• Investigation •

Assessment of single nucleotide polymorphisms associated with steroid-induced ocular hypertension

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Abstract

● **AIM:** To access the association of forty-eight single nucleotide polymorphisms (SNPs) identified from Caucasian population with steroid-induced ocular hypertension (OHT) in India population.

● **METHODS:** Fifty-four triamcinolone-acetonide (TA) and forty-seven dexamethasone (Dex) administered subjects were enrolled in the study after a written consent. Intraocular pressure (IOP) values were recorded for a period of 6-month post steroid injections and patients were grouped as steroid-responders (SR: IOP≥21 mm Hg) and non-responders (NR: IOP≤20 mm Hg). Genomic DNA was isolated from peripheral venous blood. Forty-eight SNPs identified in TA treated Caucasian patients by genome wide association study (GWAS) were genotyped using iPLEX™ MassARRAY among TA as well as Dex administered Indian patients. Genotyping data of 48 general subjects from a previous study were considered as reference controls for statistical analysis. Genotypic frequencies were calculated and *P*-value, Chi-square and odds ratio at 95% confidence-interval of group A (steroid treated *vs* controls), group B (SR *vs* NR), group C (phenotype correlation: influence of time, severity and gender on IOP rise), were calculated. *P*<0.05 was considered to be statistically significant.

● **RESULTS:** OHT was observed in 50% of TA and 26% of Dex administered patients, respectively. IOP rise was mostly severe (>30 mm Hg) and immediate (<1wk) among TA-SR patients while it was noticed to be mild (<30 mm Hg) and between 1-2mo among Dex-SR patients. Logistic regression for risk factor correlation with OHT remained non-significant, hence these factors were not considered as confounding parameters for further analysis. rs133, rs34016742, rs274554, rs10936746, rs274547, rs804854, rs7751500, rs359498, and rs7547448 SNPs significantly varied even after Bonferroni corrections (*P*<0.0025; group A). rs1879370 (TA) and rs6559662 (Dex) were significantly (*P*<0.05) associated with OHT (group B). rs133 (severe IOP rise), rs11047639 and rs1879370 (male gender), and rs11171569 (immediate IOP rise) significantly (*P*<0.05) influenced the phenotype correlation only among TA-OHT patients. However, the significance of these SNPs in group B and phenotype analysis (group C) was lost upon Bonferroni corrections (*P*<0.0025).

● **CONCLUSION:** Prevalence of OHT in study population is observed to be similar to other studies both in TA and Dex treated patients. We can correlate rs34016742 involved in diabetes signaling pathway to the occurrence of ocular edematous and inflammatory conditions. Except rs133 that is involved in neuro-degeneration and myopia occurrence, none of the other SNPs identified in Caucasian population possess any correlation with OHT incidence in TA and Dex administered Indian subjects.

● **KEYWORDS:** triamcinolone-acetonide; dexamethasone; ocular hypertension; single nucleotide polymorphisms; diabetes; neurodegeneration; myopia

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INTRODUCTION

Intravitreal steroids such as triamcinolone-acetonide (TA) and dexamethasone/Ozurdex (Dex) are the current modality of treatment for certain ocular inflammatory conditions such as macular edema resulting from chronic diabetes; termed as diabetic macular edema (DME), retinal vein occlusion (RVO) and post cataract macular edema (CME)[1-2]. However, use of these intravitreal steroids in some cases is accompanied with either unwarranted elevation of intraocular pressure (IOP; >20%), cataract (>15%), endophthalmitis (>5%), or uveitis (>5%)[3-5]. Of these, an IOP rise commonly referred as steroid-induced ocular hypertension (SI-OHT), when left untreated could result in secondary glaucoma with optic nerve head (ONH) damage and permanent vision loss. SI-OHT is reported approximately in 58.3% of patients with existing glaucoma[5] and in 20%-30% of patients with no prior history or known risk factors for glaucoma[6]. Treatment for SI-OHT is primarily with anti-glaucoma medications (AGM). If medically uncontrolled, a surgical intervention procedure (glaucoma filtration surgery) is performed.

Pathophysiology of SI-OHT is remarkably similar to that of primary open angle glaucoma (POAG) with over-expression and excessive deposition of extracellular matrix (ECM) proteins on trabecular meshwork (TM). Dysfunction of TM due to differential expression of myocilin gene and protein, drug crystallization in TM layer and the consequent obstruction of aqueous humor (AH) outflow are the proposed mechanisms of POAG[6]. However, none of these mechanisms have been evidenced into their potential role for SI-OHT. As genetic influence on SI-OHT was reported as early as in 1966, research on identification of biomarkers has primarily focused on genetic variations in the varying drug response (SI-OHT). While initial studies that explored the genetic background of SI-OHT predisposition remains inconclusive[7-12], an earlier genome wide association study (GWAS) has identified 48 single nucleotide polymorphisms (SNPs) corresponding to 33 genes to be responsible for the variability in steroid response upon TA treatment[13]. As the genetic framework varies with race and geographical distribution, identification of these SNPs in different ethnic cohort of patients would be necessary to establish a global association of SNPs with SI-OHT.

Dex sustained drug delivery implant, a recent formulation is preferred due to its prolonged activity but also induces OHT in up to 20%-30% of those administered with the drug[14-15]. No such GWAS or validation of associated SNPs to identify the genetic determinants for Dex induced OHT have been reported in any population. Present study was carried out at a tertiary ophthalmic hospital, to look for an association of the reported 48 SNPs in causing OHT following TA and Dex administration in an Indian population.

SUBJECTS AND METHODS

Ethical Approval Study was approved by the Institutional Ethics Committee (Ethics No.317-2012-P) and adhered to the Declaration of Helsinki. Peripheral venous blood was collected with duly signed informed consent. Patients didn't receive any stipend during their enrolment.

Subjects TA (n=54) and Dex (n=47) administered patients at tertiary care eye hospital, Sankara Nethralaya in Chennai, India were enrolled in this study. Inclusion criteria: DME, RVO, CME patients; exclusion criteria: patients with pre-existing glaucoma, family history of glaucoma, baseline IOP>21 mm Hg, AGM usage, shallow anterior chamber, gonioscopy data revealing closed angles, eye injury, rubeosis of iris or angle uveitis. All patients underwent standard eye examination including optic disc evaluation for glaucomatous changes, prior to steroid administration. IOP was measured before steroid administration (baseline) and on first day (day 1) after intravitreal procedure. Follow-up IOP measurements were made at 1, 3, and 6mo post injection. ΔIOP values were calculated by subtracting maximum IOP from baseline IOP and patients were grouped as steroid-responders (SR) and non-responders (NR). Steroid responsiveness mentioned in this study is based only on the IOP changes following steroid administrations; wherein, SR's have IOP≥21 mm Hg/ΔIOP ≥6 mm Hg and NR's have IOP≤20 mm Hg/ΔIOP≤5 mm Hg up to 6mo post steroid administration. Details of DME, CME and RVO resolution were not discussed in this study.

