The *p53* Codon 72 Polymorphism (rs1042522) Is Associated with Proliferative Vitreoretinopathy

The Retina 4 Project

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Purpose: To compare the distribution of a *p53* gene polymorphism among European subjects undergoing primary retinal detachment (RD) surgery in relation to the development of proliferative vitreoretinopathy (PVR).

Design: Case-controlled gene association study conducted as a component of the Retina 4 Project (a European multicenter study).

Participants and Controls: Five hundred fifty DNA samples, 134 with PVR secondary to primary RD and 416 with RD without PVR.

Methods: The *p53* codon 72 polymorphism (rs1042522) was analyzed using allele-specific primer polymerase chain reaction. Proportions of genotypes and the proline (Pro-P) homozygote groups between subsamples from different countries were analyzed in 2 phases. In the first, subsamples from Spain and Portugal were analyzed. After significant results were found, samples from the United Kingdom (UK) and The Netherlands were analyzed (second phase). Genotypic and allelic frequencies were compared between cases and controls in the global sample.

Main Outcome Measures: Single significant associations with PVR.

Results: A significant difference ($P<0.05$, Fisher exact test) was observed regarding the p53 genotype frequencies at codon 72 between the PVR cases and the non-PVR controls in Spain and Portugal (phase I), but not in the UK or The Netherlands (phase II). Analysis of Pro homozygote carriers between cases and controls revealed differences in Spain (29.01–42.18 and 2.29–10.20, respectively), Portugal (10.49–29.50 and 1.35–8.89, respectively), and The Netherlands (16.49–31.70 and 4.51–15.09, respectively), but no differences in the UK (7.68–18.1 and 4.85–13.94, respectively). The odds ratio of Pro carriers from Spain and Portugal together was 8.12 (95% confidence interval [CI], 3.72–17.69; $P<0.05$), whereas the odds ratio of Pro carriers from the UK and The Netherlands was 2.12 (95% CI, 0.96–4.68; $P = 0.07$). All control samples were in Hardy-Weinberg equilibrium. Considering the entire sample, significant differences were found in genotype frequencies between cases (RR, 30.59%; RP, 43.28%; PP, 26.11% [R = Arg; P = Pro]) and controls (RR, 39.66%; RP, 52.64%; PP, 7.69%) and in Pro homozygote carriers between controls (Pro homozygote 95% CI, 18.67–33.52) and cases (Pro homozygote 95% CI, 5.1–10.2).

Conclusions: Results indicate that the Pro variant of *p53* codon 72 polymorphism is associated with a higher risk of PVR developing after a primary RD. Further studies are necessary to understand the role of this polymorphism in the development of PVR.

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Proliferative vitreoretinopathy (PVR) is one of the major causes of failure in retinal detachment (RD) surgery,[1] affecting 5% to 10% of RD cases and accounting for approximately 75% of all primary failures after RD surgery.[1,2] It is considered an abnormal wound-healing process induced by a retinal break and escape of retinal pigment epithelium cells into a proinflammatory vitreous enviroment.[3–7] Although PVR was identified in 1983 as an independent

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entity,[8] there are no currently available treatments for its prophylaxis. Thus, in most cases, its management implicates repeated procedures at a significant cost[9] and, above all, with very poor anatomic and functional results.[10–13]

Most research has attempted to identify clinical risk factors for PVR developing; however, these variables do not completely explain the probability of its onset.[14] Single nucleotide polymorphisms have important implications for human genetic diseases. They may help to identify a genetic predisposition for certain diseases, either as a causative factor or protective risk factor. Finally, they may help to increase our knowledge of the molecular causes of some conditions.

Previous studies described the contribution of the genetic component to PVR.[15,16] With this aim, the Retina 4 project, a case-control, European, multicenter study, was coordinated. As a result of the first part of this project, a strong association between PVR development and the rs2229094 (T→C) lymphotoxin α polymorphism was reported.[16] However, the genetics of PVR seem to be complex, and probably some other genes are involved in its development.

