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Lack of Association Between Polymorphisms in the Prostaglandin $F_{2\alpha}$ Receptor (PTGFR) and Solute Carrier Organic Anion Transporter Family 2A1 (SLCO2A1) Genes and Intraocular Pressure Response to Prostaglandin Analogs

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Abstract

Purpose—To evaluate the association between variants in the prostaglandin F_{α} receptor (pTGFR) and solute carrier organic anion transporter family 2A1 (SLCO2A1) genes and IOP response to prostaglandin analogs

Methods—The medical records of subjects with previously diagnosed open angle glaucoma or ocular hypertension were searched for intraocular pressure measurements before and after prescriptions of prostaglandin analogs. Stored DNA samples were genotyped for the following SNPs: rs3753380 (promoter region) and rs3766355 (intronic region) of the prostaglandin $F_{2\alpha}$ receptor gene, and rs34550074 (Ala396Thr) of SLCO2A1. The mean change in IOP by genotype was measured.

Results—Prostaglandin analogs were prescribed to 267 subjects; 242 (204 right eyes, 205 left eyes) met the inclusion/exclusion criteria for the current study. There was no significant association between genotype and IOP response to prostaglandin. analogs (p=0.48, p=0.54, p=0.90).

Conclusion—In summary, we found no indication for an association between SNPs in the prostaglandin $F_{2\alpha}$ receptor gene or SLCO2A1 and IOP response to prostaglandin analogs in a population of European descent.

Keywords

glaucoma; pharmacogenetics; intraocular pressure; prostaglandin analog

We have shown previously that a single nucleotide polymorphism (SNP) in the ADBR2 gene is significantly associated with IOP response to topical β-blockers[1]. While beta blockers are still used frequently for the treatment of glaucoma and ocular hypertension, prostaglandin analogs are now the first choice in medical therapy to lower intraocular pressure[2]. Prior studies have shown that prostaglandin $F_{2\alpha}$ receptors exist in the trabecular meshwork[3] and that the prostaglandin transporter SLCO2A1 (OATP2A1) is found in human ocular tissues[4]. Because others have reported an association between SNPs in the

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prostaglandin $F_{2\alpha}$ receptor gene and IOP response to latanoprost in normal volunteers[5] and because there is a non-synonymous amino acid variant in SLCO2A1, a candidate gene for IOP response, we sought to evaluate the association between variants in these genes and IOP response to prostaglandin analogs.

METHODS

The electronic medical records of adults enrolled in the population-based Marshfield Clinic Personalized Medicine Research Project (PMRP)[6] biobank were searched to identify subjects with a diagnosis of intraocular hypertension or glaucoma. All participants gave written, informed consent for the project which was reviewed and approved by the Marshfield Clinic Institutional Review Board.

Previously archived DNA samples were genotyped from those subjects who had used prostaglandin analogs and had baseline and follow-up IOP measurements. Validated TaqMan™ assays were purchased from Applied Biosystems (ABI), Inc. (Foster City, California) for rs3753380 (promoter region) and rs3766355 (intronic region) of the prostaglandin $F_{2\alpha}$ receptor gene. A functionally tested TaqMan™ assay was purchased for rs34550074 (Ala396Thr) of SLCO2A1. Five DNA samples were sequenced for each SNP with 100% concordance between the TaqMan™ result and sequence.

Three time periods were assigned for analysis: 1) a baseline period prior to starting a prostaglandin medication; 2) a 30 day run-in period after starting the medication; and 3) a subsequent 60 day follow-up period for measuring response relative to baseline. Only subjects on prostaglandin for the full follow-up period were analyzed. Eyes were excluded if they had ophthalmic surgery during any of the study periods. Covariates considered in the models included gender, age, family history of glaucoma, left or right eye, surgery in the opposite eye, use of blood pressure medications, and other IOP lowering medications, included as separate variables in the models. Statistical analyses included repeated measures analyses of IOP changes over time as well as analyses of the changes from baseline to the lowest IOP within 90 days of starting the medication with respect to groups defined by SNP, with adjustment for covariates. Analyses were conducted using SAS© Version 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

Prostaglandin analogs were prescribed to 267 subjects; 242 (204 right eyes, 205 left eyes) met the inclusion/exclusion criteria for the current study. One-hundred twenty-two (50.4%) of the subjects were taking systemic antihypertensive medications and 63 of 409 eyes (15.4%) had been prescribed other IOP lowering medications. Twenty-four of 433 eyes (5.5%) had glaucoma surgery.

