Correlation of Nonsense and Frameshift Mutations With Severity of Retinal Abnormalities in Neurofibromatosis 2

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Background: Neurofibromatosis 2 (NF2) is an autosomal dominant disease that is characterized by nervous system tumors and ocular abnormalities.

Objective: To investigate genotype-phenotype correlations demonstrated for NF2-associated nervous system tumors, cataracts, and retinal lesions.

Methods: Forty-eight patients with NF2 from a tertiary neurological referral center underwent screening for constitutional *NF2* mutations with multiple screening methods. Each patient underwent a complete ophthalmic examination, including fluorescein angiography to detect retinal vascular lesions.

Results: Retinal abnormalities (epiretinal membranes or retinal microaneurysms) were present in 25 of the 48 patients (52%). The occurrence of epiretinal membranes and retinal microaneurysms was highly correlated, but retinal abnormalities were not significantly correlated with cataracts (present in 39 of 47 patients [83%]). Logistic regression with full constitutional nonsense or frameshift mutations as the reference group demonstrated that somatic mosaicism was associated with a significantly lower likelihood of retinal abnormalities (odds ratio, 0.05; 95% confidence interval, 0.01-0.49).

Conclusions: To our knowledge, this is the first genetic, clinical, and angiographic characterization of retinal abnormalities in NF2. Severe mutations are correlated with a more severe retinal involvement.

Clinical Relevance: Retinal abnormalities, which can be revealed by means of fluorescein angiography, are more common in patients with NF2 who have nonsense or frameshift mutations.

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NEUROFIBROMATOSIS 2 (NF2) is an autosomal dominant disease that is caused by inactivating mutations of the *NF2* tumor suppressor gene (GenBank AF069751).[1,2] Patients with NF2 (hereinafter referred to as NF2 patients) have a mutation in 1 of the 2 *NF2* gene copies in every cell of their bodies. This mutation is termed a *constitutional mutation*. A second mutation or loss of the other NF2 copy leads to complete loss of the *NF2* gene function and thus results in tumor development. This second mutation, which is specific for each tumor and does not exist in nontumor tissues, is called a *somatic mutation*. The characteristic nervous system tumors in NF2 are vestibular schwannomas (usually bilateral), intracranial meningiomas, spinal tumors (schwannomas, meningiomas, or ependymomas), and peripheral nerve schwannomas. Ocular abnormalities are common and may include cataracts, epiretinal membranes, retinal hamartomas, and combined pigment epithelial and retinal hamartomas.[3-6]

Genotype-phenotype correlations have been demonstrated for NF2-associated nervous system tumors and cataracts.[7-10] In general, patients with constitutional nonsense or frameshift *NF2* mutations have more severe disease (as indicated by more tumors, younger age at onset of NF2 symptoms, and a higher prevalence of cataracts), whereas patients with missense mutations, large deletions, or somatic mosaicism have milder disease (as indicated by fewer tumors, older age at onset of NF2 symptoms, and a lower prevalence of cataracts). Among patients with constitutional splice-site *NF2* mutations, mutations in 5′ exons are associated with more severe disease than are mutations in 3′ exons.[11,12]

In 3 large NF2 patient series, cataracts have been studied thoroughly but retinal lesions have been evaluated only partially by means of indirect ophthalmoscopy after dilation of the pupilla,[3-5] which is inadequate for proper assessment of reti-

nal abnormalities. The NF2-associated retinal lesions have loss of heterozygosity for chromosome 22 markers that flank the *NF2* gene.[13] In one study, 9 NF2 patients (from 5 families) each had retinal hamartomas or epiretinal membranes and constitutional *NF2* nonsense mutations[7]; however, in another study, patients with retinal hamartomas had other types of *NF2* mutations in addition to nonsense mutations.[14] In the present study, we assessed retinal abnormalities in NF2 with fluorescein angiography, the criterion standard clinical test for detecting such lesions, and evaluated genotype-phenotype correlations.

