

lens (IOL). They compared our approach with their technique<sup>2</sup> and described some advantages with their technique.

They opined that our technique did not take advantage of the intrascleral fixation of the IOL because a 25-gauge vitrectomy was performed before IOL fixation. With their technique, an anterior vitrectomy was performed using 25-gauge trocars for haptic externalization. We recommend performing a vitrectomy (not only an anterior vitrectomy) with intrascleral fixation and transscleral suturing of the IOL to avoid postoperative complications (such as retinal detachment). If the surgeon believes that an anterior vitrectomy is sufficient, it can be performed through the corneal paracentesis. The transconjunctival technique is simple and less invasive. We have modified our technique to incorporate the transconjunctival method using a double-needle technique. However, with the transconjunctival technique it is sometimes difficult to manage the length of the scleral tunnel. In addition, a long scleral tunnel sometimes warps the cornea and reduces visualization during intraocular manipulation through the tunnel.

Karadag et al worried about the risk of trauma from the first needle. The first needle has never hit the retina, iris, or ciliary body in this author's experience (about 70 cases). The movement of the needle is limited, and it is difficult to impale the needle into the surrounding tissues after haptic insertion. If surgeons are concerned about this problem, they can rotate the needle so that the sharp tip faces the center of the eye.

We reported 3 cases (8.6%) with iris capture.<sup>1</sup> Karadag et al supposed that these incidents arose from weak axial stability secondary to decreased scleral support. However, we observed good axial stability when this point was evaluated using anterior segment optical coherence tomography.<sup>1</sup> In addition, the IOL tilt in the eyes with iris capture was not large, compared with that in the cases without iris capture. Karadag et al stated that the scleral tunnel was too short (1.5 mm) in our technique. However, the haptic was supported by both the sclerotomy and the scleral tunnel (Figure 3B; available at [www.aaojournal.org](http://www.aaojournal.org)).<sup>1</sup> We speculated that the cause of the iris capture was a floppy iris and fluid flow as a result of eye movement and hard blinking. In some cases, the iris capture was improved by a supplemental iridotomy.

The insertion of the haptic into the scleral tunnel is sometimes difficult because the surgeon cannot see the entrance of the tunnel. The tunnel should be made at the bottom of the scleral groove (Figure 3B).<sup>1</sup> The haptic is easily inserted into the apposite tunnel by guiding the haptic along the bottom of the groove.

Karadag et al wrote that the amount of haptic remaining in the scleral tunnels was as important as the size of the sclerotomies. We agree. The length of the scleral tunnel is related to the stability of the IOL. In our technique, both the sclerotomy and the scleral tunnel support the haptic. Thus, the total length of the scleral support is about 3 mm. This is same as the length of the scleral tunnel in the technique described by Karadag et al. On the other hand, the size of the sclerotomy is important for avoiding complications, such as vitreous hemorrhage, hypotony, and endophthalmitis. Our technique has the advantage over previously reported techniques regarding this point.

There are 2 techniques for haptic externalization. Haptic externalization using forceps is easy to learn. However, surgeons must pay attention to the possibility of haptic breakage or deformation. A needle-guided technique can minimize the sclerotomy and avoid haptic deformation. The difficulty of inserting the haptic into the

needle can be conquered to optimize the relative location of the wounds for IOL insertion and haptic externalization.

The technique underlying the intrascleral fixation of an IOL is now being developed. We believe that the double-needle technique is ideal for minimizing wound size and avoiding haptic breakage. Surgeons should understand the characteristics of the available techniques and should choose a technique that works best for them.

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## **Re: Hagstrom et al.: Pharmacogenetics for genes associated with age-related macular degeneration in the comparison of AMD treatments trials (CATT) (*Ophthalmology* 2013;120:593-9)**

Dear Editor:

We read the article published by Hagstrom et al<sup>1</sup> entitled “Pharmacogenetics for Genes Associated with Age-related Macular Degeneration in the Comparison of AMD Treatments Trials (CATT)” with great interest. They analyzed the results of the CATT trial, originally aimed at comparing efficacy between bevacizumab and ranibizumab for the treatment of exudative age-related macular degeneration (AMD). The authors investigated whether a pharmacogenetic relationship might exist between treatment response and the following single nucleotide polymorphisms: CFH rs1061170, ARMS2 rs10490924, HTRA1 rs11200638, and C3 rs2230199. A stepwise analysis based on the total number of risk alleles was performed to evaluate the additive effects of these single nucleotide polymorphisms on clinical outcome. At 1 year, this study found no significant association between genotype and visual acuity outcomes, anatomic outcomes, or the number of injections required. The authors concluded that genetics does not have an influence on treatment response to anti-vascular endothelial growth factor (VEGF) drugs, nor does it account for the number of injections needed.

