Published in final edited form as:

Exp Eye Res. 2009 April ; 88(4): 837–844. doi:10.1016/j.exer.2008.11.003.

The genetics of primary open-angle glaucoma: A review

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Abstract

Glaucoma is the major cause of irreversible blindness worldwide. Primary open-angle glaucoma (POAG), as the most prevalent form of glaucoma, is a complex inherited disorder and affects more than 2 million individuals in the United States. It has become increasingly clear that a host of genetic as well as environmental factors are likely to contribute to the phenotype. A number of chromosomal and genetic associations have been reported for POAG. This review examines what is currently known about the underlying genetic structure, what remains to be learned, and how this may affect our medical management of this major blinding disease.

Keywords

POAG; genetics; genetic linkage; whole genome association; admixture mapping; genetic screening; myocilin; optineurin; WDR36; SNP

In this special edition of *Experimental Eye Research* that celebrates Dr Doug Johnson's life and contribution to science, we are honored to present an overview of the state of genetics of one of the most common causes of blindness in the world, primary open-angle glaucoma (POAG). Dr Johnson displayed a life-long passion to find the root causes of open angle glaucoma. Dr Johnson rightly felt that the discovery of myocilin opened the door to a new age in understanding the pathophysiology of a disease that continues to challenge scientists worldwide (Johnson, 2000). What follows is a review of the progress being made in our current understanding of the genetics of POAG and future directions of this research.

1. Introduction

Glaucoma is a heterogeneous group of disorders which constitute the leading cause of irreversible blindness worldwide (Quigley, 1996; Resnikoff et al., 2004). Glaucoma is a pathologic condition in which there is a progressive loss of retinal ganglion cells, specific visual field deficit, and a characteristic excavative atrophy of the optic nerve. POAG is the most common type of glaucoma and is characterized by the presence of glaucomatous optic neuropathy in the absence of an identifiable secondary cause. Abnormally elevated

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intraocular pressure (IOP) is frequently associated with glaucoma and is a major risk factor for this disease (Hewitt et al., 2006b; Libby et al., 2005; Tielsch et al., 1994).

2. POAG as a complex inherited disorder

The familial nature of POAG has been recognized for decades. In cross sectional studies of patients with POAG, up to 50% have a positive family history, suggesting that genetic defects might contribute to the cause of POAG (Tielsch et al., 1994). In a large population-based study conducted in the Netherlands, Wolfs and co-workers examined family members of individuals with and without POAG. These investigators found that first degree relatives of an affected individual had a 22% risk of developing POAG compared with only a 2.3% risk in family members of controls (Wolfs et al., 1998). The overall risk of developing POAG among first degree relatives of an affected individual is increased 3–9 fold (Tielsch et al., 1994; Weih et al., 2001; Wensor et al., 1998; Wolfs et al., 1998; Wu et al., 2006). This evidence strongly suggests that specific genetic defects contribute to the pathogenesis of POAG.

Our modern understanding of the genetic architecture of POAG has been steadily evolving since the first gene for POAG, myocilin (MYOC), was mapped and identified (Sheffield et al., 1993; Stone et al., 1997). The MYOC gene and other reported genes for POAG were mostly identified through family-based studies with glaucoma inherited as a Mendelian trait, where the altered function of a single gene is sufficient to cause the disease. However, it has become increasingly clear that POAG, in most cases, is inherited as a complex trait, where the disease results from the interaction of multiple genes and environmental factors (Sieving and Collins, 2007). This should not come as a surprise since the glaucoma phenotype itself is quite complex, resulting from diverse pathological processes that involve but are not limited to the aqueous humor outflow pathway, the retina and optic nerve, and even, as suggested recently, cerebrospinal fluid dynamics (Berdahl et al., 2008).

3. Genetic approaches to gene identification

Identifying genes that either cause or contribute to the development of disease is challenging, especially in complex disorders such as POAG. The most commonly used method to identify genes that are transmitted in a Mendelian pattern, such as an autosomal dominant or recessive trait, is genetic linkage analysis. This method employs the use of a family or families where multiple members are affected. The power to detect linkage is proportional to the number of individuals affected within families and the total number of families. Once linkage to a specific chromosomal locus is identified, analysis of the genes contained within the region of interest is conducted. Traditional linkage analysis has been widely and successfully used to identify genetic variants in human diseases with Mendelian inheritance, including POAG. However, despite these successes more than 90% of the genetic contribution for POAG still remains to be determined (Fan et al., 2006).