METHODS

Forty-eight NF2 patients at a tertiary neurological referral center underwent evaluation with complete ocular examinations, neurological examinations, and constitutional *NF2* mutation analysis. All patients gave informed consent and met the Manchester clinical diagnostic criteria for NF2.[15] None of the patients had vitreoretinal treatments before this study or had allergies to fluorescein sodium. All patients underwent gadolinium-enhanced magnetic resonance imaging of the brain and full spine as described previously.[16,17]

The ocular examination included tests of best-corrected visual acuity, refraction, applanation tonometry, and ocular motility. The anterior eye segment was examined with slitlamp biomicroscopy before and after dilation. Conventional fluorescein angiography was performed with a Topcon 50° camera (Topcon Medical Systems, Inc, Paramus, NJ). The extent of intraretinal leakage of fluorescein and epiretinal membranes was recorded in terms of maximal disc diameters (eg, 0.5, 1, or 2 disc diameters). Epiretinal membranes were categorized as extrafoveal (not affecting visual acuity) or foveal (affecting visual acuity) and as cellophane maculopathy (milder) or preretinal fibrosis with folds (more severe).

Genomic DNA was extracted from peripheral leukocytes. Exons 1 to 15 of the *NF2* gene were amplified and scanned with single-stranded conformational polymorphism analysis or temperature-gradient gel electrophoresis and direct sequencing as described previously.[18,19] Patients in whom *NF2* mutations were not found underwent additional screening with a newly developed gene dosage assay, multiplex ligation-dependent probe amplification, to identify exon deletions and duplications.[20]

For univariate analyses, we used the 2-tailed *t* test for continuous variables, the Wilcoxon signed rank test for ordinal variables, and the Fisher exact test for categorical variables. We evaluated genotype-phenotype correlations using odds ratios and their 95% confidence intervals from the logistic regression model. Because the occurrence of epiretinal membranes and retinal microaneurysms was highly correlated (as described in the "Results" section), the dependent variable in the logistic regression analysis was the presence or absence of either type of retinal vascular abnormality. The covariates were age at ocular examination and type of *NF2* mutation, which was classified categorically as 1 of 5 binary variables. Patients with full constitutional nonsense or frameshift mutations were the reference group for statistical comparisons. Patients with uncommon types of mutations (in-frame deletions and large deletions) were excluded from the logistic regression analysis owing to insufficient data.

The 5 binary mutation covariates were indicators of full constitutional nonsense or frameshift mutations, somatic mosaicism, splice-site mutations, and 2 categories for patients without a family history of the disease (henceforth referred to as de novo mutations) whose mutations were not found after mutation screening. As in previous studies from our institution of genotype-phenotype correlations in NF2,[9,10] patients with unfound de novo mutations were divided into 2 categories based on age at onset of NF2 symptoms, which is the single most important clinical index of disease severity.[21,22] The 2 categories were onset of symptoms of NF2 before age 20 years (severe disease) or at age 20 years or later (mild disease).[4] All patients in this study were symptomatic at the initial examination.

Patients with somatic mosaicism defined at the molecular level and those with unfound de novo mutations and mild disease were combined into a single covariate (known or probable somatic mosaicism, respectively). The NF2 patients in this study with unfound de novo mutations and mild disease most likely have somatic mosaicism. Somatic mosaicism and large deletions are the 2 most common causes of unfound constitutional *NF2* mutations when conventional mutation screening methods such as single-stranded conformational polymorphism analysis are used. However, in this study, large deletions were detected by means of multiplex ligation-dependent probe amplification, leaving somatic mosaicism as the likely cause of unfound mutations in patients with de novo mutations and mild disease. Tumor tissue was not available for molecular analysis in patients with probable mosaicism.

RESULTS

The characteristics of the study population are presented in **Table 1**. Forty patients had de novo mutations and 8 had inherited disease, as determined by family history. All patients were unrelated except for 2 siblings with nonsense mutations. The median age at ocular examination was 31 (range, 9-64) years.