The tumor-suppressor gene *p53* is crucial for cell repair of genomic mutations that may give rise to many tumors. Also, it is well known to induce cell cycle arrest, apoptosis, senescence, or differentiation after cellular stress.[17] Numerous single nucleotide polymorphisms and other polymorphic variations have been described in the *p53* gene. The codon 72 polymorphism in *p53* regulates the interaction with nuclear factor-κB and transactivation of genes involved in apoptosis, immunity, and inflammation, and it has been associated with several cancers and inflammatory processes.[18–21] This polymorphism appears in humans under 2 variants, arginine (Arg-R) or proline (Pro-P). The Arg/Arg variant encodes a highly proapoptotic protein, whereas the Pro/Pro variant has the opposite effect.[19,22,23] This property correlates with a greater capacity to interact with the Murine double minute 2 protein, which facilitates nuclear export and mitochondrial localization.[22,24] Other differences between the *p53* variants have been reported: the ability to bind components of the transcriptional machinery, to activate transcription, to induce apoptosis, and to repress the transformation of primary cells.[25]

Besides its relationship to tumors and inflammatory processes, recent studies of the central nervous system have shown that the *p53* codon 72 polymorphism is related to a poor functional prognosis in patients who have had ischemic or hemorrhagic stroke.[26] Moreover, previous studies have shown apoptosis to be a major cause of neuronal loss after trauma, ischemia, and neurodegeneration in the central nervous system.[27] These findings are relevant because retinal tissue has a similar behavior to the brain tissue, including the scarring processes.[5,28] After RD, the outer retina is separated from the underlying retinal pigment epithelium, which provides the major metabolic and nutritional support, leading to relative ischemia and hypoxia of photoreceptors. These factors promote an increase in *p53* levels and the activation of various cell death mechanisms.[27,29] It has been reported that photoreceptor death after RD and subsequent visual decline could be caused by apoptosis and other pathways for RD-associated photoreceptor death.[27,30,31] Finally, a recent report suggested that increased expression of soluble apoptosis and adhesion molecules at the time of primary RD surgery is associated with the future development of PVR.[32] However, it has been reported that apoptotic bodies derived from retinal capillary endothelium induce the release of proangiogenic cytokines and chemokines as well as the expression of adhesion molecules facilitating endothelial progenitor cell recruitment, which could favor retinal healing.[32] Thus, the purpose of this study was to analyze the distribution of the codon 72 polymorphism in exon 4 of the *p53* gene in a large consecutive sample of patients with primary rhegmatogenous RD with and without PVR recruited from several European centers.

Patients and Methods

Design and Study Population

The association study was carried out among 550 patients from 7 centers: 3 in Spain, 2 in Portugal, 1 in the United Kingdom (UK), and 1 in The Netherlands. For analysis, the global sample was divided in subsamples according to country. The study was carried out in 2 phases. In the first phase, subsamples from Spain and Portugal were analyzed. After significant results were found in this first cohort, subsequent samples from the UK and The Netherlands were analyzed (second phase). To compare whether there were differences regarding geographic localization in the odds ratio (OR) analysis, Spain and Portugal were considered as southern countries and the UK and The Netherlands were considered as northern countries. The study was approved by the institutional research committee of each center and followed the tenets of the Declaration of Helsinki. All patients provided written informed consent before entering in the study.

DNA samples from cases and controls in the Retina 4 project were analyzed for this study. All participants were patients with a primary rhegmatogenous RD who underwent surgery. Exclusion criteria were age younger than 16 years; traumatic, tractional, exudative, or iatrogenic RD; RD secondary to macular hole or giant retinal tear (larger than 3 clock hours); and PVR grade higher than B (Machemer classification)[1] on admission for surgery. Those who did not demonstrate PVR after 3 months of follow-up were included in the control group. Those in whom PVR grade C1 or higher developed, according to Machemer classification, were included as cases.

Genotyping

Genotyping of codon 72 of the *p53* polymorphism was performed at the Molecular Medicine Unit, Department of Genetics, University of Salamanca, Salamanca, Spain. Those carrying out the genotyping were blinded to the clinical status of patients and used the polymerase chain reaction-restriction fragment length polymorphism technique.[33,34]

The Tp53 polymorphism was detected by amplifying genomic DNA with the forward primer 5′TCTACAGTCCCCCTTGCCGT-3′ and the reverse primer 5′- CTGACCGTGCAAGTCACAGA-3′.[33,34] The *p53* exon 4 was amplified within a 298-base pair (bp) DNA fragment that was digested with BstU1 (*Bsh1236I Fermentas fast digest restriction enzyme* [Thermo Scientific, Germany]), and the resulting fragments were separated on 3.5% agarose gel. The polymerase chain reaction fragments containing Arg and Pro alleles, after digestion, migrated as a 291-bp fragment for Pro homozygotes, as 2 fragments of 165 and 126 bp for Arg homozygotes, and as 3 fragments of 126, 165 and 291 bp for heterozygotes.

