ATM Gene Variants in Patients with Idiopathic Perifoveal Telangiectasia

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Purpose. To investigate the prevalence of sequence variants in the *ATM* gene and to determine the frequency of major age-related macular degeneration (AMD)–associated variants in *CFH*, *CFB*, and 10q26 loci in patients with idiopathic perifoveal telangiectasia (IPT).

Methods. Thirty patients with diagnoses of IPT underwent standard ophthalmologic evaluation that included visual acuity testing, fundus photography, and fluorescein angiography. DNA was screened for variations in the *ATM* gene by a combination of denaturing high-performance liquid chromatography and direct sequencing. Major AMD-associated alleles in *CFH*, *CFB*, and 10q loci were screened by PCR-restriction fragment-length polymorphism.

Results. Nineteen female and 11 male patients (average age, 59 years) with a median visual acuity of 20/50 were evaluated. Six patients were of Asian-Indian origin, one was Hispanic, and 23 were of European-American ancestry. Nine of 30 (30%) patients had diabetes mellitus, 18 of 30 (60%) patients had hypertension, and 12 of 30 (40%) patients had a history of smoking. Screening of the *ATM* gene revealed a null allele in 2 of 23 (8.7%) patients of European ancestry, previously disease-associated missense alleles in 4 of 23 (17.4%) patients, and common missense alleles in 7 of 23 (30.4%) patients. No variants were identified in the *ATM* gene in patients of Asian or Hispanic origin. Frequencies of major AMD-associated alleles in *CFH*, *CFB*, and 10q loci in the IPT cohort were similar to those in the ethnically matched general population.

Conclusions. At least 26%, and maybe up to 57%, of IPT patients of European-American descent carried possibly disease-associated *ATM* alleles. Vascular risk factors such as hypertension, diabetes, and smoking may be associated with the pathogenesis of the disease. (*Invest Ophthalmol Vis Sci.* 2008; 49:3806–3811) DOI:10.1167/iovs.07-1357

Idiopathic macular telangiectasia, originally described and categorized by Gass and Blodi[1] into three subgroups, has recently been reclassified by Yannuzzi et al.[2] into two distinct types. Type 1 represents idiopathic aneurysmal telangiectasia, essentially a unilateral vascular abnormality that appears most commonly in men and is associated with dilated telangiectatic vessels, variably sized retinal vascular aneurysms, leakage, aneurysms with permeability defects, ischemia, and even lipid deposition in a multifocal distribution in the fundus. Type 2, known as idiopathic perifoveal telangiectasia, is an exudative telangiectatic vascular abnormality with progressive inner lamellar cystic change, retinal pigment epithelial hyperplasia, vitreoretinal interface refractile deposits, retinal–retinal and retinal–subretinal anastomoses, and subretinal neovascularization. With the use of optical coherence tomography, type 1 shows evidence of multicystic change within the macula area, whereas type 2 shows only inner lamellar cystic change and no evidence of cystoid macular edema in spite of exudative telangiectatic changes evident on fluorescein angiography.

The clinical spectrum of type 2 idiopathic perifoveal telangiectasia ranges from subtle retinal changes with minimal loss of macular transparency to more severe visual loss from neovascular complications, similar to age-related macular degeneration (AMD). Its pathogenesis, however, is poorly understood despite the potentially detrimental effects on visual function. A small number of case reports describing siblings with IPT suggest a genetic component.[3] Associations with diabetes and radiation exposure have also been suggested.[4–6]