In an effort to address the challenges associated with gene identification for common, complex disorders that do not exhibit classical Mendelian inheritance patterns, newer and more robust methods have been developed. The most promising of these is genome-wide

association with high-density single-nucleotide-polymorphism arrays. This approach utilizes datasets containing large numbers of unrelated cases and controls to determine statistical associations between common genetic variations within the human genome and disease (Collins et al., 1997; Lander and Schork, 1994; Risch and Merikangas, 1996; Risch, 2000; Wellcome Trust Case Control Consortium., 2007). Single nucleotide polymorphisms (SNPs) are the mainstay of this type of analysis. SNPs, numbering in the millions, are dispersed throughout the human genome so are ideal for genetic analysis. Although the theory underlying this approach has been known for decades, only recent advances in massive throughput genotyping have made this approach practical. It is now possible to genotype one million SNPs per individual on large datasets containing thousands of samples in just a few days. This approach has led to the identification of common disease-associated genetic variants in chronic disorders including diabetes mellitus, heart disease, cancer and others (Feero et al., 2008). Ophthalmology has greatly benefitted from this approach. Major, common genetic variants that predispose to age-related macular degeneration and pseudoexfoliation syndrome have recently been identified by genome-wide association studies (Sieving and Collins, 2007; Thorleifsson et al., 2007).

In addition to whole genome association there are additional methods being developed to determine the cause of inherited disease. Admixture mapping is a method used to localize disease-associated genetic variants that differ in frequency across populations (Zhu et al., 2008). This powerful method has been successfully used to locate the chromosomal location for a gene that causes prostatic cancer and is currently being used to locate disease-associated variants for POAG in the African-American population. (personal communication, Michael Hauser, PhD). Another area of intense interest is the role that DNA copy number variants and genetic imprinting may have in a variety of human disorders including POAG (Feinberg, 2007; McCarroll and Altshuler, 2007). As these approaches are increasingly used additional susceptibility loci and genes for POAG will be added to the list (Collins and Manolio, 2007; Willett et al., 2007).

4. Chromosomal loci for POAG

A genetic locus (singular; loci is plural) refers to a specific physical region of a chromosome that defines an area harboring a gene or genes that are associated with a specific phenotype or disease. Currently 14 chromosomal loci for POAG (GLC1A-N) are listed by HUGO (<http://www.genenames.org/index.html>) (Human Genome Organization, Geneva Switzerland) and many more have been reported in the literature (Table 1). In most cases these loci have been identified in family datasets using genetic linkage analysis. Three genes associated with glaucoma have been identified within these loci, including myocilin/TIGR (GLC1A), optineurin (GLC1E), and WDR36 (GLC1G).

5. Myocilin

Myocilin (MYOC) was identified by Stone and co-workers in GLC1A locus, which was the first reported locus for POAG located on chromosome 1 (Morissette et al., 1995; Sheffield et al., 1993; Stone et al., 1997). The myocilin protein was previously known as trabecular meshwork inducible-glucocorticoid response protein or TIGR (Polansky et al., 1997).

Disease-associated mutations of myocilin are generally associated with a juvenile or early-adult form of POAG. This genetic form of glaucoma is typically associated with high intraocular pressures and frequently requires surgical intervention for disease control. In adult POAG populations, the prevalence of myocilin mutations in POAG cases varies between 3 and 5% making it the most common form of inherited glaucoma currently known (Aldred et al., 2004; Alward et al., 1998; Baird et al., 2005b; Chakrabarti et al., 2005; Challa et al., 2002; Fingert et al., 1999; Hulsman et al., 2002; Jansson et al., 2003; Libby et al., 2005; Mukhopadhyay et al., 2002; Shimizu et al., 2000; Sripriya et al., 2004).

The MYOC gene consists of three exons. Myocilin protein has sequence similarities to the muscle protein myosin at the N-terminus, from which it gets its name, and olfactomedin at the C-terminus. Most glaucoma-associated mutations in the MYOC gene are located within the third exon which codes for the olfactomedin-like domain. Myocilin is expressed by most tissues of the eye and multiple tissues throughout the body (Fingert et al., 2002). It is interesting that despite MYOC's widespread expression pattern only glaucoma, an eye disorder, has been described as a result of abnormal genetic variants.

