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Steroid-induced ocular hypertension/glaucoma: Focus on pharmacogenomics and implications for precision medicine

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ABSTRACT

Elevation of intraocular pressure (IOP) due to therapeutic use of glucocorticoids is called steroid-induced ocular hypertension (SIOH); this can lead to steroid-induced glaucoma (SIG). Glucocorticoids initiate signaling cascades ultimately affecting expression of hundreds of genes; this provides the potential for a highly personalized pharmacological response. Studies attempting to define genetic risk factors were undertaken early in the history of glucocorticoid use, however scientific tools available at that time were limited and progress stalled. In contrast, significant advances were made over the ensuing years in defining disease pathophysiology. As the genomics age emerged, it appeared the time was right to renew investigation into genetics. Pharmacogenomics is an unbiased discovery approach, not requiring an underlying hypothesis, and provides a way to pinpoint clinically significant genes and pathways that could not have been discovered any other way. Results of the first genome-wide association study to identify polymorphisms associated with SIOH, and follow-up on two novel genes linked to the disorder, GPR158 and HCG22, is discussed in the second half of the article. However, knowledge of genetic variants determining response to steroids in the eye also has value in its own right as a predictive and diagnostic tool. This article concludes with a discussion of how the Precision Medicine Initiative®, announced by U.S. President Obama in his 2015 State of the Union address, is beginning to touch the practice of ophthalmology. It is argued that SIOH/SIG may provide one of the next opportunities for effective application of precision medicine.

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Abbreviations

(HUGO nomenclature is used for genes and their products)

AP-1	activating protein-1
BRVO	branch retinal vein occlusion
CLAN	cross-linked actin network
CRVO	central retinal vein occlusion
DME	diabetic macular edema
DMEK	Descemet's membrane endothelial keratoplasty
ECD	extracellular domain
ELAM-1	endothelial leukocyte adhesion molecule-1
eQTL	expression quantitative trait locus
FDA	Food and Drug Administration
GAP	GTPase-Accelerating Protein
GEDi	Genetic Eye Disease Panel
GEF	Guanine Nucleotide Exchange Factor
GRα	glucocorticoid receptor-α
GRβ	glucocorticoid receptor-β
IL-1	Interleukin 1 (i.e. IL1A, IL1B)
LD	linkage disequilibrium
GPCR	G protein-coupled receptor
GWAS	genome wide association study
ICD	intracellular domain
IOP	intraocular pressure
IVTA	intravitreal triamcinolone acetonide
MMP	matrix metalloproteinase
NCBI	National Center for Bioinformatics Information
NIH	National Institutes of Health
NF-κB	Nuclear Factor-κB
NGS	next-generation sequencing
NLS	nuclear localization signal
QTL	quantitative trait locus
PTSI	peroxisomal targeting signal type 1
POAG	primary open angle glaucoma
SIOH	steroid-induced ocular hypertension
SIG	steroid-induced glaucoma
SNP	single nucleotide polymorphism
TGF-β	Transforming Growth Factor-β (i.e., TGFB1, TGFB2, TGFB3)
TIGR	trabecular meshwork-inducible glucocorticoid response protein

Contents

1. Introduction

Elevated intraocular pressure (IOP) is a major risk factor for glaucoma, a group of eye diseases characterized by a progressive loss of retinal ganglion cells (Kwon et al., 2009; Quigley, 1999). Glaucoma is the second leading cause of visual impairment and blindness worldwide, affecting about 70 million people, and is the leading cause of blindness among African-Americans (Quigley, 1996; Quigley and Broman, 2006). Primary open-angle glaucoma (POAG) is the most common form of the disease, accounting for approximately 70% of all cases (Kwon et al., 2009). It has been increasingly recognized that a significant percentage of these cases are characterized by normal IOP (Anderson, 2011; Kass et al., 2002; Tielsch et al., 1991). Interestingly however, reducing IOP is an effective treatment for both high tension and normal tension forms of glaucoma (Gordon et al., 2002; Kass et al., 2002; Leske et al., 2003), and in fact, is currently the *only* treatment for glaucoma.

Ocular hypertension due to secondary factors can also lead to glaucoma. One form is initiated by glucocorticoids, which are one of two types of natural corticosteroid hormones produced by the adrenal glands (the other being mineralocorticoids). Released in response to stress, glucocorticoids regulate a natural feedback mechanism that turns down the inflammatory response. As such, they are useful pharmacologically for treating a wide variety of diseases (Rhen and Cidlowski, 2005). Cortisol is the most important human glucocorticoid, essential for life. Hydrocortisone is the name

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