The data in the figure demonstrate the change in IOP from baseline to follow-up by genotype for each of the three SNPs examined. As can be seen, there was no significant association between genotype and IOP response to prostaglandin analogs ($p=0.48$, $p=0.54$, $p=0.90$, respectively). Secondary analyses were performed with a categorical outcome variable of $\geq$ or $<$ 20% change in IOP before and after prescription of prostaglandin analogs. As with the models with a continuous change in IOP, the results were not statistically significant (data not shown).

DISCUSSION

The study by Sakurai et al found a significant association between rs3753380 and rs3766355 in the prostaglandin $F_{2\alpha}$ receptor gene and IOP response to latanaprost in normal Japanese

volunteers[4]. We were unable to replicate these findings in subjects being treated with prostaglandin analogs in a population-based clinical setting. We also did not identify a novel association between the tested DNA variant in SLCO2A1 and IOP. There are several potential reasons for the discrepant findings between our study and that of Sakurai et al, one of which is a difference in the prostaglandin analog used. The minor allele frequency for both SNPs varies between Asian and Europeans, most markedly for rs3766335 (MAF=0.1 in European and 0.45 in Japanese), and that could affect the relative association between genotype and IOP response. Observed changes in IOP in a clinical setting are influenced by issues such as adherence and concomitant medication. A prospective study with prostaglandin analogs as the initial monotherapy would help to verify these non-significant findings.

The initial estimate of the number of PMRP subjects exposed to a beta blocker was 133, and *a prior* power calculations showed that 133 subjects would provide 82% power with a true odds ratio of 4.0 (32% genotype frequency in responders compared with 10% frequency in non-responders). The final number of eligible subjects was 211, somewhat larger than estimated, and 211 subjects would provide 96% power with a true odds ratio of 4.0, as planned. However, the largest odds ratio actually observed was only 1.9, and the study was underpowered (45%) to detect odds ratios of that magnitude. Although a larger sample size may result in statistically significant results, they may or may not be clinically relevant.

In summary, we found no indication for an association between SNPs in the prostaglandin $F_{2\alpha}$ receptor gene or SLCO2A1 and IOP response to prostaglandin analogs in a population of European descent.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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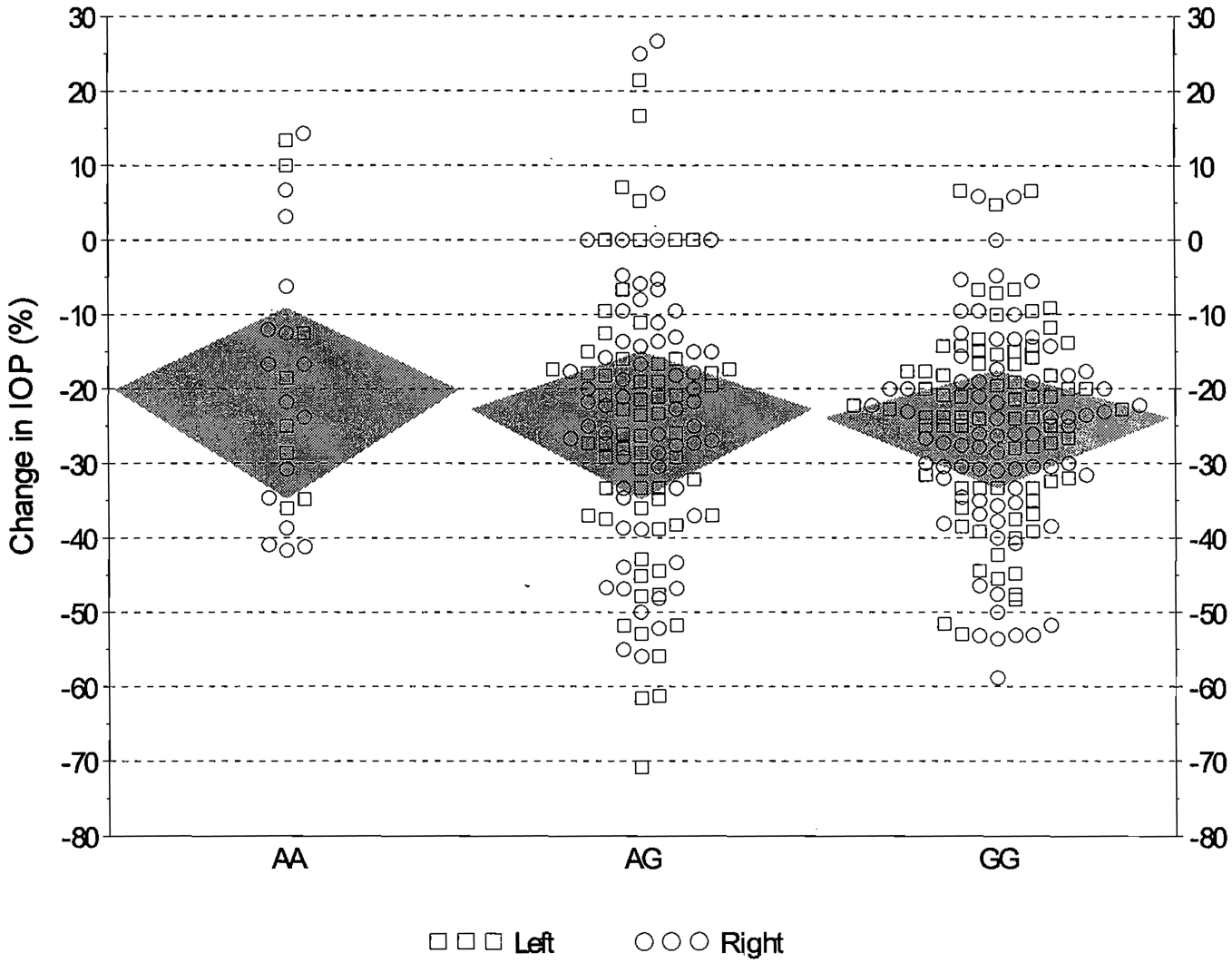
A