Table 1. Clinical Variables of Entire Sample

Characteristics	Controls No. with Retinal Detachment, n (%)	Cases No. with Proliferative Vitreoretinopathy, n (%)	Total	*P* Value
Race				
White	387 (71.5)	121 (22.36)	508	
Hispanic American	2 (50)	2 (50)	4	
Hindu	7 (46.6)	8 (53.3)	15	
Arabic North African	6 (100)	0 (0)	6	0.059
Sub-Saharan African	2 (66.6)	1 (33.3)	3	
Asian	3 (60)	2 (40)	5	
Unknown			9	
Total			550	
Phakic lens				
Yes	258 (77.24)	76 (22.75)	334	
No	137 (72.48)	52 (27.51)	189	0.224
Unknown			27	
Total			550	
Geographical location				
Northern countries (UK+Holland)	210 (77.7)	60 (22.2)	270	
Southern countries (Spain+Portugal)	197 (72.7)	74 (27.3)	271	0.171
Unknown			9	
Total			550	

UK = United Kingdom.

Statistical Analysis

The statistical analysis was conducted in both phases. The quality of data was evaluated in control subsamples by Hardy-Weinberg equilibrium using the chi-square test. Genotypic frequencies were estimated in each subsample. The proportions of genotypes and the Pro homozygote groups between subsamples were analyzed. Also, the genotypic and allelic frequencies were compared between cases and controls in the global sample.

Association was investigated using the chi-square and the Fisher exact tests. The strength of association was measured using ORs and 95% confidence intervals (CIs). Two inheritance models were considered: the codominant model, which allows every genotype to give a different and nonadditive risk, and the recessive model, in which 2 copies of the Pro allele are necessary to change the risk. The Akaike information criterion (AIC)[35] was used to choose the inheritance model that best fit the data. The statistical analyses were conducted using SPSS software version 16.0 for Macintosh (SPSS, Inc., Chicago, IL) and R software (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 550 subjects including 134 cases and 416 controls were analyzed: 203 from Spain (36.9%), 68 from Portugal (12.4%), 121 from The Netherlands (22%), and 158 from the UK (28.7%). Some important clinical variables are shown in Table 1. A multiracial population with statistical differences in the British samples in comparison with the others groups was found. All control subsamples were in Hardy-Weinberg equilibrium. Status of the lens was determined because aphakia has been related to a higher incidence of PVR.[5,14]

Phase I: Genotypic Distribution of *p53* Codon 72 Polymorphism in Spain and Portugal

The frequencies of the genotypes in each country are shown in Table 2. The comparison of proportions of genotypes between subsamples showed a significant difference ($P<0.05$) between cases and controls. Also, a significant difference ($P<0.05$) in Pro homozygote carriers between subsamples in the control group (Pro homozygote 95% CI

Table 2. Distribution of Frequencies of the Genotypes

Countries	Arginine/Arginine (%)		Proline/Proline (%)		Arginine/Proline (%)		*P* Value (Fisher Exact Test)*	*P*<0.05 95% Confidence Interval†		Odds Ratio
	Cases	*Controls*	*Cases/Controls*	*Controls*	*Cases/Controls*	*Controls*		*Cases/Controls*	*Controls*	
Spain	27.1	45.1	35.6†	6.25†	37.3	48.61	<0.05*	29.01–42.18	2.29–10.20	8.5
Portugal	33.3	43.39	20†	3.77†	46.7	52.8	<0.05*	10.49–29.50	1.35–8.89	6.5
UK	35.5	36.2	12.9	9.4	51.6	54.3	>0.05*	—	—	
The Netherlands	31	33.7	24.1†	9.8†	44.8	56.5	>0.05*	16.49–31.70	4.51–15.09	3.3

— = confidence interval not statistically significant; UK = United Kingdom.
*Comparison of proportions of genotypes between subsamples. A significant difference was observed between cases and controls in Spain and Portugal but not in the UK and The Netherlands.
†Prohomozygote carrier analysis between different countries revealed differences in Spain, Portugal, and The Netherlands but no differences in the UK.

