neuropathies.<sup>12</sup> Nevertheless, in our analysis, patients in LC2 did not have an increased risk of developing internal neurofibromas when compared with LC1 (RR 1.23 95% CI (0.85–1.77), *p* = 0.273), Table 2). The LC3, which comprised 4% of the study population, is consistent with the more severe phenotype associated with microdeletions that encompass the entire *NF1* gene generally found in 5%–10% of NF1 patients. These patients have a lower mean IQ, abnormal facial features, an elevated risk for malignant peripheral nerve sheath tumour (MPNST) and develop neurofibromas at an earlier age.<sup>21,22</sup>

A study on 2051 adults with NF1 from the Children’s Tumor Foundation’s (CTF) NF1 registry recently characterized the prevalence of 18 self-reported phenotypic traits in their NF1 population. Patient cluster analysis identified 6 disease subtypes using these 18 NF1 traits: mild, freckling predominant, neurofibroma predominant, skeletal predominant, late-onset neural severe and early-onset neural severe.<sup>23</sup> Unlike our study which performed latent class analysis to build an empirical classification scheme without any *a priori* hypotheses, the CTF study performed patient clustering with K-means clustering based on principal components analysis to identify interrelationships between NF1 traits. Among their clusters, LC1 of our study corresponds to the neurofibroma predominant cluster characterized by overall mild presentation, with a high prevalence of cutaneous neurofibromas (>100 neurofibromas 47%), itch (88%), pain (67%) and low prevalence of MPNST (1%). LC2 and LC3 of our study do not seem to correspond to any of the clusters of the CTF NF1 registry study as their predominant phenotypic trait (the presence of subcutaneous neurofibromas and dysmorphic features respectively) were not listed among the 18 studied NF1 traits. Likewise, skeletal features and neurological features were not included in our 7 indicators explaining why the skeletal predominant and neural predominant subtypes do not correspond to any of our 3 clusters. Two other important distinctions are worth mentioning: First, the NF1 phenotypic traits in our study were recorded by physicians during patient recruitment, unlike the CTF NF1 registry which relied on self-reported data. Second, the choice of our indicators was chiefly based on cutaneous and visible features, as the analysis was primarily intended for dermatologists. Finally, our classification, which was built empirically into three classes, is a simple, straightforward and intuitive one that helps provide guidance for future research.

Important strengths of our study are its large sample size and the fact that all patients had a definitive diagnosis of NF1. We chose the LCA method which is a well-established method for classifying patients with similar patterns. However, the latent classes identified depend on the initial choice of the number and

**Table 2** Multinomial univariate logistic regression with class LC1 as the reference category

|                       | LC2<br>‘Subcutaneous neurofibromas’ |                           | LC3<br>‘Dysmorphic phenotype’ |                           |
|-----------------------|-------------------------------------|---------------------------|-------------------------------|---------------------------|
|                       | RR (95% CI)                         | p <sup>†</sup> LC2 vs LC1 | RR (95% CI)                   | p <sup>†</sup> LC3 vs LC1 |
| Male sex              | <b>1.37 (1.09–1.72)</b>             | <b>0.008</b>              | 1.01 (0.50–2.01)              | 0.983                     |
| Age*                  | 0.99 (0.98–1.00)                    | 0.011                     | <b>0.93 (0.89–0.96)</b>       | <b>0.000</b>              |
| Internal neurofibroma | 1.23 (0.85–1.77)                    | 0.273                     | 0.97 (0.34–2.80)              | 0.950                     |
| Lisch nodules         | <b>0.58 (0.42–0.81)</b>             | <b>0.001</b>              | 1.52 (0.43–5.43)              | 0.518                     |
| Optic pathway glioma  | 0.94 (0.56–1.59)                    | 0.820                     | <b>4.79 (1.95–11.78)</b>      | <b>0.001</b>              |
| Epilepsy              | 1.12 (0.66–1.91)                    | 0.674                     | <b>4.52 (1.76–11.64)</b>      | <b>0.002</b>              |
| Hypertension          | 0.94 (0.64–1.38)                    | 0.756                     | 1.52 (0.57–4.03)              | 0.403                     |
| Scoliosis             | <b>0.72 (0.57–0.91)</b>             | <b>0.007</b>              | 1.35 (0.68–2.67)              | 0.397                     |
| Malignancy            | 0.81 (0.56–1.17)                    | 0.259                     | 1.51 (0.61–3.75)              | 0.371                     |

\*Increase in age by each 1 year.

† P-values from pairwise analyses; threshold = 0.016 according to Bonferroni’s correction.

Bold value indicates statistical significance.

nature of the latent indicators. This explains the difference in clusters identified in our study and in the CTF NF1 registry study. As with all hospital-based studies, selection bias cannot be excluded, and external generalizations may be limited. The study is reported in accordance with STROBE guidelines.

There is a strong overlap among the described phenotypes. This stems from the fact that classifications methods cannot establish the fact that proposed clusters correspond to a clear etiological subtype. They prove, however, to be effective tools for determining heterogeneity in the data and suggesting new hypotheses. Furthermore, the overlap of these described phenotypes probably reflects the potential impact of genetic variants both in the NF1 gene and related modifier genes.

Our findings invite the performance of a larger cohort study which would include a vaster array of indicators encompassing all the phenotypic traits described in NF1, combined with molecular studies to test whether the various latent classes reflect different underlying genetic modifiers of these phenotypic traits.