Myocilin associated glaucoma is transmitted as an autosomal dominant Mendelian trait. Carriers of disease-associated mutations develop the glaucoma phenotype in an estimated 90% of cases (Alward et al., 1998). Interestingly, individuals who are homozygous, where both MYOC copies are abnormal, for certain myocilin mutations Gln368STOP and Lys423Glu do not appear to develop glaucoma (Hewitt et al., 2006a; Morissette et al., 1998). However, one patient with a congenital form of open angle glaucoma was reportedly homozygous for the Gln48His MYOC mutation (Chakrabarti et al., 2005). In another case, a patient who was hemizygous for MYOC did not have a glaucoma phenotype (Wiggs and Vollrath, 2001). Although most MYOC mutations cause a juvenile onset form of POAG, those with the Gln368Stop mutation typically have a later adult-onset (Graul et al., 2002; Wiggs and Vollrath, 2001).

When first discovered, myocilin was a novel gene and protein. Over the past decade our knowledge about the physiological role of myocilin is improving. Although myocilin protein expression is greatly increased upon administration of glucocorticoids in trabecular meshwork cells, this property does not appear to be related to steroid-induced ocular hypertension (Fingert et al., 2001). Fautsch and coworkers demonstrated that the introduction of myocilin protein increases outflow resistance in the perfused human anterior segment model system (Fautsch et al., 2000, 2006) while Caballero et al. (2000) showed that overexpression of the N-terminal domain of MYC results in an increase of outflow facility in perfused anterior segment model system.

A number of animal model studies of myocilin have been conducted in the genetic mouse model. Neither absence of myocilin or increased expression of wild type myocilin in the trabecular meshwork produce elevated IOP (Gould et al., 2006; Kim et al., 2001). In a study examining the effect of a mutated form of myocilin, the Tyr423His mutation was introduced into a transgenic mouse model. Similar to humans, the mutated form of myocilin was not secreted and accumulated in the TM but failed to elevate IOP (Gould et al., 2006). However, in other studies utilizing the same myocilin mutation, increased IOP did occur which was

associated with loss of retinal ganglion cells, findings consistent with glaucoma (Senatorov et al., 2006; Zhou et al., 2008).

Interestingly, myocilin protein is normally found in the aqueous humor of many species including man, but this protein is absent in the aqueous humor of patients with glaucoma-associated MYOC mutations (Jacobson et al., 2001). Recent studies have shown that myocilin is associated with the shedding of small vesicles called exosomes into the aqueous humor. In other tissues exosomes contain ligands that participate in autocrine and paracrine signaling, and thus serve as vehicles that may play a role in trabecular meshwork homeostasis (Fevrier and Raposo, 2004; Hardy et al., 2005). It is possible that interference in this pathway induced by mutations in myocilin may play a role in the pathogenesis of glaucoma.

These data suggest that mutant, disease-associated forms of myocilin interfere with protein trafficking and result in the intracellular accumulation of misfolded protein. How this process causes an increase in aqueous humor outflow resistance and why the onset of glaucoma in most cases takes decades to occur remains to be determined. However, it is clear that the discovery of myocilin is leading to a better understanding of the pathobiology of POAG.

6. Optineurin

The second gene discovered that is associated with POAG was optineurin (OPTN) (Rezaie et al., 2002). OPTN is located in the GLC1E locus on chromosome 10. The phenotype for affected individuals with OPTN variants was remarkable for glaucoma associated with normal IOP, or normal tension glaucoma (NTG), in a large percentage of affected family members.

