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The ABCA4 Gene in Autosomal Recessive Cone-Rod Dystrophies

To the Editor:

Recently, Maugeri et al. (2000) reported on the screening of the *ABCA4* gene in 5 patients with autosomal recessive cone-rod dystrophies (CRD) and 15 patients with sporadic CRD originating from Germany and the Netherlands. The identification of mutations in 13/20 patients (65%) led the authors to speculate that "Mutations in the *ABCA4* (*ABCR*) gene are the major cause of autosomal recessive cone-rod dystrophy."

The present study was undertaken to evaluate the prevalence of *ABCA4* mutations in a cohort of 55 patients affected with autosomal recessive or sporadic CRD.

Within the huge family of inherited retinal dystrophies, the CRD phenotype indicates a specific form of retinal degeneration in which the cone degeneration appears early in life with a central involvement of the retina, followed by a degeneration of rods several years later (Klevering et al. 2002). This particular form of retinal dystrophy has long been regarded as "inverse retinitis pigmentosa" (RP) and can be misdiagnosed as macular dystrophy in the first stages of the disease.

Indeed, the main symptoms at onset of the disease are decrease of visual acuity, loss of color discrimination, and photophobia. The b-wave of the photopic ERG (cone response) is severely reduced, although the b-wave of the scotopic ERG is still normal. As the disease progresses, nyctalopia, progressive peripheral visual field deficit, and decreasing scotopic electroretinogram (ERG) amplitudes are observed.

Four genes (*CRX* [MIM 602225], *GUCY2D* [MIM 600179], *GCAP1* [MIM 600364], and *HRG4* [MIM 604011]) and two loci have been implicated in autosomal dominant CRD (*CORD5* [MIM 600977] and *CORD7* [MIM 603649]), whereas two other loci were reported for autosomal recessive CRD (*CORD9* [Danciger et al. 2001] and *CORD8* [MIM 605549]) and one for X-linked CRD (*RPGR* [MIM 312610]).

Conversely, the *ABCA4* gene, which was identified in 1997 as the Stargardt-causing gene, was later recognized as responsible for some forms of RP (RP19) and some CRD, depending on the nature of the *ABCA4* mutations and on the remaining protein activity (Allikmets et al. 1997; Martinez-Mir et al. 1997; Cremers et al. 1998; Gerber et al. 1998; Rozet et al. 1998, 1999).

Sixty-one individuals affected with CRD and 40 healthy relatives belonging to 55 families of various origin were recruited from genetic and ophthalmologic consultations. In 29/55 families, the disease was undoubtedly inherited as an autosomal recessive condition—23 multiplex families (11/23 consanguineous) and six simplex patients born to consanguineous parents. In the 26/55 remaining families, the patients were simplex cases. The time course of the disease was determined by interviewing at least one patient per family and, whenever possible, all affected siblings of the family. Minimal criteria for inclusion in the study were initial cone dysfunction and subsequent progressive peripheral disease.

In one affected patient per family, we screened for mutations the 50 exons of the *ABCA4* gene, as well as the flanking intronic sequences, using denaturing high-pressure liquid chromatography. On the basis of the secondary structure of each exon, the screening was performed at 1 or 2 temperatures (mutation detection rate estimated to be at least 0.98). Exons showing a shift were directly sequenced.

Sixteen different mutant alleles were identified in 13/55 patients (i.e., 23.6% of all cases). Among these 13 patients, 2 were homozygotes (from two consanguineous families), 4 were compound heterozygotes, and 7 were

single heterozygotes (see table 1). Among the 29 recognized autosomal recessive cases of CRD, only 6 were found to carry *ABCA4* mutations (20.7%), whereas, of the 26 sporadic cases of CRD, 7 harbored mutations in the gene (26.9%). The frequencies of *ABCA4* mutations in the two groups are not significantly different.

In a similar screen of 43 multiplex or consanguineous families with Stargardt disease showing genetic linkage to the *ABCA4* locus on 1p22, we identified at least one mutated allele in 34 families (data not shown). This figure is broadly in line with the findings of other groups (Allikmets et al. 1997; Rozet et al. 1998; Lewis et al. 1999; Rivera et al. 2000; Yatsenko et al. 2001) and suggests that a proportion of *ABCA4* mutations remain to be identified. These could lie in promotor or intron sequences or in undiscovered exons (e.g., *RPGR* [Vervoort et al. 2000]), or they could be deletions up to 1 mb away (e.g., PAX6 [Lauderdale et al. 2000]). We therefore conservatively estimate that this screen will have detected ~80% of the mutations present in these families, giving a corrected implication of the *ABCA4* gene in 29.5% of all cases (autosomal recessive CRD 25.9% and sporadic cases of CRD 33.6%).

This study confirms that *ABCA4* is a major gene responsible for CRD. Nevertheless, the frequency of mutations appears to be lower than reported (30% in our series vs. 65% in Maugeri's series).

Finally, this work might improve genetic counseling in this condition. Indeed, for a sporadic case of CRD with no *ABCA4* mutation, the risk of the disease to be inherited nevertheless as an autosomal recessive condition can be estimated to be 15.6% using the Bayesian calculation (calculation details on request).

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Electronic-Database Information

Accession numbers and URLs for data presented herein are as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for CORD5 [MIM 600977], CRX [MIM 602225], CORD7 [MIM 603649], GCAP1 [MIM 600364], HRG4 [MIM 604011], GUCY2D [MIM 600179], RPGR [MIM 312610], and CORD8 [MIM 605549])

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Table 1

***ABCA4* Mutations in Patients with CRD**

	ABCA4 Allele 1		*ABCA4* Allele 2		
Patient	Nucleotide Change	Effect	Nucleotide Change	Effect	Origin
16	AAC 286 GAC	N96D	—	—	France
52	ATC 466 GTC	I156V	—	—	North Africa
57	ATC 466 GTC	I156V	GGG 1819 AGG	G607R	North Africa
51	CGA 455 CAA 5084+1G/A	R152Q Frameshift	CGC 3323 TGC AGT 6764 ATT	R1108C S2256I	France
11	CGT 764 TGT	R255C	—	—	France
41	GCC 3113 GTC	A1038V	—	—	France
60	CTG 3602 CGG	L1201R	AGT 6764 ATT	S2256I	South Africa
21	CTC 5908 TTC	L1970F	—	—	France
30	AGT 6764 ATT	S2256I	—	—	Africa
48	GAA 3259 TAA	E1087X	—	—	France
2	2617 del CT	Frameshift	2617 del CT	Frameshift	Portugal
5	571-2A/G	Frameshift	571-2A/G	Frameshift	Morocco
61	CGG 4918 TGG	R1602W	GGC 5929 AGC	G1977S	England

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