Recently, Mauget-Faysse et al.[7] suggested that variants in the *ATM* gene are associated with an increased risk for radiation retinopathy. The relatively small study cohort (30 patients) included, among others, eight patients with idiopathic juxtafoveal retinal telangiectasia; possibly disease-associated *ATM* sequence changes were identified in four of these eight patients. Pathogenic *ATM* variants were originally described in patients with ataxia telangiectasia,[8] a rare autosomal recessive multisystem disorder that includes telangiectasia (usually of the conjunctiva and auricular skin region), neurodegeneration with loss of Purkinje and granule cells from the cerebellum, and immunodeficiency, and a high incidence of malignancies. The *ATM* gene consists of 66 exons spread over 150 kb on human chromosome 11q22.3-q23.1.[9] It is expressed in many tissues throughout the body and has a key role in the DNA repair response and in conducting cell cycle arrest and apoptosis.[10–13] The loss of ATM function leads to genome instability and an increased risk for cancer, neurodegeneration, and impaired glucose tolerance.[14,15] *ATM* variants have been associated not only with ataxia telangiectasia but also with a wide range of diseases such as breast and ovarian cancer and mantel cell lymphoma. It has been proposed that the impaired tolerance to oxidative stress and compromised double-strand (DS) DNA repair mechanisms attributed to the loss of *ATM* gene function, even in heterozygote carriers, may be associated with the development of retinal telangiectasia.[7]

To further analyze this hypothesis, we investigated the prevalence of *ATM* gene variants in 30 patients with bilateral acquired perifoveal telangiectasia.

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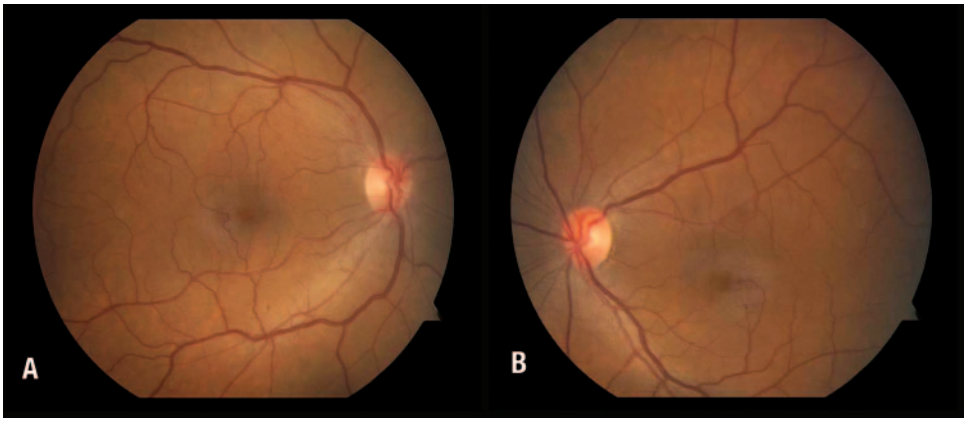

FIGURE 1. (**A**, **B**) Typical presentation of a study patient (patient 18) with bilateral idiopathic parafoveal telangiectasia. Color photography shows temporal pronounced loss of macular transparency with retinal–retinal anastomosis (**A**, *left*) and typical right-angled vessels (**B**, *right*).

PATIENTS AND METHODS

Thirty patients with diagnoses of bilateral acquired perifoveal telangiectasia were enrolled at the Vitreous–Retina–Macula Consultants of New York and the E. S. Harkness Eye Institute, Columbia Presbyterian Medical Center, in New York. Patients were selected based on their clinical and angiographic presentation (Figs. 1, 2). The study was conducted with approval of the institutional review boards of Columbia University and the Manhattan Eye, Ear and Throat Hospital (IRB AAAA4242 and IRB M00.011, respectively). In accordance with the guidelines of the Declaration of Helsinki, written informed consent was obtained from all patients before participation in the study.

All patients underwent standard ophthalmologic evaluation including best-corrected visual acuity testing, dilated fundus examination, stereofundus photography, fluorescein angiography, and, in selected patients, fundus autofluorescence. In addition, patients were asked to complete a standardized questionnaire that included questions regarding smoking habits, past and current medical history (e.g., diabetes mellitus, cardiovascular disease), and family history of macular disease.