The original report identified OPTN variants in over 16% of open angle glaucoma families. Subsequently disease-associated variants have been reported by other investigators (Fuse et al., 2004; Leung et al., 2003; Toda et al., 2004; Umeda et al., 2004; Weisschuh et al., 2005). However, most investigators have found that OPTN variants are uncommon in POAG and NTG cases (Alward et al., 2003; Ariani et al., 2006; Baird et al., 2004; Forsman et al., 2003; Jansson et al., 2005; Libby et al., 2005; Mukhopadhyay et al., 2005; Tang et al., 2003; Toda et al., 2004; Wang et al., 2004; Wiggs et al., 2003). Of those OPTN mutations studied to date, the E50K variant, although rare, appears to be most strongly associated with open angle glaucoma, particularly of the normal tension type (Hauser et al., 2006b; yala-Lugo et al., 2007). Furthermore, it is reported that NTG patients who have the E50K mutation have a more severe form of glaucoma compared to NTG patients that lack the mutation. These mutation carriers appear to have a younger age of onset, develop more advanced optic nerve cupping, and required surgical intervention more frequently than their NTG counterparts (Aung et al., 2005).

Other investigators have also reported association between OPTN variants and glaucoma. Forsman et al. (2003) found that three OPTN SNPs, Thr34Thr, Glu163Glu, and 553–5C, were associated with an increased risk of glaucoma. Additionally, specific OPTN variants

have been associated with a higher IOP in a glaucoma population in India (Sripriya et al., 2006). Although controversial, the more common Met98Lys polymorphism of OPTN may increase susceptibility to normal tension forms of open angle glaucoma, especially in Asian populations (Craig et al., 2006; yala-Lugo et al., 2007).

In a large study of Japanese patients, researchers found that the synonymous variant Thr34Thr was associated with POAG (Funayama et al., 2004). Of interest, these investigators also found that certain TNF-alpha variants in combination with OPTN variants were higher in POAG patients compared with controls and that these patients had a worse prognosis. This interaction between TNF-alpha and OPTN is consistent with the belief that many glaucoma phenotypes are polygenic in origin. Although interesting, most of these associations remain to be corroborated.

Similar to myocilin, the mechanistic role of OPTN in the pathogenesis of glaucoma is unclear. Studies of optineurin expression in the human anterior segment perfusion model have produced conflicting results (Kamphuis and Schneemann, 2003; Vittitow and Borras, 2002). There is evidence that optineurin may play a neuroprotective role by reducing retinal ganglion cell susceptibility to apoptosis. De Marco et al. (2006) found that in response to apoptotic stimuli, OPTN translocates from the Golgi to the nucleus in a manner dependent on the GTPase activity of Rab8. Overexpression of OPTN blocks cytochrome c release from mitochondria and protects cells from hydrogen peroxide-induced cell death. The OPTN E50K mutation inhibits translocation to the nucleus. Overexpression of this variant compromises mitochondrial membrane integrity increasing the susceptibility to death from external stressors (De et al., 2006). The protection against apoptosis may not translate to other tissues as overexpression in the lens of transgenic mice failed to protect against TGFb-1 induced apoptosis of lens epithelial cells (Kroeber et al., 2006).

In studies examining the cellular role of the OPTN investigators have found that OPTN negatively regulates TNF α - induced NF- κ B activation (Zhu et al., 2007). TNF α -stimulated NF κ B-dependent gene transcription is greatly enhanced if the level of expression of OPTN is reduced, lowering the apoptotic threshold. Other investigators have observed that the OPTN E50K mutation increases binding to TANK-binding kinase 1 (TBK1), which forms a complex that regulates TNF α and its pro-apoptotic effects (Morton et al., 2008). It is suggested that the OPTN E50K mutant may cause aberrant activation of TBK1 which may underlie increased susceptibility to ganglion cell loss in subjects with familial NTG. These and other studies are bringing us closer to an understanding of the role of OPTN variants and the pathogenesis of glaucoma.

7. WDR36 (WD40-repeat 36)

Sequence variants in WDR36 gene were reported to cause POAG in 2005 (Monemi et al., 2005). WDR36 encodes a protein with 951 amino acids. It is located in the GLC1G locus on chromosome 5q22. Similar to both myocilin and optineurin, the mRNA transcript is ubiquitous, and is found in various tissues of the body and throughout the structures of the eye. The prevalence of WDR36 sequence variations has been estimated to be between 1.6 and 17% of POAG patients (Hauser et al., 2006a; Hewitt et al., 2006c). Subsequent studies

in a sample of West Africans as well as other POAG families with autosomal dominant POAG have mapped to this region on chromosome 5 but have failed to identify genetic variants in WDR36 as the causative agent (Kramer et al., 2006; Pang et al., 2006; Rotimi et al., 2006). Most investigators find little or no evidence for an association between WDR36 variants in POAG compared with controls (Fingert et al., 2007; Hewitt et al., 2006c; Miyazawa et al., 2007; Pasutto et al., 2008). In one report, POAG patients with WDR sequence variations were associated with a more severe disease phenotype than those without, suggesting that sequence variants in WDR36 may play a role in disease susceptibility rather than causation (Hauser et al., 2006a). WDR36 functions in ribosomal RNA processing and interacts with p53 stress response pathway, suggesting the possible involvement of p53 in glaucoma (Skarie and Link, 2008).