Sample Collection, DNA Extraction and SNP Genotyping Genomic DNA was extracted using Qiagen DNA extraction kit, according to the manufacturer's protocol. Of 48 SNPs were genotyped by iPlex GOLD SNP genotyping Sequenom MassARRAY® System (Sandeigo, USA). Briefly, forward, reverse and extension primers (Table 1) were designed using MassARRAY Assay Design Suite. With 50 ng of DNA, polymerase chain reaction was performed, amplified DNA fragments were treated with shrimp alkaline phosphatase to dephosphorylate and remove the unincorporated dNTPs. iPLEX single base extension primers with extension enzyme and mass modified dideoxynucleotide terminators were added to the products, purified using a resin coated plate, transferred to a SpectroChip array and analyzed by Matrix assisted laser desorption/ionization- (MALDI)-time of flight (TOF) Mass spectrometry (MS). SPECTROTYPER software was used to analyze specific chromatogram peaks corresponding to the nucleotides.

Table 1 Details of primers used in the study

SNP_ID	2nd-PCRP	1st-PCRP
rs312046	ACGTTGGATGCCATGGAAATGCAGAGAGAG	ACGTTGGATGGGAAAATCCCTCTGGATGTG
rs10134871	ACGTTGGATGGGCTTTGTACATAGTAAATGG	ACGTTGGATGCTGTCTGAGGAATTCAAGCC
rs259911	ACGTTGGATGAAATTGGGAGAAAGGATGGG	ACGTTGGATGTTTGCGTTAACAGCAGGGTC
rs7325084	ACGTTGGATGGCTTGGGATATCGTCTGCTC	ACGTTGGATGAACTCCCAGAGAAGAGAGAC
rs2382962	ACGTTGGATGCAGACACCCGAGAGATTTGC	ACGTTGGATGGAAATACTTTTCCCATAACC
rs10751260	ACGTTGGATGGCACCAACATAGTAGTTGCT	ACGTTGGATGGGTAACCAAATCACCACCTG
rs464690	ACGTTGGATGGATGGTATAGTCTTTTGTCC	ACGTTGGATGTAAACCCAAGGAAGGATAAC
rs11171569	ACGTTGGATGGAGTAAGACTGTGGCTCAAA	ACGTTGGATGAAACACATATAGATCTCAC
rs804854	ACGTTGGATGGCTCAAGAGAAAGGATGCAG	ACGTTGGATGAGAGGCTCAGAGCTAAGAAC
rs7547448	ACGTTGGATGTTGCCTCATTCTAAATTCCC	ACGTTGGATGGGATGATGGACTTAAAATA
rs866279	ACGTTGGATGTCCTTGTCCCCACTCTCTG	ACGTTGGATGGCCGATAAAGATAGATATCC
rs1740317	ACGTTGGATGCTGCAGGTCATATAGGAAGC	ACGTTGGATGCACCGTCAGTAAAAGCTTCC
rs274551	ACGTTGGATGTTCATGCTTTCCTCCCACTC	ACGTTGGATGGCACAGCACAGAGAGATTAG
rs11047639	ACGTTGGATGTCTGTGACCACTGAAGTAGG	ACGTTGGATGTGCCACTTCTAAGTGGAAGC
rs10936746	ACGTTGGATGCAAGCTATAAGCTTTAGACG	ACGTTGGATGGTGTGTATATGCATGCAATG
rs8080886	ACGTTGGATGGTTCTTCCCAAAGTCATCTC	ACGTTGGATGATGGTCACCATCCTCTGTTG
rs274547	ACGTTGGATGGGCACAGGCTCACTAAATTC	ACGTTGGATGTGCCTTGGGAAATGAGAAAG
rs7002473	ACGTTGGATGAAGTAAAATTGATCCTCAG	ACGTTGGATGGGGCAAGAGCAGAAGTAAAG
rs359498	ACGTTGGATGCAACTGGCAGGGCTAAATTG	ACGTTGGATGCCAAAGATCAGCATCTCTCC
rs16878394	ACGTTGGATGTCAAAGAGACCATGGAGTAG	ACGTTGGATGCCACATCATTCTATGTAGC
rs16925580	ACGTTGGATGTCCATCTGCTCTATATTGCC	ACGTTGGATGTCTGTTTGCCGAATGTTGCC
rs6526393	ACGTTGGATGGGAGGGGCTCATTAATTGTG	ACGTTGGATGACAGAGCCTAGACTCTCAAC
rs1766864	ACGTTGGATGGAACTTTGCTTGAACTAAC	ACGTTGGATGCATAGTGTTGATCTACTATTG
rs34016742	ACGTTGGATGTACGCTGTGCTTCTCAAAGG	ACGTTGGATGAGGTGAATGCTTGGTATTGG
rs2256917	ACGTTGGATGAACCAGAAGCCCTAAGACAG	ACGTTGGATGTGCCCAATTGGTTCCTAAGC
rs1130674	ACGTTGGATGCACTCATCCCTGTCTTCCAC	ACGTTGGATGCACCGCTCTCCAGGAATTTC
rs10112966	ACGTTGGATGTCTCATCGGGGTGGCTGTG	ACGTTGGATGGCCTGGCCTCTTTTATCTTA
rs13149290	ACGTTGGATGTCTCTACTCAGACCCAGTTG	ACGTTGGATGCATCTGTGGCATTTCAGTTC
rs1879370	ACGTTGGATGCAGCAGAGATCATGGAGTAG	ACGTTGGATGTTCTCAAGAGTGAGCTCAGG
rs6596075	ACGTTGGATGAAAGGATGACCCTGTCACTG	ACGTTGGATGGAAGAGCTCTGCCTTCAAAC
rs11654944	ACGTTGGATGTACACACAACTGGGATGAAC	ACGTTGGATGTCCATCTTTATAATGTTTTC
rs274554	ACGTTGGATGCCCAAATTGGGCAAGGATTC	ACGTTGGATGAATTGTGGAGGCTGTTGTGG
rs16993820	ACGTTGGATGTCATTACCCTAATAGTCCTC	ACGTTGGATGACCATAACCACGTGAGGAAG
rs1000677	ACGTTGGATGACAGTGCTCCATCAACCTTC	ACGTTGGATGGGATCAGAGGAAAGAGAACG
rs6559662	ACGTTGGATGTCCTTGTAGGCTGCTTTAGG	ACGTTGGATGACGGTATGGAAGCGTATTTC
rs2382961	ACGTTGGATGGGCAGAGAAAACACGTCATC	ACGTTGGATGCCCCGCTGTCATTTTTTAAC
rs16842190	ACGTTGGATGTAAAGGATGGGAGAGCTTGG	ACGTTGGATGGTCACTTCTTCATTATCAAC
rs4649436	ACGTTGGATGGGCTTTTTCTACCCTAGCTG	ACGTTGGATGTGTGGTTTCTCCATCTACTC
rs2861445	ACGTTGGATGAACACAAACGCCCAGAAGAG	ACGTTGGATGTGGTCCTACCTCGGTTTTAC
rs750581	ACGTTGGATGCTACTCCCTTGCAGCAGAAG	ACGTTGGATGTTGAACTCTGCAGGAGGAAG
rs274552	ACGTTGGATGTTTGAGGAGGAGGGAGAAGG	ACGTTGGATGTCTGTGGGATACTAAGATAG
rs7751500	ACGTTGGATGAGACTTTCCTTATCCTCCCC	ACGTTGGATGTGTTGAAAGCACTGGGTTAG
rs16842228	ACGTTGGATGGACTTACTTATCGTATCAC	ACGTTGGATGAGCTTCTCTGTTACAGTGTG
rs11032376	ACGTTGGATGAGGTGAGGCAAGAAAGCTAC	ACGTTGGATGGCATTAAAATGTTATTTATTTG
rs6699851	ACGTTGGATGGCTAGAATTCTTCCATGGAG	ACGTTGGATGTCTCCATCTCAATGTCTGCC
rs133	ACGTTGGATGGACAGGAGAAGAGAGTGTTG	ACGTTGGATGTGGGAAGCATGAGAACATGG
rs9864066	ACGTTGGATGCATGGTCAGTGATTGATTAG	ACGTTGGATGGGAAGAAAGATCATGCTCTG