Table 3. Models of Inheritance in the Global Sample and Results of Odds Ratios Using a Recessive Model for Spain plus Portugal and The Netherlands plus the United Kingdom

Model	Genotype	Controls (*n*)	Controls (%)	Cases (*n*)	Cases (%)	Odds Ratio	95% Confidence Interval	*P* Value	Akaike Information Criterion*
Codominant	Arg/Arg	165	39.7	41	30.6	1.00		<0.001	588.6
	Arg/Pro	219	52.6	58	43.3	1.07	0.68–1.67		
	Pro/Pro	32	7.7	35	26.1	4.40	2.44–7.93		
Dominant	Arg/Arg	165	39.7	41	30.6	1.00		<0.001	611.1
	Arg/Pro-Pro/Pro	251	60.3	93	69.4	1.49	0.98–2.26		
Recessive	Arg/Arg-Arg/Pro	384	92.3	99	73.9	1.00		<0.001	586.7
	Pro/Pro	32	7.7	35	26.1	4.24	2.50–7.19		
Overdominant	Arg/Arg-Pro/Pro	197	47.4	76	56.7	1.00		<0.001	611.2
	Arg/Pro	219	52.6	58	43.3	0.69	0.46–1.02		
Spain+Portugal		186	94.4	50	67.6	1.00		<0.001	291.3
		11	5.6	24	32.4	8.12	3.72–17.69		
The Netherlands+UK		198	90.4	49	81.7	1.00		0.07	291.3
		21	9.6	11	18.3	2.12	0.96–4.68		

Arg = arginine; Pro = proline; UK = United Kingdom.
*A measure of the relative goodness of fit of a statistical model. It generally can be used for the identification of an optimum model in a class of competing models. Given a set of candidate models for the data, the preferred model is the 1 with the minimum Akaike Information Criterion value.

for Spain and Portugal, 29.01–42.18 and 10.49–29.50, respectively) and in the cases group (Pro homozygote 95% CI for Spain and Portugal, 2.29–10.20 and 1.35–8.89, respectively) was found. The OR of Pro carriers considering a recessive model (Arg/Arg plus Arg/Pro vs. Pro/Pro; AIC = 291.3 vs. 293.2 of codominant model) was 8.12 (95% CI, 3.72–17.69; $P<0.05$; Table 3).

Phase II: Genotypic Distribution of *p53* Codon 72 Polymorphism in the United Kingdom and The Netherlands

The frequencies of the genotypes in patients from the UK and The Netherlands are shown in Table 2. Distribution of genotypes between subjects from those countries did not show statistical differences. However, when the Pro homozygote carriers between cases and controls were analyzed, a significant difference in the group of Dutch patients was found (Pro homozygote 95% CI, 16.49–31.70 and 4.51–15.09, respectively; $P<0.05$). Although not statistically significant in patients from the UK, a similar trend was seen (Pro homozygote 95% CI, 7.68–18.1 and 4.85–13.94, respectively; $P>0.05$). No differences were found in the OR distribution of homozygous carriers of the Pro variant in patients from the UK and The Netherlands together considering a recessive model (AIC = 291.3 vs. 293.2 of codominant model; OR, 2.12; 95% CI, 0.96–4.68; $P = 0.07$; Table 3).

When all patients were grouped (Table 4), significant differences in the distribution of genotypes between the controls and cases ($P<0.05$) were found. Also, homozygous carriers of the Pro variant were more frequent in PVR cases than in controls ($P<0.05$; 95% CI, 18.67–33.52 and 5.1–10.2 for cases and controls, respectively). The OR of the Pro variant in the global sample using a recessive model (AIC = 586.7 vs. 588.6 of codominant model) was 4.24 (95% CI, 2.50–7.19; Table 3).

Discussion

Proliferative vitreoretinopathy is considered a multifactorial disease,[15,16] and it may result from interactions between genetic and environmental factors.[14–16] The lack of satisfactory results in the identification of patients at risk of developing PVR after RD by clinical characteristics[14] justifies the efforts to elucidate the genetic components[15,16] as a potential means of identifying high-risk patients before surgery and possibly to modify the treatment strategy in a more customized way.