8. Gene variants associated with POAG

In addition to the genes described above, over 20 gene variants have been associated with POAG as summarized in Table 2. These include apolipoprotein E (APOE), optic atrophy 1 (OPA1), tumor protein p53 (TP53), tumor necrosis factor (TNF), IL-1, and cytochrome P450 1B1. CYP1B1 has been reported to be associated with early-onset POAG in Spanish, French, and Indian populations (Vasiliou and Gonzalez, 2008). Variants of OPA1 have been associated with normal tension glaucoma in Japanese and Caucasian populations. OPA1 variants are not associated with glaucoma in Caucasian, African-American, and West African POAG cases with elevated IOP (Liu et al., 2007). Most gene associations with POAG have not been corroborated by other investigators or in other populations.

9. POAG genetics and clinical medicine

Clearly, an explosion in the understanding of the underlying genetic architecture of complex inherited disorders is underway (Feero et al., 2008). This is being driven by powerful new methods for genetic discovery, logarithmic growth in genotyping technology, and the assemblage of increasing large, robust clinical datasets. This knowledge will ultimately lead to a vastly improved understanding of the molecular mechanisms of complex diseases like glaucoma (Wiggs, 2007). As the underlying genetics of POAG improve so will the contribution of environmental factors, which to date, are poorly understood (Duggal et al., 2005; Fan et al., 2004).

Ultimately, genetic screening will greatly improve our ability to predict the risk of developing disease as well as disease severity. As important, expanding comprehension of the molecular pathways that produce disease will guide the development of more effective treatment options for individuals as well as their families. For diseases like POAG, where end organ damage is untreatable, the ability to accurately predict disease prior to symptomatic vision loss is critical.

Currently, identification and diagnosis of new glaucoma cases is achieved either by routine screening or examinations prompted by perceived risk. Traditional vision screening for disorders like POAG consumes limited and costly resources. Furthermore, the resulting examination provides at best a “snap shot” in the lives of those screened where a negative

result only applies to a single time point. So screening becomes a never ending process and is practiced on very large at risk populations, most of whom will never develop the disease of concern. For this reason, it is not surprising that there is considerable debate regarding the utility of glaucoma screening (Einarson et al., 2006; Mills, 2008; Quigley et al., 2002).

Interestingly, genetic screening, a technology that is becoming more widespread and increasingly affordable, may be increasingly utilized by developed nations as well as areas of the world that are medically underserved. Once risk assessment reaches a sufficient threshold of accuracy, genetic screening would provide *focused* delivery of medical resources on much smaller at risk populations. Furthermore, this method of screening would apply to multiple disorders, whether common or rare, simultaneously. Although very early, this approach to health care delivery is now moving into the marketplace and will likely have a powerful effect on us all (<http://www.23andme.com>) (Hunter et al., 2008).

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Table 1

Currently reported POAG chromosomal loci

Chromosomal location	POAG phenotype	Locus name	Candidate gene	References
1q23-q24	JOAG, Adult-onset	GLC1A	MYOC	(Sheffield et al., 1993; Stone et al., 1997)
2cen-q13	Adult-onset	GLC1B		(Stoilova et al., 1996)
2p12	Elevated IOP			(Duggal et al., 2007)
2p16.3-p15	JOAG, Adult-onset	GLC1H		(Lin et al., 2008; Suriyapperuma et al., 2007)
3p22-p21	Adult-onset	GLC1L		(Baird et al., 2005a)
3q21-q24	Adult-onset	GLC1C		(Wirtz et al., 1997)
5q22.1	Adult-onset	GLC1G	WDR36	(Monemi et al., 2005)
5q22.1-q32	JOAG	GLC1M		(Pang et al., 2006)
7q35-q36	Adult-onset	GLC1F		(Wirtz et al., 1999)
8q23	Adult-onset	GLC1D		(Trihan et al., 1998)
9q22	JOAG	GLC1J		(Wiggs et al., 2004)
10p13	Adult-onset, NTG	GLC1E	OPTN	(Rezaie et al., 2002; Sarfarazi et al., 1998)
15q11-q13	Adult-onset	GLC1I		(Allingham et al., 2005)
15q22-q24	JOAG	GLC1N		(Wang et al., 2006b)
19p13.2	Elevated IOP			(Duggal et al., 2007)
20p12	JOAG	GLC1K		(Wiggs et al., 2004)