Blood samples were obtained, and the isolated DNA was screened for variations in the entire coding sequence and intron/exon junctions of the *ATM* gene by a combination of denaturing high-performance liquid chromatography and direct sequencing. *CFH*, *CFB*, and *LOC387715* alleles were screened by PCR-restriction fragment-length polymorphism, as described previously.[16,17] Statistical analyses were performed by Fisher exact test, *t*-test, or both.

RESULTS

Nineteen female and 11 male patients (average age, 59 years; range, 39–76 years) were enrolled in the study (Table 1). Best-corrected visual acuity at presentation ranged from 20/20 to 20/400, with median visual acuity of 20/50. Five patients had fibrovascular proliferations consistent with choroidal neovascularization, two patients had a crystalline maculopathy, seven patients had parafoveal areas of hyperpigmentation, and three patients had only minimal changes with discrete alteration of the macular transparency on funduscopic examination (Figs. 1, 2).

Six patients described themselves as of Asian origin (five of these patients were of Asian Indian [Hindu] descent), one was of Hispanic origin, and the remainder (23) were of European-American ancestry. Five patients reported family histories of ocular telangiectasia or macular degeneration, further suggesting a significant genetic component in IPT; however, family members were unavailable for genetic analyses. One patient had a history of breast cancer. None of the patients had undergone radiation treatment for medical purposes; one patient worked in a dental laboratory and could not exclude previous exposure to radiation. There was no family history of ataxia–telangiectasia in the entire study group.

Nine of 30 (30%) patients had been previously diagnosed with diabetes mellitus, 18 of 30 (60%) patients had been diagnosed with hypertension, and 12 of 30 (40%) patients had histories of current or past smoking. Two patients had previously undergone cardiac surgery with coronary stent placement. Only 4 of 30 (13%) patients—two European-American, one Hispanic, and one Asian—had no history of potential cardiovascular risk factors (Table 1).

Screening of the *ATM* gene identified amino acid changes in 23 patients of European-American ancestry (Table 1); 2 of 23 (8.7%) patients had a known AT-causing frameshift mutation (c.1027-1030delGAAA; p.E343fs) according to the database of *ATM* variants (http://chromium.liacs.nl/lovd/index.php?select_db=ATM).

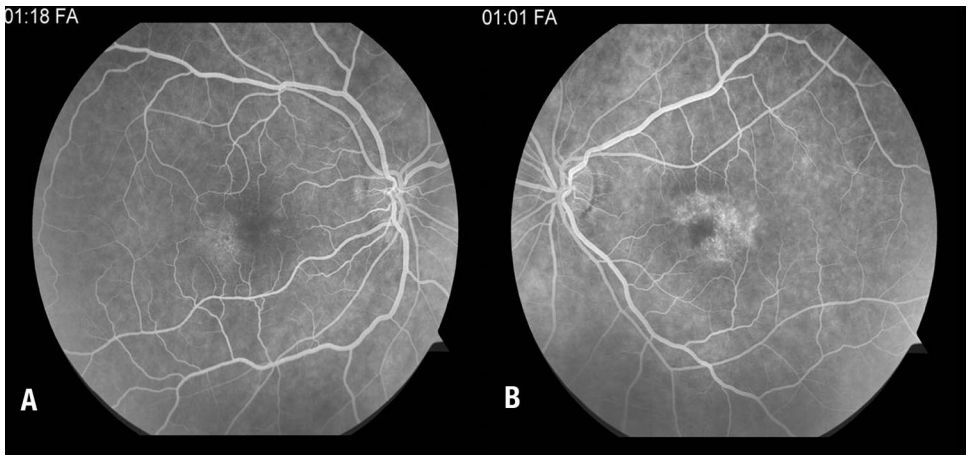

FIGURE 2. (**A**, **B**) Fluorescein angiography of a study patient with bilateral parafoveal telangiectasia. Early fluorescein angiography of patient 18 shows temporal juxtafoveal telangiectatic changes (**A**, *left*) and mild intraretinal leakage (**B**, *right*).

