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### Meta-Analysis of Associations of the Ser217Leu and Ala541Thr Variants in *ELAC2* (*HPC2*) and Prostate Cancer

To the Editor:

Several factors can contribute to variability in association-study findings. They include, but are not limited to, population-specific linkage disequilibrium between causal variants and marker variants, multilocus interactions, gene-environmental interactions, inadequate statistical power, and different selection criteria for case and control individuals. Meta-analyses afford the opportunity to combine evidence across studies, thereby increasing sample size and power and allowing a more global interpretation of the total data available. We have performed a meta-analysis for data pertaining to the association of alleles of variants Ser217Leu (MIM 605367.0001) and Ala541Thr (MIM 605367.0002) in the *ELAC2* (*HPC2*) gene (MIM 605367) and prostate cancer (MIM 176807) (GenBank accession number AF304370).

The *ELAC2* gene on chromosome 17p11.2 was the first candidate gene for prostate cancer susceptibility to be identified from a linkage analysis and positional cloning project (Tavtigian et al. 2001). Two segregating mutations (1641insG and Arg781His) were found in two extended Utah pedigrees; in addition, the less common alleles of two missense variants (Ser217Leu and Ala541Thr) were observed to be associated with familial prostate cancer (from pedigrees at high risk of prostate cancer [ $n = 429$ ]) when compared with control individuals at low risk (i.e., men who were cancer-free and were not members of pedigrees with a high risk of prostate cancer [ $n = 148$ ]). Initial results indicated that individuals homozygous for Leu217 and individuals carrying the Thr541 allele were at significantly increased risk for prostate cancer and, furthermore, that a combination across both genotypes was the most significant, with an odds ratio (OR) of 2.94 (95% CI 1.52–5.69) (see table 3 of Tavtigian et al. 2001).

Several groups have attempted to confirm these findings, with varying levels of success (only two of the total six studies found significant evidence for the same var-

iants). In brief, Rebbeck et al. (2000) found that carriage of both Leu217 and Thr541 significantly was associated with prostate cancer, in a study of 359 men with newly diagnosed prostate cancer and 266 male age- and race-matched control individuals with an OR of 2.37 (95% CI 1.06–5.29) (see table 2 of Rebbeck et al. 2000). Xu et al. (2001) studied two groups of patients: those with familial disease ( $n = 134$ ) and those with sporadic disease ( $n = 228$ ), in comparison with control individuals at low risk (men who had normal results of a digital rectal examination [DRE] and normal levels of prostate-specific antigen [PSA] [ $n = 182$ ]). No analyses yielded significant results, although several exhibited trends in the expected direction; for example, the OR for carriers of Leu217 compared with control individuals was 1.49 (95% CI 0.94–2.35) (see table 5 of Xu et al. [2001]). Vesprini et al. (2001) studied 431 men with screen-detected prostate cancer, 513 men with elevated PSA but no detectable prostate cancer (the prevalence of benign and neoplastic prostate disease in this group was high), and 922 healthy women. No significant results were found, with the most interesting finding from this study being that there were more double homozygotes among the men with prostate cancer than among either control group ( $P = .18$ ) and, in addition, that there was a modest association between carriage of Thr541 and a family history of prostate cancer ( $P = .04$ ). Suarez et al. (2001) studied 257 men with familial prostate cancer and 355 low-risk control individuals (i.e., those with normal DRE results and normal PSA levels, age >65 years, and no family history of prostate cancer); they found a non-significant trend for carriage of Leu217 and a significant association between carriage of the Thr541 allele and prostate cancer ( $P = .008$ ). Wang et al. (2001) found no evidence for an association of either variant when 446 men with familial prostate cancer were compared with 502 population-based control individuals; however, a novel germline nonsense mutation (Glu216Stop) was found to play an interesting role in a large nuclear family that included multiple individuals with prostate cancer. Rokman et al. (2001) studied 107 men with familial prostate cancer, 467 men with sporadic disease, 223 men with benign prostatic hyperplasia (BPH), and 568 male blood donors. The Leu217 and Thr541 alleles were not found to be elevated significantly in men with prostate cancer (familial or sporadic); however, Thr541 was found