PCRP: Polymerase chain reaction primers.

Table 2 Demographics of TA and Dex administered study population

Parameters	TA		Dex	
Steroid responsiveness	SR	NR	SR	NR
No. of patients	27	27	12	35
Age (y)	54.59±9.16	55.03±10.61	54.16 ±11.83	57.65±6.01
Sex				
Male	23 (85.18%)	23 (85.18%)	10 (83.33%)	23 (65.71%)
Female	4 (14.81%)	4 (14.81%)	2 (16.66%)	12 (34.28%)
ΔIOP (mm Hg)[a]	20.07±10.98	2.96±2.48	15.83±7.48	2.88±2.12
Time of IOP rise among SR				
Day 1	12 (45%)		0	
Month 1	6 (22%)		10 (83%)	
Month 3	6 (22%)		2 (17%)	
Month 6	3 (11%)		0	
Magnitude of ΔIOP rise among SR				
<10 mm Hg	4 (15%)		2 (17%)	
11- 20 mm Hg	12 (44%)		8 (67%)	
21-30 mm Hg	8 (30%)		1 (8%)	
31- 40 mm Hg	1 (4%)		1 (8%)	
>41 mm Hg	2 (7%)		0	
Risk factor analysis	OR (95%CI)	*P*	OR (95%CI)	*P*
Age	0.99 (0.09-1.05)	0.867	0.95 (0.88-1.76)	0.22
Sex	2.42 (0.63-9.29)	0.198	1.59 (0.36-6.98)	0.87
DM	2.2 (0.63-7.74)	0.22	0.39 (0.09-1.76)	0.22
Hypertension systemic	2.97 (0.97-9.12)	0.06	1.12 (0.3-4.15)	0.87
Myopia	0.5 (0.13-1.95)	0.32	1.4 (0.29-6.68)	0.67
Hypercholesterolemia	0.3 (0.08-1.1)	0.07	1.31 (0.35-4.93)	0.69

TA: Triamcinolone-acetonide; Dex: Dexamethasone; IOP: Intraocular pressure; SR: Steroid responder; NR: Steroid non-responder; OR: Odds ratio; CI: Confidence interval; DM: Diabetes mellitus. Data are represented as mean±SD or *n* (%). [a]*P*=0.001 (SR *vs* NR).

Twenty SNPs previously identified using Affymetrix 250K NSP array from 48 healthy subjects in a previous study of the institute were used as control for data analysis. Association studies were performed between the following groups: A) Steroid treated (54 TA and 47 Dex) and healthy controls (*n*=48); B) SR and NR; C) Phenotype correlation: influence of time, severity [high-SR (IOP≥31 mm Hg) and mild/moderate-SR (IOP≤30 mm Hg)], gender on IOP rise.

Statistical Analysis Clinical parameter correlation was performed using statistical package for the social sciences (SPSS) purchased from IBM, version 14. Hardy-Weinberg equilibrium (HWE) test was performed using Chi-square (χ^2) analysis (α=0.05, df=2). Univariate logistic regression was performed for the reported risk factors of SI-OHT such as diabetes mellitus, connective-tissue disorders, and myopia along with age and sex criteria. Genotypic proportions were calculated using SNPSTATS (http://bioinfo.iconcologia.net/SNPstats) fisher exact test. *P*-value with odds ratio at 95% confidence interval (CI) was calculated. $P \leq 0.05$ was considered to be statistically significant.

Functional Analysis Functional annotation of significant SNPs, was performed using dbSNP, regulomeDB, variant effect predictor (VEP) and polymiRTS databases.