In addition, recent research has highlighted the involvement of extrinsic and intrinsic pathways of apoptosis in retinal cells after RD and the existence of other mechanisms of cell death after RD when apoptotic pathways are inhibited.[27] The initiation of apoptosis and other death pathways, such as programmed necrosis, involves the activation of certain specific receptors on the cell surface. These death receptors mainly comprise the tumor necrosis factor (TNF) receptor family tumor necrosis factor receptor 1 (TNFR1) and TNF-related apoptosis-inducing ligand (TRAIL).[27]

Table 4. Distribution of p53 Codon 72 Polymorphism in the Entire Sample

Genotypes	Arginine/ Arginine	Arginine/ Proline	Proline/ Proline	Total	*P* Value*	95% Confidence Interval
Cases	41 (30.59%)	58 (43.28%)	35 (26.1%)†	134 (100%)	<0.05	18.67–33.52
Controls	165 (39.66%)	219 (52.64%)	32 (7.69%)	416 (100%)		5.1–10.2
Total	206	277	67	550		

*Fisher exact test.
†Analysis of pro-homozygote carriers between case and control group.

In recent years we have been exploring the genetic contribution to PVR. As a result of these studies, they have identified the potential contribution of tumor growth factor β[16] and lymphotoxin α[17] in PVR. Lymphotoxin α and TNF-α are proinflammatory cytokines that have a wide range of biologic functions involved in inflammation, apoptosis, and cell proliferation[36]; in addition, their intraocular levels are increased in eyes with PVR.[37–39]

p53 Is a protein involved in regulating apoptosis and has increased intracellular levels in response to DNA damage, uncontrolled cell proliferation, or telomere erosion.[40,41] The *p53* Arg72Pro polymorphism is located in exon 4 and consists of a change of guanine to cytosine at position 2 of codon 72, which is located in the Pro-rich region (at the N-terminal extreme) involved in the apoptotic functions of the p53 protein.[42] The Arg→Pro change affects the primary structure of the protein and generates functional differences because the Arg variant is associated with increased apoptosis.[22,43]

Several studies have reported the potential role of this polymorphism as a risk factor for several cancers and some inflammatory processes[18–21] in which apoptosis seems to have a crucial role. It recently was reported that carriers of the Arg/Arg genotype have a poorer functional prognosis after a stroke, probably associated with an increase of apoptotic death of neurons.[26] Furthermore, it has been associated with an increased risk of primary open-angle glaucoma compared with healthy subjects.[44]

Proliferative vitreoretinopathy remains the most common cause of recurrent RD after RD surgery. The development of PVR is a complex process involving humoral and cellular factors, and the distribution of genotypes of the *p53* codon 72 polymorphism in patients with PVR was considered a target for increasing the knowledge of this severe complication of RD.

The current results show that Spanish and Portuguese carriers of the homozygous Pro variant in homozygosis have a 4-fold increased risk to PVR after RD compared with those who carry the homozygous Arg variant (Table 2). This observation was confirmed in Dutch patients but not in a British population (although a similar trend was seen). The absence of correlation in the British group could be explained by the observation that frequency of the *p53* codon 72 alleles differs with latitude, increasing the Pro variants within populations close to the equator, whereas the Arg variant predominates in northern latitudes.[21,45]

However, because the Dutch patient genetic profiles were similar to those from Spain and Portugal, there must be some other factors implicated in this difference. In this sense, the possibility that differences could be the result of ethnic diversity in the group of patients from the UK cannot be ruled out because many patients undergoing RD treatment in London have ancestry from the Indian subcontinent.

Results of this work indicate that carriers of the Pro allele of the *p53* gene, associated with a decrease in apoptotic function of *p53*, have a higher risk of PVR developing after RD. It can be speculated that the reduction in the levels of apoptosis could energize migrating retinal pigment epithelium cells and inflammatory mediators directly, allowing a more aggressive cellular response. Alternatively, a greater resistance to apoptosis could sustain ischemic photoreceptors for longer periods, allowing these cells to release more cytokines and other growth factors to generate a more aggressive PVR response through secondary mechanisms and globally increase the intraocular inflammation after RD.

In summary, this study highlights the role of genetics as useful in the identification of high-risk patients who may be susceptible to PVR and indicates that the Pro allele could be a significant risk factor for PVR development after a primary RD and could be used as a possible marker of risk of PVR after RD. In conclusion, these results support a key role for *p53*-mediated apoptosis in the generation of PVR after RD surgery.

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