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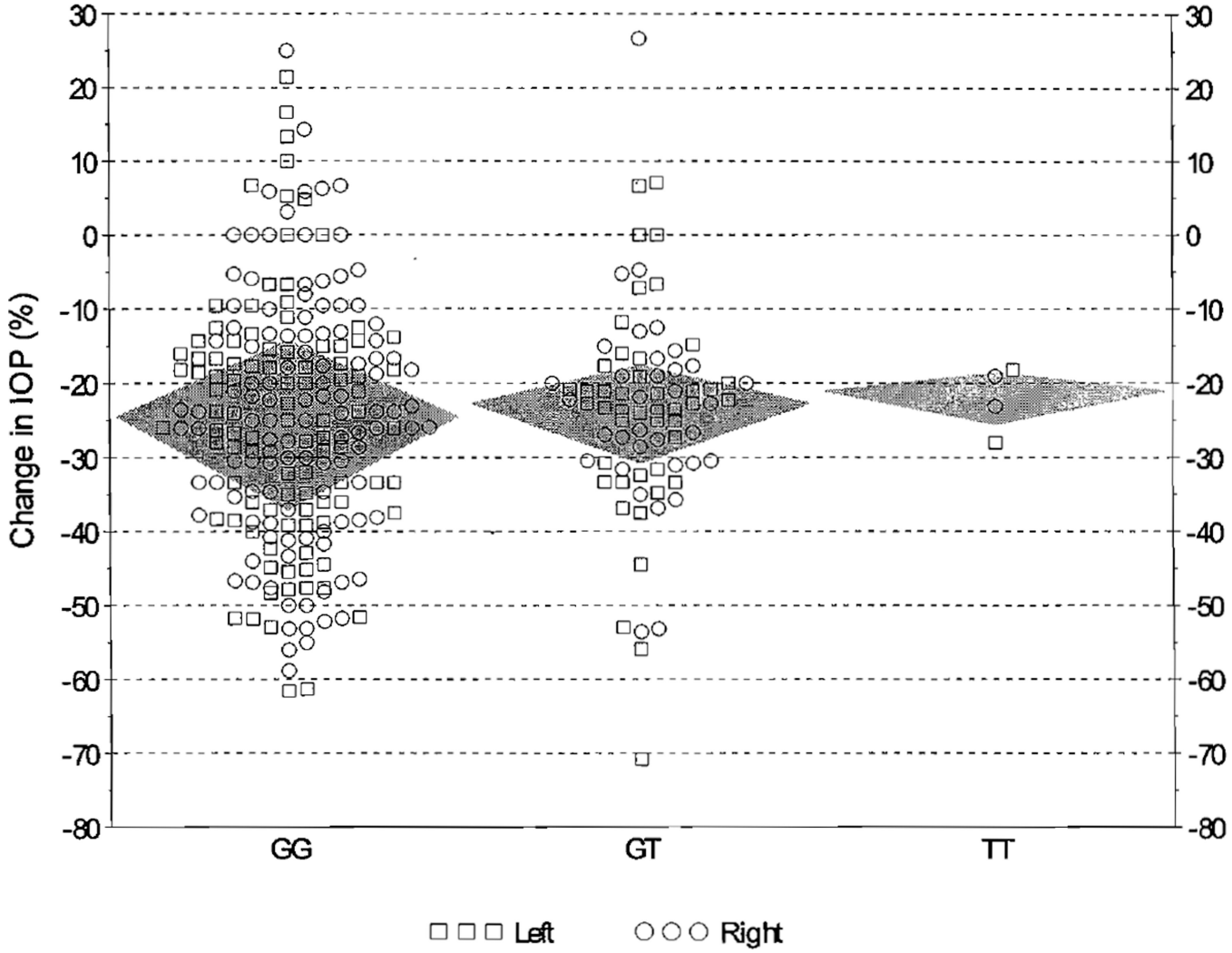

