Chorioretinal Alterations and Genetic Findings in Neurofibromatosis type 2

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- **Purpose:**. The present study aims to describe ophthalmological and molecular findings in a series of eight patients with a clinical diagnosis of neurofibromatosis type 2 (NF2).
- **Methods:** Eye examination was performed in 16 NF2 eyes and it included measurement of the visual acuity, biomicroscopy, dilated fundus examination, color fundus photography, infrared photography and spectral domain optical coherence tomography (SD-OCT). Molecular analysis was performed with whole-exome sequencing using DNA derived from peripheral blood mononuclear cells from each individual.
- **Results:** Ophthalmological features were observed in all patients, and range widely from subtle retinal alterations identified only by SD-OCT to severe ocular involvement present at birth. Three categories of mutations were found: three patients with premature termination codon (nonsense) mutations, two patients with frameshift mutations and one patient with splice site mutation. Three novel mutations were found.
- **Discussion:** NF2 is an autosomal-dominant disease, characterized by bilateral vestibular schwannomas, multiple central nervous system (CNS) tumors, skin tumors and juvenile cataract. A well-defined spectrum of ocular features has been specifically associated with NF2. NF2 disease-causing mutations includes nonsense, splice site and missense mutations. Genotype-phenotype correlations in NF2 have been proposed, with nonsense and frameshift mutations being associated with the most severe clinical presentation. Correlations between truncating mutations and ocular alterations have also been observed. A descriptive study of ocular and molecular characteristics in NF2 patients is of significant value, since there are few previous reports on this subject. The clinical and genetic findings, including three novel mutations add new information on the understanding of genotype-phenotype correlations.

Table 1. The main ophthalmological and molecular characteristics of the studied group of patients with NF2

Patient	Gender	Age	First Symptom	Mutation	Cataract	Hamartoma	Flame Shape ERM	Strabismus	Retinal tuft	Choroidal nodules
1	M	50 years	Limbs paresis	Negative	+	-	-	-	+	-
2	F	33 years	Facial pain	Negative	-	-	-	-	+	-
3	M	28 years	Convulsion	Nonsense chr22.30.050.691 C>T	+	+	-	+	-	-
4*	M	19 years	Strabismus	Frameshift chr22.30.064367.30.062.368 AG>A	+	-	+	+	-	+
5	M	14 years	Café au lait spots	Nonsense crh22.30.051.652 C>T	-	-	+	-	+	-
6*	F	24 years	Limbs paresis	Frameshift chr22:30.057.260-30.057.268 AACAGACTG>A	-	+	+	-	-	-
7	M	16 years	Cataract	Intrônic, 2pb crh22.30.069.477 T>G	+	+	+	-	-	+
8*	F	15 years	Strabismus	Frameshift crh22.30.032.802.30.032.809 CTGGTTCT>C	+	+	+	+	+	+

* Patients with novel mutations

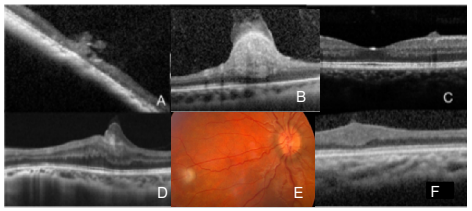

Figure 1. A) SD-OCT of case 8 showing a peripheral retina tuft. **B)** SD_OCT of case 6 showing a typical NF2 hamartoma. **C)** SD-OCT of case 2 showing an evident retinal tuft in parafoveal region. **D)** SD-OCT of case 7 showing a small retinal hamartoma evident only by SD-OCT. **E)** Retinography of case 6 showing a typical NF2 hamartoma. **F)** SD-OCT of case 8 showing an intraretinal retinal hamartoma.

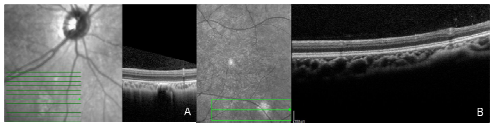

Figure 2. A) Infra-red imaging and SD-OCT of case 4 showing a choroidal nodule similar to choroidal nodules described in NF1 patients. **B)** Infra-red imaging and SD-OCT of case 8 showing a choroidal nodule.