TABLE 1. Genetic and Clinical Characteristics of the Study Population

Case	Nucleotide Changes	Amino Acid Changes	Sex	Age (y)	Ethnicity	Smoking (y)	Diabetes	Hypertension
1	2119T>C	S707P	M	76	Italian	Yes (23)	Yes	Yes
2	—	—	F	55	Hindu	No	No	Yes
3	—	—	M	71	Jewish	No	No	No
4	1027_1030 delGAAA	E343fs	M	48	Jewish	No	Yes	Yes
5	—	—	M	50	Polish	Yes (33+)	No	No
6	2119T>C	S707P	M	60	Italian	No	No	No
7	—	—	F	47	Hindu	No	No	No
8	4362A>C	K1454N	F	60	German/English	Yes (39+)	No	No
9	5557G>A*	D1853N	M	56	Russian/German	Yes (35)	Yes	Yes
10	3161C>G	P1054R	F	70	German/Italian	No	Yes	Yes
11	—	—	F	69	Italian	Yes (46)	Yes	Yes
12	5557G>A*	D1853N	F	54	Scandinavian/English	Yes (35)	No	No
13	—	—	M	74	German	No	Yes	Yes
14	—	—	M	56	French/English	Yes	No	No
15	—	—	F	61	Polish	No	No	Yes
16	4258C>T	L1420F	F	61	German/English	No	No	Yes
17	—	—	M	39	Hispanic/Puerto Rican	No	No	No
18	5557G>A*	D1853N	F	62	Russian/Jewish	Yes (44+)	No	Yes
19	1027_1030 delGAAA	E343fs	F	50	Czech/Polish	No	No	Yes
20	—	—	F	63	Hindu	No	Yes	Yes
21	—	—	F	42	Hindu	No	Yes	No
22	—	—	F	60	Russian	Yes (9)	No	No
23	—	—	M	75	German	No	No	Yes
24	—	—	F	53	Asian	Yes (19)	No	Yes
25	5557G>A*	D1853N	F	72	Romanian/Russian	Yes (12)	No	Yes
26	—	—	F	51	German/Irish	No	No	No
27	5557G>A*	D1853N	F	48	Italian	Yes (8)	No	No
28	—	—	M	66	Russian	No	No	Yes
29	—	—	F	63	Hindu	No	Yes	Yes
30	378T>A 2442C>A	D126E D814E	F	72	Spanish/Egyptian	No	No	Yes

* Common allele.

Both patients had functionally significant telangiectasia and advanced vascular and pigmentary abnormalities at a relatively young age (fifth decade of life). They had no other diagnoses of possible *ATM* (or AT)-associated phenotypes (such as telangiectasia of the skin or conjunctiva) other than diabetes in one patient and a reported family history of cancer in the other patient. Like all patients in this study, neither of them had a history of radiation exposure.

Patient 4, a 48-year-old male of European/Jewish ancestry, had progressive bilateral visual deterioration resulting from advanced telangiectatic changes, and he had a history of diabetes and hypertension. Both eyes showed retinal vascular abnormalities with crystalline deposits and pigmentary migration in the perifoveal area (Figs. 3A, 3B). In addition, the right eye showed a small juxtafoveal, choroidal neovascularization (Figs. 3C, 3D) that was subsequently treated with laser photocoagulation.

Patient 19, a female of Eastern European descent, sought treatment initially at age 50 for decreased vision in her left eye. Visual acuity measured 20/30 in her right eye and 20/100 in her left eye. She had hypertension but had no history of diabetes or cancer, though her family history was significant for both. Fluorescein angiography documented crystalline deposits and advanced telangiectatic, vascular abnormalities encompassing not only the temporal macular but the entire perifoveal area as well as the foveal avascular zone (Figs. 4A, 4B). In the next 2.5 years, vascular abnormalities increased but no choroidal component developed (Figs. 4C, 4D). Although her left eye stabilized but did not improve after two sub-Tenon injections of triamcinolone, the right eye deteriorated to 20/60.