The patients considered in this pharmacogenetic analysis represented a subgroup of the CATT trial cohort (834 out of the whole sample of 1149). However, subjects analyzed for genetics were significantly younger than those who were not included in the genetic study. They also had better initial visual acuity and smaller lesions. Although the CATT study represents the largest cohort of AMD patients in which the role of major AMD risk alleles has been

analyzed, other consistent studies have arrived at opposite conclusions. Smailhodzic et al<sup>2</sup> studied 420 eyes of 397 patients with neovascular AMD. They demonstrated a cumulative effect of high-risk alleles CFH rs1061170, ARMS2 rs10490924, and VEGFA rs699947 that was associated with an earlier onset of the disease, in combination with poorer response rates to ranibizumab treatment. The reasons for these discrepancies in various conclusions remain controversial. Several studies have tried to identify factors capable of predicting clinical outcome after anti-VEGF treatment. Some rely on ocular features, such as the choroidal neovascularization phenotypes, lesion size, and initial visual acuity, which seem to be associated with significantly different outcomes. Other patient characteristics, such as age at diagnosis, the presence of concomitant systemic diseases like diabetes and hypertension or certain lifestyle habits, such as smoking, might influence functional outcomes after treatment. A habit of smoking has not only been associated with increased incidence of advanced AMD but it may also condition response to laser treatment.<sup>3</sup> Lee et al<sup>4</sup> found that in a group of 420 patients with exudative AMD cigarette smoking was an independent risk factor for lower visual acuity gains, after intravitreal ranibizumab treatment. In mouse models, nicotine increases the size and severity of experimental choroidal neovascularization.<sup>5</sup> In a retrospective study of 102 patients with exudative AMD, we observed that a smoking habit in patients carrying the CFH gene risk alleles may account for a 20-letter outcome difference compared with those classified as never smokers along with no CFH risk alleles (Piermarocchi S. Effects of genetic and epigenetic risk factors on response to ranibizumab in exudative AMD. Paper presented at: Retina Society 46th Annual Scientific Meeting, September 29, 2013; Beverly Hills, CA). It is therefore reasonable to admit that, owing to the high percentage of current or former smokers (57.9%) in the genetic CATT study sample, the role of genetic risk alleles capable of potentially influencing the treatment response to anti-VEGF, might have at least partially been underestimated. Furthermore, the significantly younger age, better initial visual acuity, and smaller lesions in the CATT subgroup that were involved in the genetic analysis may have further contributed to masking the possible role of a genetic predisposition to worse results. In our opinion, the possible role of genetic and epigenetic factors in influencing variable responses to anti-VEGF treatment remains an open issue. Well-designed studies are required to provide unbiased results, which may help to refine more efficient strategies of drug administration for exudative AMD.

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## Author reply

Dear Editor:

We read with interest the letter from Piermarocchi that discusses a possible link between smoking, genetic influences, and response to anti-vascular endothelial growth factor (VEGF) therapy in patients with neovascular age-related macular degeneration. The author cites his retrospective study of 102 patients in whom he observed a 20-letter difference in visual acuity (VA) between smokers who had >1 complement factor H (CFH) risk allele versus nonsmokers with no risk alleles. The author questions whether or not the role of genetic risk alleles may have been underestimated in the Comparison of AMD Treatments Trials (CATT) genetic study owing to the high percentage of current or former smokers.

We performed an analysis for genotypic association between CFH, smoking, and VA in CATT participants (n = 834). Eighty-three patients who never smoked and had no risk alleles (TT) had a mean VA improvement from baseline of 8.7 letters at 1 year. Among 158 current and former smokers homozygous for the risk allele (CC), the mean VA improvement was 7.0 letters. This difference of 1.7 letters was not significant and considerably less than the 20 letters reported by Piermarocchi. In addition, among the 351 never smokers, there was no difference in mean change in VA across all 3 CFH genotypes ( $P = 0.76$ ).

In a previous CATT publication that examined baseline predictors of 1-year VA, we did not identify smoking as an independent predictor of VA or VA gain.<sup>1</sup> This is in contrast with Lee et al,<sup>2</sup> who identified smoking as a risk factor for lower VA gain in 420 patients.

The CATT is a large, prospective, clinical trial with protocol defined outcomes assessed in masked fashion by independent examiners as opposed to the retrospective series by Piermarocchi and Lee. Although we agree that the role of genetic factors influencing response to anti-VEGF therapy remains an open issue, our prospective study does not identify a link between smoking, influence of the single nucleotide polymorphisms we analyzed, and response to anti-VEGF therapy. An ongoing exome analysis in CATT study participants may identify novel polymorphisms associated with response to anti-VEGF therapy in patients with neovascular age-related macular degeneration.

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