Table 2

Gene variants associated with POAG

Gene	symbol	Gene name	Genomic location	OMIM	KEGG pathway	POAG phenotype
	Population		References			
300034	Renin-angiotensin system	NTG	Japanese	(Hashizume et al., 2005)	Angiotensin II receptor, type 2	Xq22-q23
ANP	Atrial natriuretic polypeptide	1p36.2	108780	POAG	Caucasian	(Tunney et al., 1996)
APOE	Apolipoprotein	19q13.2	107741	NTG, POAG	Japanese, Chinese, Tasmania, French	(Copin et al., 2002; Lam et al., 2006; Mabuchi et al., 2005; Vickers et al., 2002)
CDH-1	Cadherin 1	16q22.1	192090	POAG	Chinese	(Lin et al., 2006)
CYP1B1	Cytochrome P450, 1B1	2p22-p21	601771	POAG	Indian, French, Spanish	(Bhattacharjee et al., 2008; Melki et al., 2004)
EDNRA	Endothelin receptor type A	4q31.2	131243	NTG	Korean, Japanese	(Ishikawa et al., 2005)
GSTM1	Glutathione S-transferase M1	1p13.3	138350	POAG	Arabs, Turkish, Estonian	(bu-Amero et al., 2008; Juronen et al., 2000; Unal et al., 2007)
HSPA1A	Heat shock 70 kDa protein 1A	6p21.3	140550	POAG, NTG	Japanese	(Tosaka et al., 2007)
IGF2	Insulin-like growth factor2	11p15.5	147470	POAG	Chinese	(Tsay et al., 2003)
IL1α	Interleukin-1 α	2q14	147760	POAG	Chinese	(Wang et al., 2006a)
IL1β	Interleukin-1 beta	2q14	147720	POAG	Chinese	(Lin et al., 2003b)
MTHFR	Methylene-tetrahydrofolate reductase	1p36.3	607093	NTG, POAG	Korean, Germany	(Junemann et al., 2005; Woo et al., in press)
NOS3	Nitric oxide synthase 3	7q36	163729	POAG with migraine history	Caucasian	(Logan et al., 2005; Tunny et al., 1998)
OCLM	Oculomedin	1q31.1	604301	POAG	Japanese	(Fujiwara et al., 2003)
OLFM2	Olfactomedin 2	19p13.2		POAG	Japanese	(Funayama et al., 2006)
OPA1	Optic atrophy 1	3q28-q29	605290	NTG	Japanese, Caucasian	(Liu et al., 2007)
P21	P21	6p21.2	116899	POAG	Chinese	(Tsai et al., 2004)
PON1	Paraoxonase 1	7q21.3	168820	NTG	Japanese	(Inagaki et al., 2006)
TAP1	ABC transporter, MHC, 1	6p21.3	170260	POAG	Chinese	(Lin et al., 2004)
TLR4	Toll-like receptor 4	9q32-q33	603030	NTG	Japanese	(Shibuya et al., 2008)
TNFA	Tumor necrosis factor alpha	6p21.3	191160	POAG	Japanese, Chinese	(Lin et al., 2003a)

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Gene	symbol	Gene name	Genomic location	OMIM	KEGG pathway	POAG phenotype
TP53	Tumor protein 53	17p13.1 191170	MAPK and p53 pathway, apoptosis	POAG	Chinese, Caucasian	(Lin et al., 2002)

KEGG, *Kyoto Encyclopedia of Genes and Genomes*; OMIM, *Online Mendelian Inheritance in Man*.