Epiretinal membranes (**Figure 1**) or retinal microaneurysms (**Figure 2**) were present in 25 of the 48 patients (52%). Epiretinal membranes were present in 17 patients (35%) and in 27 eyes, including 15 eyes with foveomacular membranes, 12 with extrafoveal membranes, 19 with cellophane maculopathy, and 8 with preretinal fibrosis with folds. Retinal microaneurysms were present in 24 patients (50%) (42 eyes), and intraretinal leakage of fluorescein was present in 19 (40%) (32 eyes). Retinal hamartomas were present in 3 patients (6%) (4 eyes, including 1 with a combined pigment epithelial and retinal hamartoma).

As expected, the occurrence of the several types of retinal abnormalities was highly correlated (Fisher exact test, $P < .001$ for each association). Epiretinal membranes were present in 26 of the 42 eyes with retinal microaneurysms but in only 1 of the 54 eyes without retinal microaneurysms. Intraretinal leakage of fluorescein was present in 32 of the 42 eyes with retinal microaneurysms but in none of the 54 eyes without retinal microaneurysms. Intraretinal leakage of fluorescein was present in 25 of the 27 eyes with epiretinal membranes but in only 7 of the 69 eyes without epiretinal membranes. In eyes with intraretinal leakage of fluorescein and epiretinal membranes, the extent of leakage was significantly associated with the extent of epiretinal membranes (Wilcoxon signed rank test, $P = .01$).

Cataracts were present in 39 of 47 patients (83%) and in 73 of 94 eyes (1 patient did not have data on cataracts). There were posterior subcapsular cataracts in 50 eyes, mixed cataracts (posterior subcapsular and cortical cataracts) in 16 eyes, and cortical cataracts in 7 eyes.

Table 1. Clinical Characteristics of the Study Population by Category of *NF2* Mutation[a]

Clinical Characteristic	Nonsense or Frameshift Mutation		Splice-Site Mutation	Unfound De Novo Mutations, Age at Onset of NF2 Symptoms, y	
	NF2	Mosaic *NF2*		<20	≥20
No. of patients	18	4	6	7	9
Female	8 (44)	2 (50)	4 (67)	4 (57)	5 (56)
Inheritance, de novo mutations	12 (67)	4 (100)	5 (83)	7 (100)	9 (100)
Age at onset of NF2 symptoms, y, mean (SD)	17 (12)	32 (10)	20 (14)	11 (5)	29 (7)
Vestibular schwannomas, bilateral	18 (100)	4 (100)	6 (100)	7 (100)	7 (78)
Intracranial meningiomas	10 (56)	2 (50)	1 (17)	4 (57)	4 (44)
Spinal tumors	9 (50)	2 (50)	6 (100)	6 (86)	7 (78)
Epiretinal membranes	10 (56)	0	3 (50)	3 (43)	0
Ocular abnormalities					
Retinal microaneurysms	11 (61)	0	4 (67)	4 (57)	0
Intraretinal leakage of fluorescein	10 (56)	0	3 (50)	3 (43)	0
Retinal hamartomas	1 (6)	0	0	2 (28)	0
Cataracts[b]	17 (94)	3 (75)	6 (100)	4 (67)	6 (67)

Abbreviation: NF2, neurofibromatosis 2.
[a] Excludes 2 patients with large deletions and 2 patients with in-frame deletions. Unless otherwise indicated, data are expressed as percentage of patients.
[b] One patient with an unfound de novo mutation did not have information on cataracts.

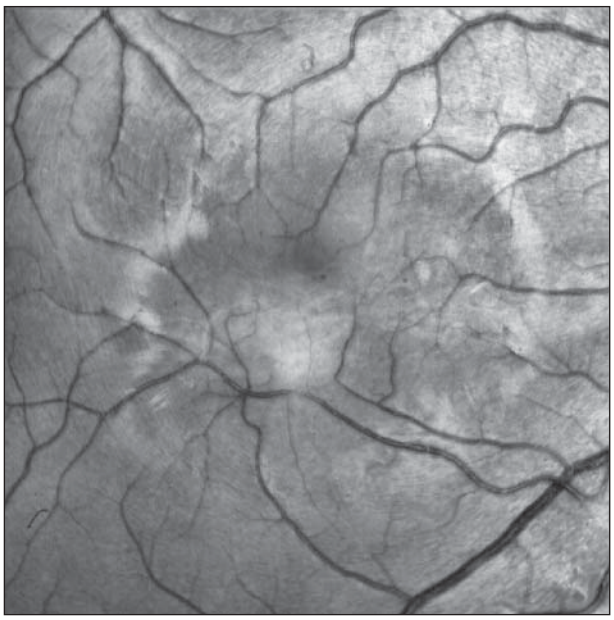

Figure 1. Epiretinal membrane in the eye of a patient with neurofibromatosis 2.