**Table 1****Raw Genotypic Counts for Ser217Leu and Ala541Thr**

VARIANT AND GENOTYPE	AUTHOR (RACE OF STUDY POPULATION)													
	Rebbeck (Various) <sup>a</sup>		Suarez (White) <sup>b</sup>		Tavtigian (White) <sup>c</sup>		Vesprini (Various) <sup>d</sup>		Wang (White)		Xu (White) <sup>f</sup>		Xu (White) <sup>g</sup>	
	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control
Ser217Leu:														
SS	144	118	120	190	204	76	220	259	198	232	58	97	172	97
SL	139	111	114	134	168	63	169	213	205	221	61	71	156	71
LL	<u>17</u>	<u>21</u>	<u>23</u>	<u>31</u>	<u>57</u>	<u>9</u>	<u>42</u>	<u>41</u>	<u>41</u>	<u>49</u>	<u>15</u>	<u>14</u>	<u>34</u>	<u>14</u>
Total	300	250	257	355	429	148	431	513	444	502	134	182	362	182
Ala541Thr:														
AA	269	232	232	342	387	143	404	478	399	450	111	166	322	166
AT,TT	<u>21</u>	<u>8</u>	<u>25</u>	<u>13</u>	<u>42</u>	<u>5</u>	<u>27</u>	<u>35</u>	<u>46</u>	<u>52</u>	<u>13</u>	<u>16</u>	<u>34</u>	<u>16</u>
Total	290	240	257	355	429	148	431	513	445	502	124	182	356	182

<sup>a</sup> Table 2 of Rebbeck et al. (2000) with additional clarification from the authors to enable Ser217 recessive analysis; >80% of patients were white, and case and control individuals were race and age matched.

<sup>b</sup> Table 1 of Suarez et al. (2001).

<sup>c</sup> From table 3 of Tavtigian et al. (2001), with counts for SS and SL separated.

<sup>d</sup> From table 2 of Vesprini et al. (2001). Only male control individuals were included in the present analysis; >80% of the study population were white.

<sup>e</sup> From tables 4 and 5 of Wang et al. (2001). Case individuals were ascertained from 181 families (180 white non-Hispanic and 1 of Hispanic ancestry).

<sup>f</sup> Patients with familial prostate cancer only; from table 5 of Xu et al. (2001).

<sup>g</sup> Patients with either familial or sporadic cancer; from table 5 of Xu et al. (2001).

to be significantly elevated in men with BPH, and the rare allele of a novel variant (Glu622Val) was found to be significantly increased in both groups with prostate cancer. All studies found Thr541, the less common variant, to be in very strong disequilibrium with Leu217. This disequilibrium makes it essentially impossible to distinguish the effects of Thr541 alone from the joint effect of the two missense changes in the Leu217 + Thr541 allele.

We constructed a Mantel-Haenszel meta-analysis of data from these studies, to consolidate the evidence of association between alleles of Ser217Leu and Ala541Thr and prostate cancer. The Mantel-Haenszel  $\chi^2$  test and the Mantel-Haenszel estimate of the OR (e.g., see Kirkwood 1988) were used to provide a summary test and OR, which control for confounding factor(s)—across the various data sources—that may distort results if data are simply pooled. Data from Rokman et al. (2001) could not be incorporated, since their data were presented by allele rather than by genotype. As is evident from the brief descriptions given here, classifications for affected and control individuals varied substantially across studies. For this reason, we analyzed case and control individuals in three groupings: men with familial prostate cancer versus low-risk control individuals (FAM vs. LOW); all men with prostate cancer versus low-risk control individuals (ALL vs. LOW); and all men with prostate cancer versus all control individuals (ALL vs. ALL). Table 1 shows the raw genotypic counts from the studies

used in our analyses, and table 2 reports the results for each of the three case/control comparison groups for Leu217 (recessive and dominant), Thr541 (dominant), and a multilocus analysis across both variants (Leu217 dominant and Thr541 dominant).