RESULTS

Subjects Clinical characteristics of our TA and Dex administered study cohort are represented in Table 2. Steroids were predominantly administered among male (>70%) population (TA: 46 male, 8 female and Dex: 33 male, 14 females) of age greater than 50y (TA: 54.59±9.82y and Dex: 56.76±7.82y) in our study cohort. TA was administered to twenty-one macular edema (ME), fourteen RVO, and nineteen CME subjects. And, Dex was administered to twenty-seven ME, fifteen RVO, and five CME subjects. SR (*n*=27) and NR (IOP≤20 mm Hg; *n*=27) were distributed equally (50%) under TA treated group. NR patients were seen at a higher percentage (74%; *n*=35) compared to SR patients (26%; *n*=12) among Dex treated group. No significant difference [*P*=0.87 (TA) and 0.19 (Dex)] among age distribution was observed between SR and NR of both the steroid treatment groups, respectively. Males had higher SI-OHT among TA (85%) and Dex (83%) treatment groups, respectively. In SR category, IOP rise was mostly observed between day 1 and 1wk (45%) after TA treatment and between 1 and 2mo (83%) post Dex administration, respectively. The change (Δ) in IOP measurements was significantly (*P*=0.001) higher in SR than NR for both the steroid administered groups; that ranged from 10-60 mm Hg and 10-40 mm Hg for TA and Dex administrations, respectively. In our study cohort,

Table 3 Distribution of 20 SNPs between steroid treated and healthy control subjects in association with SI-OHT

SNO	rs ID	Genotype	Steroid treated group			Control			OR (95%CI)	*P*
		A-B	AA	AB	BB	AA	AB	BB		
TA										
1	rs9864066	A-C	40	14	0	37	13	0	1 (0.41-2.40)	1.000
2	rs133	G-T	21	23	10	2	27	21	0.07 (0.01-0.30)	0.000[a]
3	rs34016742	T-C	50	4	0	0	3	47		0.000[a]
4	rs11047639	G-T	42	12	0	35	15	0	0.67 (0.28-0.61)	0.665
5	rs11032376	A-G	45	7	2	39	10	1	0.71 (0.27-1.89)	0.566
6	rs274554	C-T	38	16	0	4	13	33	0.04 (0.01-0.12)	0.000[a]
7	rs274547	T-A	41	13	0	4	13	33	0.03 (0.01-0.09)	0.000[a]
8	rs6596075	C-G	38	16	0	33	13	4	0.82 (0.36-1.87)	0.105
9	rs1879370	A-T	39	14	1	43	7	0	2.36 (0.87-6.40)	0.185
10	rs16842228	G-T	52	2	0	44	5	1	0.28 (0.05-1.47)	0.246
11	rs10936746	G-A	42	9	2	1	5	43	0.01 (0.00-0.04)	0.000[a]
12	rs804854	T-A	49	5	0	2	9	39	0.00 (0.00-0.02)	0.000[a]
13	rs7751500	T-G	48	6	0	3	9	38	0.01 (0.00-0.03)	0.000[a]
14	rs13149290	T-C	9	38	7	8	26	16	0.95 (0.34-2.70)	0.058
15	rs359498	C-T	46	7	1	3	4	43	0.01 (0.00-0.04)	0.000[a]
16	rs11171569	C-G	35	17	2	32	16	2	0.97 (0.43-2.16)	0.995
17	rs6559662	C-T	53	1	0	46	2	2	0.22 (0.02- 2.01)	0.262
18	rs7547448	T-C	52	1	0	1	0	48	0.00 (0.00-0.01)	0.000[a]
19	rs1000677	A-G	45	7	2	39	10	1	0.71 (0.27-1.89)	0.566
20	rs274552	C-G	38	16	0	33	15	2	0.82 (0.37-1.87)	0.327
Dex										
1	rs9864066	A-C	35	12	0	37	13	0	0.98 (0.39-2.43)	0.999
2	rs133	G-T	21	14	12	2	27	21	0.05 (0.01-0.24)	0.000[a]
3	rs34016742	T-C	46	1	0	0	3	47		0.000[a]
4	rs11047639	G-T	36	10	1	35	15	0	0.71 (0.29-1.77)	0.382
5	rs11032376	A-G	33	13	1	39	10	1	1.50 (0.60-3.76)	0.671
6	rs274554	C-T	26	21	0	4	13	33	0.07 (0.02- 0.23)	0.000[a]
7	rs274547	T-A	27	20	0	4	13	33	0.06 (0.02- 0.21)	0.000[a]
8	rs6596075	C-G	26	21	0	33	13	4	1.57 (0.69-3.56)	0.036[a]
9	rs1879370	A-T	40	6	1	43	7	0	1.08 (0.35-3.34)	0.579
10	rs16842228	G-T	42	4	0	44	5	1	0.70 (0.18-2.65)	0.609
11	rs10936746	G-A	37	9	1	1	5	43	0.01 (0.00-0.05)	0.000[a]
12	rs804854	T-A	37	10	0	2	9	39	0.01 (0.00-0.05)	0.000[a]
13	rs7751500	T-G	37	10	0	3	9	38	0.02 (0.00-0.07)	0.000[a]
14	rs13149290	T-C	16	20	11	8	26	16	0.37 (0.14-0.97)	0.117
15	rs359498	C-T	38	8	1	3	4	43	0.02 (0.00-0.06)	0.000[a]
16	rs11171569	C-G	28	17	2	32	16	2	1.21 (0.53-2.74)	0.903
17	rs6559662	C-T	45	2	0	46	2	2	0.51 (0.09-2.93)	0.383
18	rs7547448	T-C	44	2	1	1	0	48	0.00 (0.00-0.01)	0.000[a]
19	rs1000677	A-G	32	14	1	39	10	1	1.66 (0.67-4.12)	0.531
20	rs274552	C-G	26	21	0	33	15	2	1.57 (0.69-3.56)	0.154

OR: Odds ratio; CI: Confidence interval; SI-OHT: Steroid induced ocular hypertension. [a]*P* values are significant.

all SR patients responded well to AGM usage and no surgical intervention was required. Logistic regression analysis for multiple covariates of age, sex, diabetes mellitus, and myopia factors did not show any significant difference (Table 2) on comparison between SR and NR for both the steroid treatment groups.

SNP Genotyping A single SNP (rs1799919) that failed to pass the quality threshold was excluded from genotyping panel. SNPs at 7 loci (rs750581, rs6699851, rs6526393, rs2256917, rs1766864, rs16878394, rs4649436), without any minor alleles are represented in Tables 3-6. Power of the study was 0.913

Table 4 Distribution of 20 SNP between SR and NR subjects in association with SI-OHT