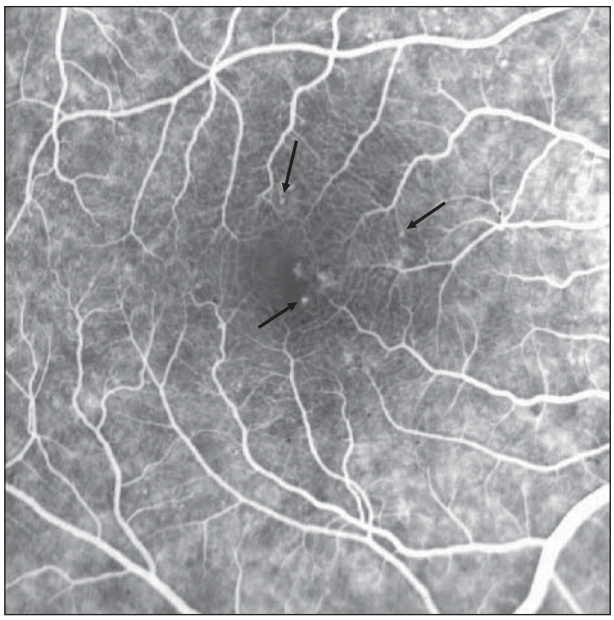

Figure 2. Retinal microaneurysms (arrows) in the eye of a patient with neurofibromatosis 2.

The occurrence of retinal abnormalities and cataracts was not significantly correlated.

Twelve of 48 patients (25%) (15 eyes) had visual acuity that was decreased to 20/40 or less. The specific causes of visual loss could be determined in 10 of the 15 eyes, and in these 10 eyes, there was usually more than 1 cause of visual loss. The specific causes of visual loss were cataracts in 9 eyes (including 6 with mixed cataracts), epiretinal membranes in 6, retinal hamartomas in 4, optic nerve tumors in 2, corneal opacification in 2, corneal scarring in 1, and ptosis in 1. Retinal microaneurysms were not associated with visual loss.

Constitutional *NF2* mutations were found in 25 of the 40 patients with de novo mutations (62%) and in all 8 inherited cases. Compared with full constitutional nonsense or frameshift *NF2* mutations, somatic mosaicism was associated with a significantly lower likelihood of retinal vascular abnormalities (odds ratio, 0.05; 95% confidence interval, 0.01-0.49) (**Table 2**). The patient's age at the ocular examination did not contribute significantly to the logistic regression model.

COMMENT

To our knowledge, this is the first study to describe retinal vascular abnormalities such as retinal microaneurysms in NF2.

The lower likelihood of retinal lesions in somatic mosaicism extends genotype-phenotype correlations that

Table 2. Results of Logistic Regression Analysis With Presence or Absence of Retinal Abnormalities as the Dependent Variable

Type of *NF2* Mutation	Prevalence of Retinal Abnormalities[a]	OR (95% CI)
Nonsense or frameshift		
Classic NF2	0.67	1 [Reference]
Somatic mosaicism (known or probable)[b]	0.05	0.05 (0.01-0.49)
Splice-site	0.67	1.00 (0.14-7.10)
Unfound de novo mutation, with onset of NF2 symptoms <20 years of age	0.57	0.67 (0.11-3.99)

Abbreviations: CI, confidence interval; NF2, neurofibromatosis 2; OR, odds ratio.
[a] Indicates epiretinal membranes or retinal microaneurysms. Age at ocular examination did not contribute significantly to the model.
[b] Known somatic mosaicism is defined at the molecular level; probable somatic mosaicism includes patients with unfound de novo mutations and onset of NF2 symptoms at 20 years or older.

have been reported previously for NF2-associated nervous system tumors and cataracts.[9,10] That epiretinal membranes are highly associated with retinal microaneurysms is expected because the latter are very commonly found in combined hamartomas and in areas of chronic traction. The lack of correlation of cataracts with retinal abnormalities may stem from the fact that cataracts are so common in these patients and that they are present in patients with or without detectable retinal changes. Another reason for this might be related to the different embryological and fetal development of the lens and the retina.