Our summary analysis of Thr541 data argues strongly in favor of two points. First, there is substantial evidence that carriage of the Thr541 allele, either alone or in combination with carriage of the Leu217 allele, is significantly associated with prostate cancer. Results of the comparisons FAM versus LOW and ALL versus LOW are highly significant for both these tests ( $P = .0080-.00011$ ). Second, the results are most significant in the more extreme case/control comparison group (FAM vs. LOW), with effect sizes decreasing as the case/control comparison broadens. For example, for the Thr541 dominant analysis, the ORs decrease from 1.96 (95% CI 1.19–3.22) to 1.81 (95% CI 1.23–2.68) to 1.25 (95% CI 0.97–1.60) (without data of Tavtigian et al. [2001]), or, similarly, from 2.23 (95% CI 1.44–3.46) to 2.01 (95% CI 1.40–2.88) to 1.35 (95% CI 1.07–1.72) (with data of Tavtigian et al. [2001]) as the comparison groups are expanded from FAM versus LOW to ALL versus LOW to ALL versus ALL, respectively. The dilution of significance and risk-size estimate as the case/control comparison group broadens is to be expected and is consistent with a true genetic risk. Patients with sporadic cancer are more likely to have a larger environmental and smaller genetic component, and population control

individuals are likely to harbor a substantial portion of men with prostate cancer, given the high disease rate.

The summary analysis of Leu217 data does not support the original finding by Tavtigian et al. (2001) that homozygotes for Leu217 are at increased risk for prostate cancer. Evidence from the meta-analysis is consistent with a very modest dominant effect. This may indicate that the best model for Leu217 is codominant. Significant results for Leu217 dominant are weaker than those for Thr541, but, as with Thr541, there appears to be a dilution of the effect of Leu217 as the case/control comparison broadens. Leu217 results are more often significant in the most extreme (FAM vs. LOW) case/control comparison and are never significant in the broadest (ALL vs. ALL) comparison. Also supportive of a very modest effect of Leu217 are the ORs for the combined multilocus analysis, which were found to be consistently, although modestly, higher than ORs for the Thr541 dominant analysis.

Our analyses here suggest that the original maximal OR risk estimates of 3.1 (carriage of Thr541 under a FAM vs. LOW comparison [table 3 of Tavtigian et al. 2001] and 2.37 (carriage of Thr541 under an ALL vs. LOW comparison [table 2 of Rebbeck et al. 2000]) for *ELAC2* variants on prostate cancer risk were inflated. Summary results indicate risk ratios as high as 2.4 when highly discordant groups (FAM vs. LOW, in the multilocus analysis including Tavtigian data) are compared, but the results project much lower risks, in the range of 1.3 (ALL vs. ALL, in the Thr541 dominant analyses), for the risk in the general population. If we assume a carrier frequency of 6.6% for risk genotypes (using pooled data), an OR of 1.3 translates to a population-attributable risk of 2% (Lillienfeld and Lillienfeld 1980). This is perhaps a more realistic expectation for common variants in a complex disease, and it suggests that studies may have been underpowered. In conclusion, our summary analyses indicate convincing evidence for the role

**Table 2**

**Results of Mantel-Haenszel Meta-Analysis, Including and Excluding Data of Tavtigian et al. (2001) for the Three Case/Control Comparisons**