SNO	rs ID	Genotype A-B	SR			NR			OR (95%CI)	*P*
			AA	AB	BB	AA	AB	BB		
TA										
1	rs9864066	A-C	20	7	0	20	7	0	1.00 (0.30-3.38)	1.00
2	rs133	G-T	12	11	4	9	12	6	0.73 (0.21-1.88)	0.65
3	rs34016742	T-C	24	3	0	26	1	0	3.25 (0.32- 33.41)	0.58
4	rs11047639	G-T	24	3	0	18	9	0	0.25 (0.06-1.06)	0.15
5	rs11032376	A-G	22	4	1	23	3	1	1.31 (0.31-5.51)	0.92
6	rs274554	C-T	21	6	0	17	10	0	0.49 (0.15- 1.61)	0.49
7	rs274547	T-A	20	7	0	21	6	0	1.23 (0.35- 4.28)	0.95
8	rs6596075	C-G	21	6	0	17	10	0	0.49 (0.15-1.61)	0.49
9	rs1879370	A-T	15	11	0	23	3	0	5.62 (1.34-23.56)	0.04[a]
10	rs16842228	G-T	25	2	0	27	0	0		0.35
11	rs10936746	G-A	21	4	1	21	5	1	0.83 (0.22-3.16)	0.95
12	rs804854	T-A	24	3	0	25	2	0	1.56 (0.24-10.19)	0.90
13	rs7751500	T-G	23	4	0	25	2	0	2.17 (0.36-13.01)	0.69
14	rs13149290	T-C	3	19	5	6	19	2	2.29 (0.51-10.29)	0.32
15	rs359498	C-T	23	4	0	23	3	1	1.00 (0.22-4.49)	0.56
16	rs11171569	C-G	14	12	1	21	5	1	3.25 (1.00-10.58)	0.12
17	rs6559662	C-T	26	1	0	27	0	0		0.60
18	rs7547448	T-C	25	1	0	27	0	0		0.59
19	rs1000677	A-G	22	4	1	23	3	1	1.31 (0.31-5.51)	0.92
20	rs274552	C-G	21	6	0	17	10	0	0.49 (0.15-1.61)	0.49
Dex										
1	rs9864066	A-C	8	4	0	27	8	0	1.69 (0.40-7.10)	0.773
2	rs133	G-T	8	2	2	13	12	10	0.30 (2.22-1.18)	0.205
3	rs34016742	T-C	12	0	0	34	1	0		0.839
4	rs11047639	G-T	8	4	0	28	6	1	2.00 (0.40-8.60)	0.438
5	rs11032376	A-G	7	5	0	26	8	1	2.06 (0.50-8.16)	0.405
6	rs274554	C-T	8	4	0	18	17	0	0.53 (0.40-2.09)	0.657
7	rs274547	T-A	8	4	0	19	16	0	0.59 (0.40-2.34)	0.756
8	rs6596075	C-G	8	4	0	18	17	0	0.53 (0.40-2.09)	0.657
9	rs1879370	A-T	10	2	0	30	4	1	1.20 (0.20-7.18)	0.763
10	rs16842228	G-T	11	1	0	31	3	0	0.94 (0.10-10.00)	0.999
11	rs10936746	G-A	8	4	0	29	5	1	2.42 (0.40-10.70)	0.311
12	rs804854	T-A	8	4	0	29	6	0	2.42 (0.40-10.70)	0.497
13	rs7751500	T-G	8	4	0	29	6	0	2.42 (0.40-10.70)	0.497
14	rs13149290	T-C	5	4	3	11	16	8	0.64 (3.43-2.48)	0.735
15	rs359498	C-T	10	2	0	28	6	1	0.80 (0.20-4.51)	0.837
16	rs11171569	C-G	8	4	0	20	13	2	0.67 (0.40-2.63)	0.651
17	rs6559662	C-T	10	2	0	35	0	0		0.048[a]
18	rs7547448	T-C	12	0	0	32	2	1		0.577
19	rs1000677	A-G	7	5	0	25	9	1	1.79 (0.50-6.97)	0.514
20	rs274552	C-G	8	4	0	18	17	0	0.53 (0.40-2.09)	0.657

OR: Odds ratio; CI: Confidence interval; SI-OHT: Steroid induced ocular hypertension; TA: Triamcinolone-acetonide; Dex: Dexamethasone.
[a]*P* values are statistically significant.

Table 5 Distribution of remaining 20 SNP between SR and NR subjects associated with steroid-induced ocular hypertension

SNO	rs ID	Genotype	Total			Steroid responders			Steroid non-responders			OR (95%CI)	*P*
			AA	AB	BB	AA	AB	BB	AA	AB	BB		
TA													
1	rs10112966	T-C	13	22	19	7	10	10	6	12	9	0.82 (0.23-2.85)	0.856
2	rs10134871	T-C	10	44	0	5	22	0	5	22	0	1.00 (0.25-3.95)	1.000
3	rs10751260	C-G	41	13	0	24	3	0	17	10	0		0.084
4	rs1130674	A-G	38	16	0	19	8	0	19	8	0	1.00 (0.31-3.22)	1.000
5	rs16925580	C-G	53	1	0	26	1	0	27	0	0		0.601
6	rs1740317	A-G	53	1	0	26	1	0	27	0	0		0.601
7	rs2382962	A-G	33	17	4	16	10	1	17	7	3	1.17 (0.39-3.49)	0.458
8	rs259911	G-T	45	8	1	20	6	1	25	2	0	4.38 (0.82-23.43)	0.169
9	rs274551	C-T	40	14	1	20	7	0	20	7	0	1.00 (0.30-3.38)	1.000
10	rs312046	C-T	51	3	0	26	1	0	25	2	0	0.48 (0.04-5.64)	0.838
11	rs464690	T-C	53	1	0	26	1	0	27	0	0		0.601
12	rs7002473	G-A	38	16	0	20	7	0	18	9	0	0.70 (0.22-2.27)	0.837
13	rs7325084	A-G	27	23	4	14	11	2	13	12	2	0.86 (0.30-2.51)	0.961
14	rs8080886	A-G	45	7	1	23	2	1	22	5	0	0.57 (0.12-2.69)	0.318
15	rs866279	A-G	42	12	0	20	7	0	22	5	0	1.54 (0.42-5.64)	0.807
16	rs11654944	C-G	44	10	0	23	4	0	21	6	0	0.61 (0.15-2.46)	0.782
17	rs16842190	G-A	52	2	0	25	2	0	27	0	0		0.354
18	rs16993820	A-G	53	0	1	26	0	1	27	0	0		0.601
19	rs2382961	T-A	7	18	29	1	13	13	6	5	16	7.43 (0.83-66.63)	0.024
20	rs2861445	G-C	10	44	0	4	23	0	6	21	0	1.64 (0.41-6.64)	0.782
Dex													
1	rs10112966	T-C	10	17	20	0	5	7	10	12	13		0.105
2	rs10134871	T-C	2	5	40	1	1	10	1	4	30	0.32 (0.02-5.62)	0.699
3	rs10751260	C-G	35	12	0	8	4	0	27	8	0		0.773
4	rs1130674	A-G	38	8	1	11	1	0	27	7	1	0.35 (0.04-3.19)	0.629
5	rs1740317	A-G	45	1	1	12	0	0	33	1	1		0.699
6	rs2382962	A-G	31	10	6	10	2	0	21	8	6	0.30 (0.06-1.58)	0.228
7	rs259911	G-T	38	9	0	9	3	0	29	6	0	1.61 (0.33-7.78)	0.837
8	rs274551	C-T	27	20	0	8	4	0	19	16	0	0.59 (0.15-2.34)	0.756
9	rs312046	C-T	44	3	0	12	0	0	32	3	0		0.577
10	rs464690	T-C	1	46	0	1	11	0	0	35	0		0.225
11	rs7002473	G-A	20	27	0	4	8	0	16	19	0	1.68 (0.43-6.64)	0.756
12	rs7325084	A-G	23	21	3	7	4	1	16	17	2	0.60 (0.16-2.27)	0.653
13	rs8080886	A-G	43	4	0	10	2	0	33	2	0	3.30 (0.41-26.51)	0.502
14	rs866279	A-G	37	10	0	10	2	0	27	8	0	0.68 (0.12-3.74)	0.903
15	rs11654944	C-G	37	8	1	11	1	0	26	7	1	0.30 (0.03-2.65)	0.503
16	rs16842190	G-A	5	41	1	1	11	0	4	30	1	1.42 (0.14-14.11)	0.795
17	rs16993820	A-G	44	1	1	12	0	0	32	1	1		0.691
18	rs2382961	T-A	6	11	29	0	3	9	6	8	20		0.287
19	rs2861445	G-C	16	30	1	5	7	0	11	23	1	0.64 (0.17-2.48)	0.707
20	rs4649436	A-G	45	1	1	12	0	0	33	1	1		0.699