Four (17.4%) patients were heterozygous for *ATM* missense alleles, such as S707P and P1054R, which have been suggested to be disease associated in breast cancer and other malignancies,[18–20] and 7 of 23 (30.4%) patients had variants previously classified as common missense alleles, including a heterozygous D1853N variant in five patients. The last variant, which occurs at allele frequencies of 9% to 14% in populations of European ancestry (and which occurred at a rate of 11% in our study), has been suggested in at least one study[21] to modulate the penetrance of colorectal cancer. Therefore, potentially disease-associated variants in the *ATM* gene were identified in at least 26% (6 of 23) but maybe in as many as 57% (13 of 23) of patients of European-American ancestry. No possibly disease-associated variants were identified in the seven patients of Asian and Hispanic origin (Table 1); however, these results must be interpreted with caution because of the limited size of the study cohort.

Screening of the study cohort for the Y402H (c.1204T>C) variant of the *CFH* gene, which has been associated with increased risk for AMD,[16,22–24] revealed that only 7% of all patients were homozygous (CC) for the high-risk genotype (402H). Although the analyzed cohort was small, this fraction was even lower than the proportion of CC homozygotes (13%) in ethnically matched unaffected controls as determined in our earlier study of AMD.[16] For comparison, the frequency of the CC genotype in AMD patients was 32% in that study.[16] The same result was obtained when screening for the two major protective variants in the *CFB* gene and the *LOC387715* S69A variant from the 10q locus. The fraction of IPT patients harboring *CFB* protective alleles or the risk allele from 10q corre-