COMPARISON, INCLUSIVENESS, AND MEASURE <sup>a</sup>	ANALYSIS			
	Leu217 Dominant	Leu217 Recessive	Thr541 Dominant	Multilocus <sup>b</sup>
<b>FAM vs. LOW:</b>				
Without Tavtigian:				
<i>P</i>	.017	.48	.0080	.0026
OR (95% CI)	1.37 (1.06–1.78)	1.18 (.75–1.85)	1.96 (1.19–3.22)	2.21 (1.32–3.69)
Total sample size	928	928	918	529
With Tavtigian:				
<i>P</i>	.016	.044	.00033	.00011
OR (95% CI)	1.30 (1.05–1.61)	1.48 (1.01–2.16)	2.23 (1.44–3.46)	2.44 (1.55–3.83)
Total sample size	1,505	1,505	1,495	856
<b>ALL vs. LOW:</b>				
Without Tavtigian:				
<i>P</i>	.11	.81	.0029	.0023
OR (95% CI)	1.17 (.96–1.42)	.96 (.67–1.37)	1.81 (1.23–2.68)	1.86 (1.25–2.77)
Total sample size	1,706	1,706	1,680	985
With Tavtigian:				
<i>P</i>	.075	.31	.00014	.00012
OR (95% CI)	1.17 (.98–1.39)	1.18 (.86–1.62)	2.01 (1.40–2.88)	2.05 (1.42–2.96)
Total sample size	2,283	2,283	2,257	1,312
<b>ALL vs. ALL:</b>				
Without Tavtigian:				
<i>P</i>	.21	.86	.081	NA
OR (95% CI)	1.09 (.95–1.24)	1.02 (.81–1.29)	1.25 (.97–1.60)	NA
Total sample size	3,596	3,596	3,571	NA
With Tavtigian:				
<i>P</i>	.15	.29	.013	NA
OR (95% CI)	1.10 (.97–1.24)	1.13 (.90–1.41)	1.35 (1.07–1.72)	NA
Total sample size	4,173	4,173	4,148	NA

<sup>a</sup> FAM vs. LOW comparison includes data from Xu et al. (2001) (familial prostate cancer only) and Suarez et al. (2001). ALL vs. LOW comparison includes data from Xu et al. (2001) (familial and sporadic prostate cancer), Suarez et al. (2001), and Rebbeck et al. (2000). ALL vs. ALL comparison includes data from Xu et al. (2001) (familial and sporadic prostate cancer), Suarez et al. (2001), Rebbeck et al. (2000), Vesprini et al. (2001) (male control individuals only), and Wang et al. (2001).

<sup>b</sup> Association test for carriage of both Leu217 and Thr541 versus carriage of neither. “NA” indicates that data were not available from the relevant published papers to perform the multilocus analysis.

of *ELAC2* in prostate cancer, suggest moderate familial risk, and estimate that risk genotypes in *ELAC2* may cause 2% of prostate cancer in the general population.

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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 prostate cancer [MIM 176807], HPC2/*ELAC2* [MIM 605367], Ser-to-Leu change at amino acid 217 [MIM 605367.0001], and Ala-to-Thr change at amino acid 541 [MIM 605367.0002])

GenBank, <http://www.ncbi.nlm.nih.gov/Genbank/> (for variant Ser217Leu [AF304370])

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### Regarding “Testing for Population Subdivision and Association in Four Case-Control Studies”

To the Editor:

Ardlie et al. (2002) recently found no evidence for population structure in separate case-control studies of type 2 diabetes and hypertension in U.S. whites and only weak evidence of structure in a case-control study of hypertension in African Americans. These results are consistent with the theoretical results of Wacholder et al. (2000), who found that the magnitude of bias due to unrecognized population stratification is likely to be small under most plausible scenarios. To further evaluate the potential bias due to stratification for these and other conditions, we conducted a series of case-control studies for six common phenotypes in a population-based sample of U.S. adults.

The study population included 444 unrelated adults (231 African Americans and 213 non-Hispanic whites) randomly selected from five U.S. communities as part of the Hypertension Genetic Epidemiology Network (HyperGEN) of the National Heart, Lung, and Blood Institute (NHLBI) Family Blood Pressure Program (Williams et al. 2000). The study was approved by the institutional review boards at each institution, and appropriate informed consent was obtained from human subjects. Phenotypes measured included: (1) obesity (BMI  $\geq 30$ ), (2) hypercholesterolemia (total plasma cholesterol  $\geq 240$  mg/dl or current use of medications to lower cholesterol), (3) hypertension (systolic blood pressure  $\geq 140$  mmHg, diastolic blood pressure  $\geq 90$  mmHg, or current use of medications to lower blood pressure), (4) diabetes (fasting serum glucose  $\geq 126$  mg/dl, nonfasting glucose  $\geq 200$  mg/dl, self-reported physician diagnosis of diabetes, or current use of hypoglycemic medications), (5) renal dysfunction (serum creatinine  $\geq$  sex-specific 90th percentile [1.4 mg/dl in men and 1.1 mg/dl in women]), and (6) cardiovascular disease (self-reported history of heart attack, stroke, or coronary artery bypass surgery). For each

phenotype, those who did not meet the case definition served as control individuals.