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### Authors contribution

PW conceived and designed the study and is the guarantor for the study. ES performed the data analyses. CB wrote the initial draft of the article, to which all the authors contributed. All authors have given final approval for the final version to be published. The NF-France network contributed to the patients' inclusion.

### Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

### References

- Wallace MR, Marchuk DA, Andersen LB *et al.* Type 1 neurofibromatosis gene: identification of a large transcript disrupted in three NF1 patients. *Science* 1990; **249**: 181–186.
- Kallionpaa RA, Uusitalo E, Leppavirta J, Poyhonen M, Peltonen S, Peltonen J. Prevalence of neurofibromatosis type 1 in the Finnish population. *Genet Med* 2018; **20**: 1082–1086.
- Bergqvist C, Servy A, Valeyrie-Allanore L *et al.* Neurofibromatosis 1 French national guidelines based on an extensive literature review since 1966. *Orphanet J Rare Dis* 2020; **15**: 37.
- Easton DF, Ponder MA, Huson SM, Ponder BA. An analysis of variation in expression of neurofibromatosis (NF) type 1 (NF1): evidence for modifying genes. *Am J Hum Genet* 1993; **53**: 305–313.
- Sabbagh A, Pasmant E, Laurendeau I *et al.* Unravelling the genetic basis of variable clinical expression in neurofibromatosis 1. *Hum Mol Genet* 2009; **18**: 2768–2778.
- Pasmant E, Vidaud M, Vidaud D, Wolkenstein P. Neurofibromatosis type 1: from genotype to phenotype. *J Med Genet* 2012; **49**: 483–489.
- Upadhyaya M, Huson SM, 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. *Am J Hum Genet* 2007; **80**: 140–151.
- 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**: 1052–1063.
- Koczkowska M, Chen Y, Callens T *et al.* Genotype-phenotype correlation in NF1: evidence for a more severe phenotype associated with missense mutations affecting NF1 codons 844–848. *Am J Hum Genet* 2018; **102**: 69–87.
- Pemov A, Sung H, Hyland PL *et al.* Genetic modifiers of neurofibromatosis type 1-associated cafe-au-lait macule count identified using multi-platform analysis. *PLoS Genet* 2014; **10**: e1004575.
- Sabbagh A, Pasmant E, Imbard A *et al.* NF1 molecular characterization and neurofibromatosis type I genotype-phenotype correlation: the French experience. *Hum Mutat* 2013; **34**: 1510–1518.
- Sbidian E, Bastuji-Garin S, Valeyrie-Allanore L *et al.* At-risk phenotype of neurofibromatose-1 patients: a multicentre case-control study. *Orphanet J Rare Dis* 2011; **6**: 51.
- Sbidian E, Hadj-Rabia S, Riccardi VM *et al.* Clinical characteristics predicting internal neurofibromas in 357 children with neurofibromatosis-1: results from a cross-sectional study. *Orphanet J Rare Dis* 2012; **7**: 62.
- Mensink KA, Ketterling RP, Flynn HC *et al.* Connective tissue dysplasia in five new patients with NF1 microdeletions: further expansion of phenotype and review of the literature. *J Med Genet* 2006; **43**: e8.
- Venturin M, Gervasini C, Orzan F *et al.* Evidence for non-homologous end joining and non-allelic homologous recombination in atypical NF1 microdeletions. *Hum Genet* 2004; **115**: 69–80.
- Pasmant E, Sabbagh A, Spurlock G *et al.* NF1 microdeletions in neurofibromatosis type 1: from genotype to phenotype. *Hum Mutat* 2010; **31**: E1506–1518.
- Mautner VF, Kluwe L, Friedrich RE *et al.* Clinical characterisation of 29 neurofibromatosis type-1 patients with molecularly ascertained 1.4 Mb type-1 NF1 deletions. *J Med Genet* 2010; **47**: 623–630.
- Cannon A, Chen MJ, Li P *et al.* Cutaneous neurofibromas in Neurofibromatosis type I: a quantitative natural history study. *Orphanet J Rare Dis* 2018; **13**: 31.
- Westerhof W, Konrad K. Blue-red macules and pseudoatrophic macules: additional cutaneous signs in neurofibromatosis. *Arch Dermatol* 1982; **118**: 577–581.
- Zeller J, Wechsler J, Revuz J, Wolkenstein P. Blue-red macules and pseudoatrophic macules in neurofibromatosis 1. *Ann Dermatol Venereol* 2002; **129**: 180–181.

- 21 De Raedt T, Brems H, Wolkenstein P *et al.* Elevated risk for MPNST in NF1 microdeletion patients. *Am J Hum Genet* 2003; **72**: 1288–1292.
- 22 Leppig KA, Kaplan P, Viskochil D, Weaver M, Ortenberg J, Stephens K. Familial neurofibromatosis 1 microdeletions: cosegregation with distinct facial phenotype and early onset of cutaneous neurofibromata. *Am J Med Genet* 1997; **73**: 197–204.
- 23 Tabata MM, Li S, Knight P, Bakker A, Sarin KY. Phenotypic heterogeneity of neurofibromatosis type 1 in a large international registry. *JCI Insight* 2020; **5**:e136262. <https://doi.org/10.1172/jci.insight.136262>