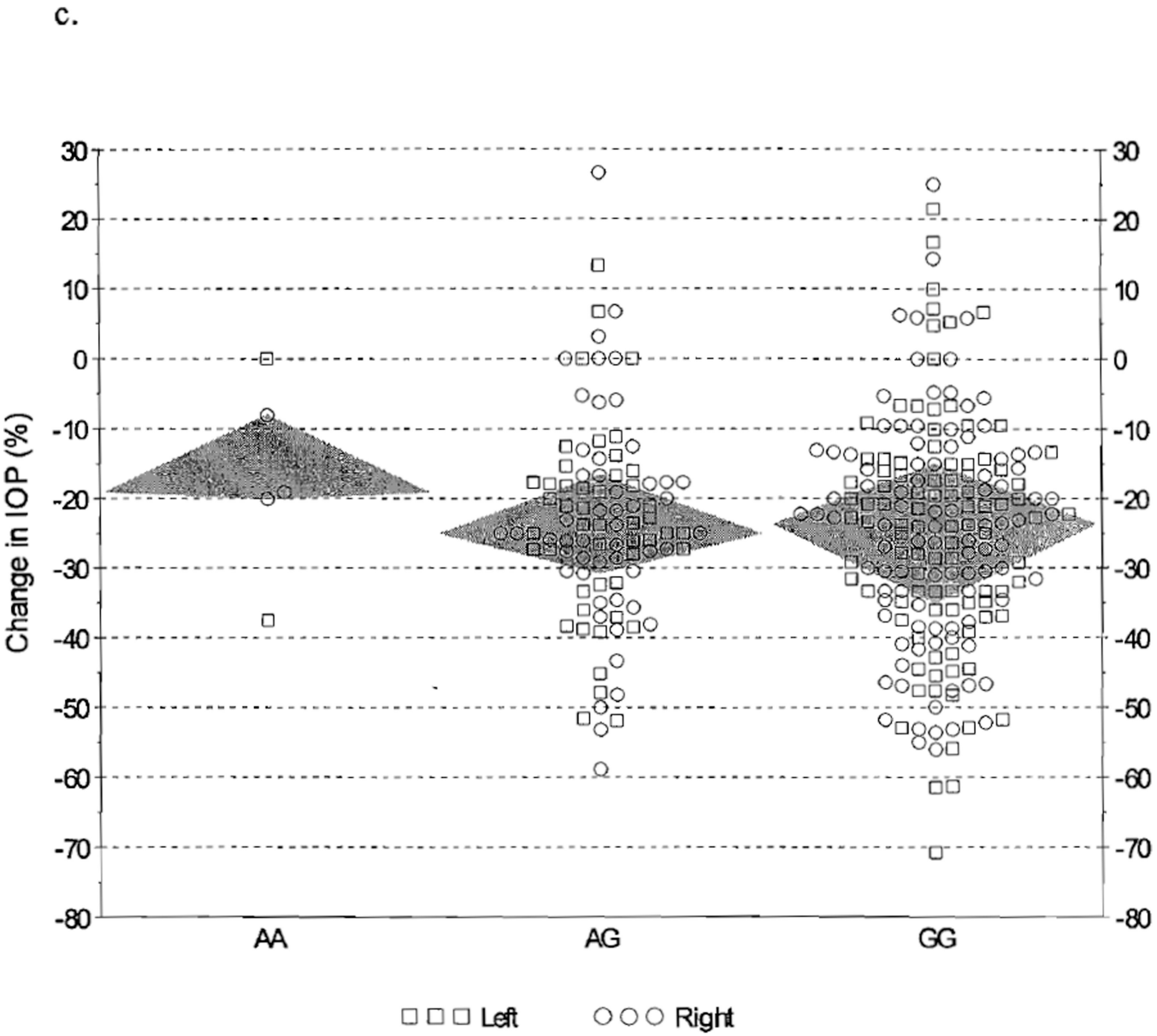

Figure 1.

a. Change in intraocular pressure from baseline to follow-up by RS3753380 (PTGFR) genotype.

b. Change in intraocular pressure from baseline to follow-up by RS3766355 (PTGFR) genotype.

c. Change in intraocular pressure from baseline to follow-up by RS34550074 (SLCO2A1) genotype.