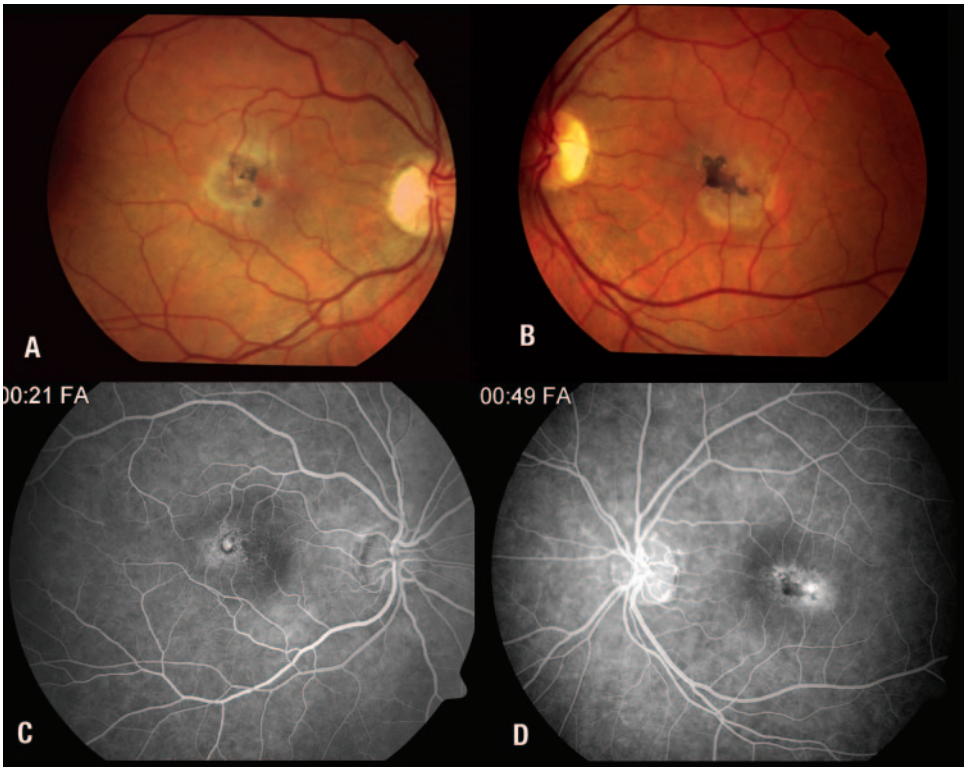

FIGURE 3. (**A**–**D**) Macular changes in patient 4 carrying the AT-associated c.1027-1030delGAAA mutation. Note crystalline deposits and pigment migration (**A**, **B**; *top*) and vascular and telangiectatic changes, including a small juxtafoveal, choroidal neovascularization, in the right eye (**C**, **D**; *bottom*).

lated well with the control group and not with the cohort of AMD patients.[17]

DISCUSSION

ATM was characterized in 1988 as the causal gene for autosomal recessive ataxia telangiectasia (AT), a rare disorder resulting in cerebral ataxia, telangiectasia of the skin and eye, extreme cellular sensitivity to radiation, and predisposition to cancer.[8] Most AT patients are compound heterozygotes for *ATM* deleterious alleles and, therefore, practically lack the ATM protein. Several subsequent studies have suggested that certain *ATM* missense alleles can act in a dominant-negative fashion in heterozygous carriers and can result in AT-like phenotypes or increase susceptibility to cancer.[7,18–21,25]

ATM-deficient cells have impaired repair mechanisms in response to double-stranded DNA breaks secondary to ionizing radiation. It has been hypothesized that chronic oxidative

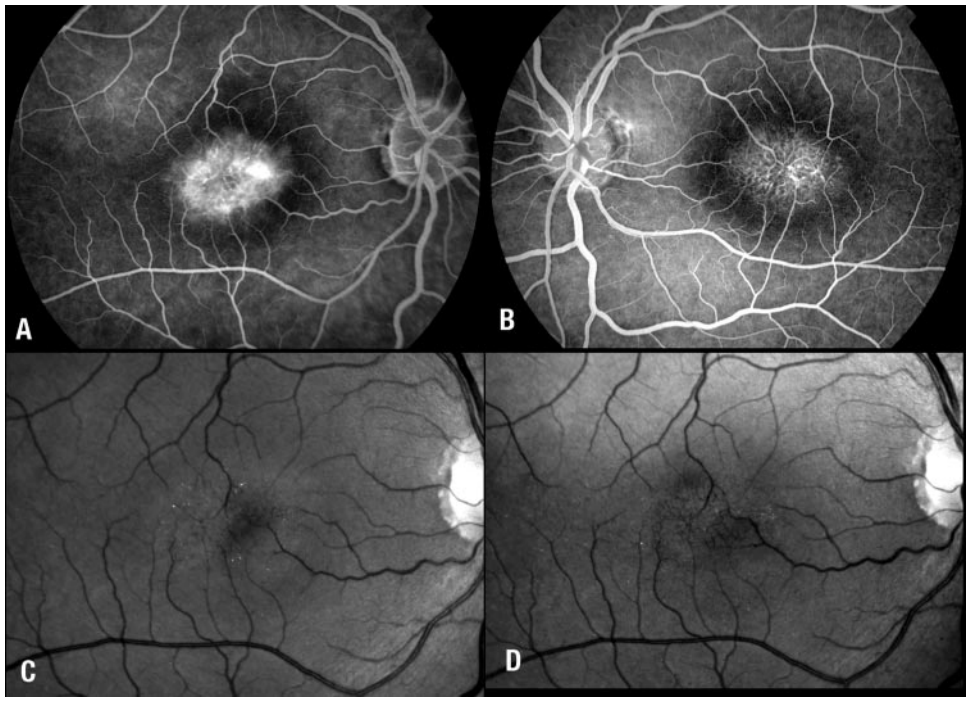

FIGURE 4. (**A**–**D**) Vascular proliferation in the second carrier of the c.1027-1030delGAAA mutation in the *ATM* gene (patient 19). Note the foveal avascular zone (**A**, **B**; *top*). Red-free photography highlights the progression of the vascular changes between baseline presentation (VA 20/30) (**C**, *bottom left*) and at follow-up 2.5 years later (VA 20/60) in the left eye (**D**, *bottom right*).