OR: Odds ratio; CI: Confidence interval; TA: Triamcinolone-acetonide; Dex: Dexamethasone.

(TA) and 0.895 (Dex) for the treatment groups, respectively.

Group A Table 3 denotes the genotypic distribution of 20 SNPs available from a previous study in the institute; healthy reference control group (*n*=48), compared with steroid [TA (*n*=54), Dex (*n*=47)] treated cohort. Ten SNPs (rs133, rs34016742, rs274554, rs274547, rs10936746, rs804854, rs359498, rs7751500, rs7547448, and rs6596075) showed statistically significant ($P<0.05$) difference in distribution

Table 6 Distribution of significant SNPs involved in larger phenotype (IOP)

Parameters (A, B)	Rs ID	Genotype	Group A			Group B			OR (95%CI)	*P*
			AA	AB	BB	AA	AB	BB		
TA SR: immediate (A) *vs* others (B)	rs11171569	C-G	9	2	0	5	10	1	0.10 (0.016-0.650)	0.034
TA-SR: high-SR (A) *vs* moderate SR (B)	rs133	G-T	8	5	0	3	6	4	0.18 (0.034-1.03)	0.042
Male: TA-SR (A) *vs* TA-NR (B)	rs11047639	G-T	20	2	0	11	8	0	0.14 (0.02-0.76)	0.049
	rs1879370	A-T	11	10	0	17	1	0	15.45 (1.72-138.23)	0.014

OR: Odds ratio; CI: Confidence interval; SR: Steroid responders; NR: Steroid non-responders; TA: Triamcinolone-acetonide; Dex: Dexamethasone.

between steroid treated population and controls. Frequency of wild-type homozygous genotype of rs133, rs34016742, rs274554, rs10936746, rs274547, rs804854, rs7751500, rs359498, rs7547448 varied significantly in both steroid treated groups, even after Bonferroni correction (P<0.0025). Additionally, heterozygous genotype of rs6596075 was significantly higher (P<0.05) in Dex treated group than in controls; however, its significance was lost upon Bonferroni correction (P>0.0025).

SR *vs* NR (Group B) Table 4 summarizes the genotypic distribution of 20 SNPs between SR and NR of steroid treatment groups in association with SI-OHT. Two SNPs (rs1879370 and rs6559662) were observed to be significantly different between SR and NR of TA and Dex administered groups, respectively. Higher frequency of heterozygous genotype (AT) of rs1879370 was observed among TA-SR compared to TA-NR, P=0.04; OR 5.62 [1.34-23.56 (95%CI)]. Similarly, higher frequency of heterozygous genotype (CT) of rs6559662 (P=0.048) was observed among Dex-SR compared to Dex-NR. However, significance of rs1879370 and rs6559662 was lost after Bonferroni correlation corrections (P>0.0025).

Distribution of the remaining 20 SNPs (without control population comparison) analyzed within steroid treated SR and NR cohort did not show any statistically significant difference after Bonferroni correction (P>0.0025; Table 5).

Association of SNPs with Elevated IOP (Group C) Analysis of 20 SNPs for its influence in time of IOP rise, magnitude or severity of IOP rise and gender distribution with the respective genotypic *P*-values are presented in Table 6. None of these 20 SNPs were observed to be associated with IOP rise among Dex treated cohort (P>0.05).

Time of IOP rise: High frequency of CG genotype of rs11171569 among TA-SR showed an immediate rise in IOP [P=0.034; OR 0.10 (0.02-0.65; 95%CI)] when compared to TA-SR, who had IOP rise from 1 to 6mo post steroid administration. Degree of IOP rise: GT genotype of rs133 varied significantly (P=0.042) between high-SR and moderate-SR of TA treatments with OR 0.18 [0.03-1.03 (95%CI)]. SNPs rs11047639 and rs1879370 were significantly different (P<0.05) among the male gender of TA-SR compared with TA-NR groups. Males with high frequency of GT genotype (rs11047639) was observed in TA-SR group [P=0.049, OR 0.14 (0.02-0.76, 95%CI)] compared to TA-NR group. Similarly, higher frequency of AT genotype (rs1879370) was observed in TA-SR group [P=0.014; OR 15.45 (1.72-138.2, 95%CI)] compared to TA-NR group. Significance of all these SNPs (rs11171569, rs133, rs11047639, and rs1879370) associated with larger phenotype (IOP) was lost after Bonferroni corrections (P>0.0025).

Genotypic frequency *P*-values of the remaining SNPs involved in elevation of IOP are listed in Table 7. Distribution of the SNPs in general cohorts are provided in Table 8.