Retinal microaneurysms are also found in more common retinal diseases like diabetes mellitus or hypertension. None of our patients had diabetes, and 1 patient had hypertension but no irregularity of the retinal arteries, crossing signs, or hemorrhage. Therefore, we do not consider the microaneurysms related to hypertension. With fluorescein angiography, retinal microaneurysms were detected only at the posterior pole because the fluorescein angiogram covered 30° of the central retina.

There are genotype-phenotype correlations for retinal abnormalities in other tumor suppressor gene syndromes. In von Hippel-Lindau (VHL) disease, *VHL* mutations that lead to amino acid substitutions are associated with a higher number of retinal hemangioblastomas than are mutations that lead to truncated proteins.[23] In adenomatous polyposis coli (APC), the occurrence of congenital hypertrophy of the retinal pigment epithelium is dependent on the location of the *APC* mutation.[24,25]

Retinal telangiectasia occurs in Coats disease (idiopathic congenital retinal telangiectasia with exudative retinopathy that may be associated with exudative detachment), and exudative retinopathy occurs in many other diseases such as retinoblastoma, facioscapulohumeral muscular dystrophy, and retinitis pigmentosa.[26] Epiretinal membranes are caused by the loss of the spatial barrier between the retinal pigment epithelium and the vitreal cavity. Epiretinal membranes can be developmental abnormalities but also can be caused by inflammation, trauma, posterior vitreous detachment, retinal detachment or breaks, or retinal vascular disorders. Retinal hamartomas and retinal pigment epithelial alterations are developmental abnormalities of tissues that arise from the neural crest. During embryogenesis, neural crest cells are situated beneath the surface ectoderm at the sites that give rise to the lens, the retinal pigment epithelium, the inner layer of the optic stalk, and retinal glial cells. It may be possible to study the developmental biology of NF2-associated retinal abnormalities in *NF2* knockout mouse models.[27,28]

Epiretinal membranes and cataracts are common in the general population in people who are older than 50 years.[29,30] In this study, none of the patients with epiretinal membranes was older than 50 years at the time of the ocular examination, but cataracts in 2 patients who were 59 and 64 years of age at the time of the ocular examination cannot be attributed unambiguously to NF2.

Intact vision is especially important for the daily function and quality of life of NF2 patients who have multiple nervous system tumors, deafness, and facial nerve dysfunction. In this study, 25% of the patients had visual loss in at least 1 eye. This is a considerably higher proportion than the 11% of patients with visual loss in the National Institutes of Health's longitudinal study of NF2.[5] This may be due, in part, to the different proportion of patients with severe NF2 in the 2 studies (approximately 70% in the Hamburg patient series and approximately 50% in the National Institutes of Health patient series).

About half of the NF2 patients in the present study had retinal abnormalities. The results of this study do not support the use of fluorescein angiography in routine ophthalmic examinations for NF2 patients because retinal microaneurysms were not associated with visual loss. However, a thorough retinal examination should be part of the clinical evaluation for NF2 patients, for at-risk members of NF2 families, and for people without a family history of the disease who are suspected of having NF2. Adults with NF2 usually have symptoms that are related to vestibular schwannomas, but young people with NF2 often have symptoms that are related to other lesions, such as ocular abnormalities.[5,31] Therefore, a careful retinal examination should be performed in all patients with any detectable NF2 mutation or in any patient with early onset of symptoms because the only patient category that did not develop retinal abnormalities included those patients in whom *NF2* mutations had not been found and who were older than 20 years. Identification of epiretinal membranes or retinal hamartomas in young people may facilitate early diagnosis of NF2 and thereby aid in clinical management.

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