stress resulting in DNA damage activates ATM and leads to increased apoptotic activity.[26,27] Dodson et al.[27,28] suggested that the cAMP-response element binding protein (CREB) is phosphorylated by ATM at Ser121 in response to ionizing radiation and oxidative stress. CREB is an essential transcription factor that plays key roles in cell proliferation, homeostasis, and survival[29] and, therefore is expressed in many cell types, including Müller cells and retinal pigment epithelium.[30] Therefore, it is plausible that changes in the signaling pathway caused by ATM dysfunction may alter the genetic and cellular responses to oxidative stress in the cells of susceptible retinas. This could also explain the high number of patients with cardiovascular risk factors, including diabetes mellitus and smoking, in our study group. Specifically, a wide degree of cellular perturbations may occur in the Müller cells of patients with diabetes, including alterations in glutamate transport, reactive gliosis, and upregulation of VEGF, suggesting that these cells may be susceptible to conditions provoking oxidative stress, particularly if they lack ATM function to eliminate damaged cells. A perturbed neurovascular relationship of Müller cells with underlying capillaries may subsequently result in anatomic and physiological retinal vascular changes observed in IPT, though the predilection for these alterations to occur in the macular region remains peculiar and unexplained in the disorder.

The fraction of heterozygous carriers of potentially disease-associated *ATM* variants in our IPT cohort significantly exceeded the expected frequency of heterozygous carriers in the general population of European ancestry, as determined in large epidemiologic studies from Europe and the United States.[31,32] In these, the carrier frequency of pathogenic *ATM* alleles in the general population has been estimated at 0.5% to 1%,[31,32] which is statistically significantly different from the same frequency, 8.7% (2 of 23; $P = 0.02$), in the IPT cohort. Interestingly, this fraction perfectly correlates with the fraction of Dutch patients with breast cancer who carried AT-causing mutations.[33] The frequency of possibly disease-associated *ATM* missense alleles, excluding the common D1853N SNP, is approximately 20% in European breast cancer patients,[34] which is again lower than the analogous fraction (35%, 8 of 23; $P = 0.05$) in this study. The association of *ATM* missense alleles with cancer has varied between studies. The relatively rare S707P variant (allele frequency, 0.005–0.02)[18] has been (marginally) associated with breast cancer in several studies.[18,19] We detected this variant in 2 of 23 patients in our study, resulting in higher allele frequency (0.043). The overall frequency of P1054R, L1420F, and D1853N variants was not statistically different in breast cancer patients and controls[18]; however, there was a trend for an association for D1854N homozygotes, P1054R heterozygotes, and node-positive breast cancer patients in the same study.[18]

In summary, patients with bilateral IPT of European-American ancestry have a higher than expected frequency of possible disease-associated *ATM* gene variants. In addition, vascular risk factors such as hypertension, diabetes, and smoking may play significant roles in triggering the development of the disorder. Unlike AMD, IPT clearly lacks the immune-modulated disease component because frequencies of major AMD-associated alleles from the three major loci are comparable to these in the ethnically matched general population. Although further studies on larger cohorts of IPT patients are necessary to confirm the findings of this study, the presented results suggest an intriguing hypothesis that variations in *ATM* may be associated with, or may modulate, IPT in a significant number of patients with the disease.

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E R R A T U M

Erratum in: "Expression of ZnT and ZIP Zinc Transporters in the Human RPE and Their Regulation by Neurotrophic Factors" by Leung et al. (*Invest Ophthalmol Vis Sci.* 2008;49:1221–1231.)