DISCUSSION

SI-OHT is of prime concern among ophthalmologists, as it leads to irreversible blindness in 20%-40% of steroid administered patients[6]. Pharamcogenetic studies are of importance in understanding this varying steroid response[13] and no such SI-OHT association studies are available in an Indian population. Hence, we aimed to validate the SNPs identified in Caucasian cohort, involved in TA and Dex induced OHT, in an Indian population. From the clinical characteristics of our study cohort (Table 2), it was observed that ocular edematous and inflammatory conditions mostly occurred among male subjects (70%) of age 50y, for whom steroids were administered[16-17]. Male population (80%) had higher SI-OHT prevalence in our cohort, which is in par with previous reports[18]. Immediate (1d/1wk) and severe (40-60 mm Hg) IOP rise among TA-SR patients, in contrary to the delayed (1-2mo) and less severe (30-40 mm Hg) IOP rise among Dex-SR treated cohort observed in this study might be attributed to the difference in drug characteristics or formulations. Crystalline nature of TA that is available in suspension form may result in a burst release of drug, clogging TM layer and blocking AH outflow[19-20]. Immediate IOP rise on day 1 may be misleading in categorizing patients as SR; which might be due to result of injection procedures[21]. However, our study cohort was carefully chosen wherein, patients having IOP rise on day 1 to 1wk, underwent through evaluation by clinicians, were monitored regularly and used AGM for more than 30d to control IOP rise. This cohort was then considered as SR group. Delayed (1-2mo) IOP rise among Dex-SR can be attributed to

Table 7 *P* values of SNPs in association with larger phenotype (IOP)

SNO	rsID	1mo *vs* others	High-SR *vs* mild-SR	Male-SR *vs* male-NR
TA				
1	rs10936746	0.65	0.527	0.808
2	rs11047639	0.63	0.162	0.049[a]
3	rs11171569	0.03[a]	0.617	0.256
4	rs274547	0.59	0.858	0.740
5	rs34016742	0.63	0.793	0.666
6	rs359498	0.20	0.604	0.547
7	rs7547448	0.44	0.595	0.642
8	rs804854	0.63	0.793	0.994
9	rs1000677	0.52	0.653	0.269
10	rs11032376	0.52	0.374	0.269
11	rs13149290	0.52	0.106	0.231
12	rs133	0.25	0.029[a]	0.956
13	rs16842228	0.96	0.313	0.403
14	rs1879370	0.67	0.255	0.014[a]
15	rs274552	0.87	0.995	0.806
16	rs274554	0.87	0.995	0.806
17	rs6559662	0.70	0.617	0.642
18	rs6596075	0.87	0.995	0.806
19	rs7751500	0.32	0.508	0.896
20	rs9864066	0.75	0.484	0.992
Dex				
1	rs10936746	0.91	0.911	0.193
2	rs11047639	0.91	0.687	0.329
3	rs11171569	0.69	0.687	0.580
4	rs274547	0.91	0.911	0.635
5	rs34016742	0.00		0.799
6	rs359498	0.55	0.549	0.546
7	rs7547448	0.00		0.629
8	rs804854	0.91	0.911	0.379
9	rs1000677	0.71	0.710	0.139
10	rs11032376	0.71	0.710	0.068
11	rs13149290	0.36		0.130
12	rs133	0.52	0.519	0.101
13	rs16842228	0.76	0.761	0.970
14	rs1879370	0.55	0.861	0.546
15	rs274552	0.91	0.911	0.501
16	rs274554	0.81	0.911	0.806
17	rs6559662	0.86	0.861	0.086
18	rs6596075	0.51	0.911	0.501
19	rs7751500	0.91	0.911	0.379
20	rs9864066	0.91	0.911	0.557

TA: Triamcinolone-acetonide; Dex: Dexamethasone. [a]*P* values are significant.

the sustained delivery system of Dex implant (Ozurdex)[22-23]. This varying time of IOP rise between two currently used steroids, necessitates careful IOP monitoring, at least for a minimum period of 3mo post steroid administration, as the ignored OHT may lead to irreversible glaucoma. Since, no significant association (P>0.05) was identified among the predicted risk factor for SI-OHT by univariate logistic regression test[24], these factors were not considered as confounding parameters for further analysis. Additionally, this may suggest the probable role of genetic factors in regulating the phenotype alteration (IOP) upon steroid administration.

We performed a replication study for the 48 SNPs identified in Caucasian cohort associated with TA-OHT, unlike the previous studies that validated only the targeted SNPs for few genes[9-12]. From the clinical parameters, it was observed that time and magnitude of IOP rise and male gender had predominantly influenced SI-OHT in both the steroid treated groups. Hence, we performed an association study of these factors with SI-OHT. Nine SNPs were identified to be different in distribution between steroid treated patients from the reference control cohort in our study (Table 3). This indicates that these SNPs may be associated with the occurrence of ocular edematous and inflammatory conditions of DME, RVO and CME.

rs133 is present at the chromosome position of 7:24913359 of oxysterol binding protein like 3 (*OSBPL3*) gene. This gene is involved in synthesis of bile salts and acids. In the current study, rs133 was associated with severe OHT (IOP >31 mm Hg) among TA-SR group. VEP tool which determines the effect of variants reports a modifier impact for this variant (100% intron variant activity). *OSBPL3* has less likely effect on the binding of MYC associated Zinc finger (MAZ) protein. dbSNP database reports that MAZ is expressed in retina, choroid, sclera, retinal pigment epithelial cells. MAZ controls the loop formation of lens fiber generation and its gene expression[25]. MAZ has been suspected to be involved in neurodegeneration and was reported to predict the onset of glaucoma[26]. *OSBPL3* is also informed as a risk factor of myopia in an US based study[27]. Since association of myopia is suggested risk factor for SI-OHT occurrence[28] and we also found myopia is significantly associated (P=0.042) with severity of IOP rise in our SR (n=27) patient cohort, we predict that the presence of this SNP may indicate severe IOP rise following TA administration. No regulatory effects and miRNA interactions has been reported till date by polymiRTS database.