We constructed contingency tables and performed  $\chi^2$  tests of association for these six phenotypes with each of 368 STR markers typed by the NHLBI Mammalian Genotyping Service at Marshfield, WI (screening set 10). Like Ardlie et al. (2002), we then computed a statistic,  $\chi_s^2$ , to test for overall differences in allele frequencies between each set of case individuals and control individuals (Pritchard and Rosenberg 1999). To simplify the analysis and ensure that expected values in contingency tables were sufficiently large ( $> 5$ ) for the classical  $\chi^2$  test, we converted each STR marker to a biallelic marker by selecting one index allele for each marker and then collapsing all other alleles for that marker into a single alternative allele. Index alleles for each marker were selected by first choosing alleles with allele frequencies of at least 15% in both African Americans and whites and then selecting the allele that demonstrated the largest absolute difference in allele frequencies between racial groups.

The prevalence of several of the phenotypes differed substantially between racial groups (table 1). In crude analysis pooling both racial groups, the percentage of markers nominally associated ( $P < .05$ ) with each phenotype was higher than expected, under the null hypothesis, for diabetes (8.4%), hypertension (7.9%), renal dysfunction (7.6%), and hypercholesterolemia (5.4%) but not for cardiovascular disease (4.9%) or obesity (4.9%). The summary test for stratification incorporating all 368 markers (i.e., 368 df) was statistically significant for diabetes, renal dysfunction, and hypertension (table 1), indicating overall differences in allele frequencies between case individuals and control individuals. However, after adjustment for race or stratification by race, there was no evidence of cryptic stratification for any of the six phenotypes, with the possible exception of obesity in whites.

Our results provide further evidence that hidden or unrecognized population stratification is unlikely to be a serious threat to the validity of case-control designs

that appropriately account for ethnicity in either the design or analysis phase of the study (Wacholder et al. 2000; Ardlie et al. 2002). Because of the large number of markers tested, it is likely that our study was even more sensitive to subtle background genetic differences between case individuals and control individuals than that conducted by Ardlie et al. (2002), which included only 9 STR markers and 35 SNP markers. We think that other factors, such as selection bias, chance, publication bias, gene-environment interactions, and differences in linkage disequilibrium patterns across study populations, are more plausible explanations for inconsistency of results between genetic association studies.

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**Table 1**  
Summary Tests for Population Stratification by Phenotype

Phenotype	NO. OF CASE SUBJECTS (PREVALENCE)		ALL SUBJECTS, UNADJUSTED		ALL SUBJECTS, ADJUSTED FOR RACE		AFRICAN AMERICANS ONLY		WHITES ONLY	
	African Americans	Whites	$\chi_s^2$	<i>P</i>	$\chi_s^2$	<i>P</i>	$\chi_s^2$	<i>P</i>	$\chi_s^2$	<i>P</i>
Obesity	110 (48%)	82 (39%)	379.5	.33	336.8	.88	329.5	.93	431.9	.01
Hypercholesterolemia	44 (19%)	55 (26%)	401.4	.11	360.9	.59	358.4	.63	362.5	.57
Hypertension	130 (56%)	91 (43%)	456.2	.001	371.9	.43	391.7	.19	384.4	.27
Diabetes	46 (20%)	23 (11%)	507.2	<.001	395.7	.15	373.9	.41	381.4	.30
Renal dysfunction	29 (13%)	11 (5%)	442.5	.005	374.2	.40	388.4	.22	367.6	.50
Cardiovascular disease	30 (13%)	20 (9%)	378.6	.34	373.2	.41	377.1	.36	354.7	.68

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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**

Patient	<i>ABCA4</i> ALLELE 1		<i>ABCA4</i> ALLELE 2		Origin
	Nucleotide Change	Effect	Nucleotide Change	Effect	
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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