The corrected table is printed below.

TABLE 1. ZnT Transporters Expressed in RPE Cells from Microarray Analyses and EST Database Mining

Gene	GenBank Accession No.	Primer Sequences		Amplicon Size (bp)
		Forward	Reverse	
ZnT1	NM_021194	GCATCAGTTTATGAGGCTGGTCCT	CAGGCTGAATGGTAGTAGCGTGAA	352
ZnT2	NM_032513	CTGGCCTTTGCCTTTATGAATCTG	GGACACTCTCAGGGCAACAGAAGT	352
ZnT3	NM_003459	ATGGTCACTGGCATCCTCCTGTA	AGATGGAGAAGAGGAAGGTGCTGA	364
ZnT4	NM_013309	TGTTAACTGACCTAAGCGCCATCA	GGTTACGTTCACACCCAGAACCTC	351
ZnT5	NM_024055	GATCCTAGGAAACTAGTGGGAAACTGAG	GTCCACAAAGAGTGAGGCCAAAAA	691
ZnT6	NM_017964	CCCATGAGTGTGTACAGTGGGAAA	GCATTGGGATTACGTGATGATCTG	352
ZnT7	NM_133496	AGAGGGTACAGCAGTTGCAAGGAG	AAAGCATGAACGGCTGACTCTACC	354
ZnT8	NM_173851	TACGATGCACTCACTCACCATTCA	AGCTGTTACTTCGGCTCCACTCAG	353
ZnT9	NM_006345	TTGCCTGGATTTATACCGGTTCAG	CCGAGCATTCCTACGAAGTTCATT	350
ZIP1	NM_014437	GATTGGGGAAGACACTTGACTGCT	GAAAGAGGAAGGGGATTTGTTTGG	351
ZIP2	NM_014579	CCCTTGTCCTCTTGCTGTCACTCT	AGCTCCCGTGGAAGAATTTCTAGG	352
ZIP3	NM_213568	GTGGAGATATGAGGACCCCCTGTT	GATGAACTCAGCGCTAACCGATCT	351
ZIP4	NM_017767	AGACTGAGCCCAGAGTTGAGGCTA	TGTCGCAGAGTGCTACGTAGAGGA	352
ZIP5	NM_173596	GAGCAGGAGCAGAACCATTACCTG	CAATGAGTGGTCCAGCAACAGAAG	354
ZIP6	NM_012319	CATAGCCATGAAGAACCAGCAATG	GAGAATCAAAGTGGGAGGGCTCTT	355
ZIP7	NM_006979	ACTGAAGGAGGAGCAGTGGGCAGT	AGGCCCTAATGCCAAAGTAACCAT	353
ZIP8	NM_022154	CCTCGGATTGATTTTGACTCCACT	AGCAGGATTTGCATAGCATGTCAC	352
ZIP9	NM_018375	GCCTAAAGAACTGGAAAGCCCACT	GTGTTTCACTTGCTTGGTGGTGTT	354
ZIP10	NM_020342	TAGCCGTCTTCTGTCATGAACTGC	TCATAGAGGGCAATCACCAGCATA	355
ZIP11	NM_139177	TCTCCTAAGCATTTTGGTGGCCTA	TCTCTTCTTTCCACAGGGCTCACT	351
ZIP12	NM_152725	CAACCACTCAAGAAGCCTCATCAA	AAGTACTGCCTGGTGAAAGCCAAG	351
ZIP13	NM_152264	AAGAAGATCGGGCTCCTGACAAC	GAGAACAGCACCATTACCACGATG	350
ZIP14	NM_015359	CATTTGGTTTCAACCCTCTGGAAG	TTTCAGCCAGTAGCAAGCACTCTG	350

These primers were all used in RT-PCR experiments at an annealing temperature of 58°C for 35 cycles to confirm expression of the genes in human primary cultures of fetal and adult RPE cells and in ARPE19.