In our study on 101 Indian subjects, except rs133 we couldn't associate remaining 8 SNPs with SI-OHT or glaucoma (Tables 4, 5; P>0.05), which might be attributed to the smaller cohort size and the difference in ethnicity. rs34016742 present at the chromosome position of 3:185753143 in insulin like growth factor binding protein 2 (*IGF2BP2*) gene is associated with

Table 8 Distribution of SNP in general population

rs ID	Minor allele frequency								
	TOPMED	PAGE	GnomAD	1000 G	Estonian	ALSPAC	TWINSUK	Northern Sweden	Vietnamese
rs10936746	0.19482		0.2176	0.146	0.31	0.267	0.267	0.29	0.06
rs11047639	0.2209		0.2213	0.159	0.244	0.275	0.289	0.26	0.06
rs11171569	0.23355		0.2347	0.254	0.273	0.23	0.219	0.23	0.46
rs274547	0.25563		0.2459	0.256	0.146	0.151	0.172	0.16	0.11
rs34016742	0.02499		0.0222	0.023	0.013	0.017	0.017	0.01	0.01
rs359498	0.0776		0.0713	0.103	0.001	0.003	0.003		0.01
rs7547448	0.09616		0.0854	0.089	0.012	0.012	0.011	0.01	
rs804854	0.09991		0.0978	0.070	0.117	0.145	0.138	0.18	0.00
rs1000677	0.1603		0.1501	0.209	0.112	0.082	0.073	0.07	0.36
rs11032376	0.12133		0.1181	0.163	0.11	0.082	0.073	0.06	0.32
rs13149290	0.28861	0.3878	0.2613	0.43	0.209	0.225	0.221	0.23	0.23
rs133	0.26510		0.2561	0.289	0.278	0.284	0.287	0.29	0.35
rs16842228	0.07777		0.0713	0.067	0.043	0.052	0.057	0.07	0.01
rs1879370	0.1872		0.2089	0.141	0.301	0.237	0.232	0.26	0.02
rs274552	0.25188		0.2431	0.252	0.146	0.151	0.172	0.16	
rs274554	0.25533			0.254	0.146	0.151	0.171	0.16	0.11
rs6559662	0.10300	0.1376	0.0893	0.092	0.023	0.038	0.034	0.03	0
rs6596075	0.25808	0.3186	0.2482	0.258	0.147	0.151	0.172	0.16	0.11
rs7751500	0.15404	0.1463	0.1456	0.12	0.115	0.145	0.139	0.18	0.00
rs9864066	0.18228		0.1778	0.124	0.208	0.285	0.261	0.27	0.01

diabetes signaling. Diabetes is involved in ME and RVO progression[29-30]. Diabetes is also a risk factor for glaucoma progression and SI-OHT[31]. Except rs34016742 (*IGF2BP2*), none of the other SNPs (rs274554, rs274547, rs359498 rs10936746, rs808548, rs7751500, rs7547448) with in their genes possess any correlation with the occurrence of ocular edematous conditions or any of its driving factors. rs274554 (chromosome position-5:132389258) and rs274547 (chromosome position-5:132395612) in solute carrier family 22 member 5 (*SLC22A5*) gene is involved in carnitine dysfunction. rs359498 (chromosome position-4:161937830) is present in Follistatin like 5 gene (*FSTL5*), which aids in calcium ion binding activity. The disease association of SNP rs10936746 at (chromosome position 3:173256741) LOC105374224 is not known. SNPs rs808548, rs7751500, and rs7547448 has no gene component or functional pathway associations according to dbSNP database.

Role of the remaining SNPs which were not significantly differed between steroid treated and control population but that were associated with SI-OHT (Table 4) or elevated IOP (Table 6) are discussed in Table 9.

rs6559662 is associated with Dex-OHT and is involved in neurological disorder, Alzheimer's disease (AD; Table 9). This made us to lay interest on *APBAI* gene, as glaucoma and AD share common feature of age-related neurodegeneration (irreversible loss of neurons). AD patients possess higher risk for glaucoma but their association is controversial[32-34]. Amyloid beta (AB) protein is an early stage definitive diagnostic marker for AD[35]. It has also been suggested that Amyloid precursor protein (APP) and AB accumulation in retinal ganglion cells (RGC), ONH, retinal nerve fibre and dural complex, alters the metabolism of APP elimination and RGC's loss that has a secondary direct influence on IOP rise in mouse OHT models[36]. Brimonidine (neuro-protective AGM) that is used as secondary treatment for AD, reduced AB proteins in mouse retina. AB proteins largely secreted in eye fluid could serve as a therapeutic target for stress-related glaucoma[37]. AB proteins are better biomarker for AD's early detection than assays using cerebrospinal fluid (easy, minimal invasive and inexpensive procedure)[38-39]. In this similar fashion, presence of CC genotype of rs6559662 in AB gene among Dex treated patients can acts as an indicator for Dex-OHT.

SNPs involved in OHT progression varied between TA and Dex administered groups. This differential response of SNPs to TA and Dex induced OHT might be due to the difference in chemical structure and formulation of these steroids. Potential limitations of this study are the smaller cohort size and the details of smoking habit and alcohol consumption were missing for few patients. Even though smoking and alcohol consumption was not reported to influence SI-OHT[24], the stratification analysis for these factors would have been valuable.

Table 9 SNPs involved in steroid-induced ocular hypertension

SNP	Intron position	Variant description	Genes and pathway affected	Functional analysis	Ocular and systemic associations
rs1879370 associated with TA-OHT and male gender of TA-SR	3:173284335	None	None	VEP: 33% regulatory region variant, 33% intronic variant effect and 33% non-coding transcript variant effect. PolymiRTS: no regualtory and miRNA interactions. RegulomeDB (5): minimal binding evidence	None
rs6559662 associated with Dex-OHT	9:69637580	3-intron variant and 1-geneic upstream variant	Amyloid beta precursor protein family 1 (*APBA1 gene*) involved in brain functioning	VEP: 50% regulatory region variant and 50% intronic variant activity. RegulomeDB: nil. PolymiRTS: No regulatory effects and miRNA interactions	Expressed highly in brain phenotype correlation involves the occurrence of cognitive disease (dbSNP)
rs11171569 associated with immediate IOP rise among TA-SR	12:55573234	1-upstream transcript variant	Olfactory receptor family 2 subfamily AP member 1 gene (*OR2AP1*) associated with smelling capability	VEP: 33% non-coding transcript variant, 50% intron variant, 17% upstream variant activity. RegulomeDB (6): minimal binding activity. PolymiRTS: no regualtory and miRNA interactions	Detection of chemical stimulus involved in sensory perception of smell (dbSNP)
rs11047639 associated with male gender of TA-SR	LOC52825W 12:24798554	Intergenic: present between ribosomal protein L21 and branched chain amino acid	None	100% intergenic variant, regulome (2b). Likely to affect binding	None

SNP: Single nucleotide polymorphism; VEP: Variant effect predictor; TA: Triamcinolone-acetonide; Dex: Dexamethasone; IOP: Intraocular pressure.

In conclusion, SI-OHT was observed in fifty percentage of TA and twenty-six percentage of Dex administered patients. rs133 (myopia and neurodegeneration) is associated with severe IOP rise and rs34016742 (diabetes) is associated with the ocular edematous and inflammatory conditions, for which these intravitreal steroids were preferred. Myopia, neurodegeneration, and diabetes are the reported risk factors for SI-OHT progression. Further, GWAS are desirable to identify novel SNPs associated with SI-OHT progression.

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