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The Australian Twin Registry as a Resource For Genetic Studies into Ophthalmic Traits

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The Australian Twin Registry (ATR) is a not-for-profit organization that coordinates research involving Australian twins and researchers. The ATR is one of the largest volunteer registries of its kind and contains over 33,000 twin pairs. The purpose of this review is to provide a broad overview of recent ophthalmic studies that have utilized the ATR for recruitment purposes. Such studies include the Australian Twin Eye Study (ATES) and the Genes in Myopia (GEM) study. The ATES and GEM studies have undertaken studies into the genetic influences on a number of ophthalmic traits through the use of heritability studies, linkage studies, genome-wide association studies, and candidate gene-based studies. An overview of these studies is provided in this review, as well as a description of the recruitment methodologies for both the ATES and GEM studies.

Keywords: twins, Australia, ATES, GEM, ophthalmology

Twins provide a valuable resource for the study of human diseases. This review will focus on ophthalmic studies that have utilized Australian twin cohorts to understand the genetics of eye conditions. In particular, we will discuss those recruited with assistance from the Australian Twin Registry (ATR). We focus on cohorts from the Australian Twin Eye Study (ATES) and the Genes in Myopia (GEM) Study. Altogether, over 1,500 twin pairs have volunteered for these eye disease studies from different geographical locations around Australia.

The ATR

The largest collection of twins in Australia resides with the ATR. The ATR is a not-for-profit organization that facilitates research involving twins as well as their relatives, to improve the health and well being of all Australians (http://www.twins.org.au/; Hopper, 2002). The ATR was established in 1981 and is funded by an Enabling grant from the Australian Federal Government through the National Health and Medical Research Council in Australia. Any twin pairs, regardless of age, zygosity, gender, or health status, who have an interest in participating in health research projects, are invited into the registry. Currently there are over 33,000 twin pairs who are members of the ATR, making it one of the largest volunteer registries of its kind in the world. The ATR has facilitated research between twins and researchers in a wide range of projects, including those in diabetes, epilepsy, cardiovascular disease, and alcohol use. The ATR has also been a valuable resource for recruitment of twins into ophthalmic studies, with two major studies — the ATES and GEM studies — undertaken to date. The purpose of this review is to provide an overview and highlight the utility of this twin registry to further our understanding in ophthalmic studies.

Aims and Recruitment

ATES

The ATES (also known as the Twins Eye Study in Tasmania [TEST]) commenced in 2000 with the main goal of identification of the hereditary influences on glaucoma, including its underlying endophenotypes such as intra ocular pressure, cup-to-disc ratio, and its confounding measures such as central corneal thickness, optic disc size, and refraction. The ATES utilized a five-stage strategy to recruit twin pairs (Mackey et al., 2009). The first stage of recruitment involved directly approaching twins who had already agreed

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TABLE 1

Characteristics of Twin Pairs Recruited Into the Australian Twin Eye Study (ATES) and the Genes in Myopia (GEM) Study

	ATES	GEM
Total (*N*)	950	612
MZ (*N*)	386	345
DZ (*N*)	565	267
Age (years)	>5	>18
Male (%)	43.6	34.2
Female (%)	56.4	65.8

to participate in the Tasmanian Asthma Study (TAS) and the Tasmanian Infant Health Survey (THIS); the former was originally established to study the etiology of sudden infant death syndrome (Dwyer & Ponsonby, 1992; Wharton et al., 2006). In total, 346 individuals from the THIS and 23 from the TAS agreed to be part of the ATES.

The second wave of recruitment into the ATES was conducted through the ATR, beginning in 2001 through an application entitled the 'Twin study of ophthalmic screening parameters'. All twins in the ATR over the age of 5 were invited to participate, to incorporate both a pediatric group into the ATES as well as older twins, such that age effects could be determined. In total, 686 twin pairs were approached, with 228 agreeing to participate, giving a participation rate of 33%. The third wave of recruitment involved word of mouth and media publicity. The fourth wave of recruitment was via a mail-out to high schools in Tasmania. The final stage of recruitment, which occurred concurrently with stages 1–4, was identification of twins from the Brisbane Adolescent Twins Study (BATS) that was initially established as part of a skin cancer study (McGregor et al., 1999). In total, 463 twin pairs from the BATS were recruited into the ATES. Characteristics of the entire ATES cohort are described in Table 1.

GEM Study

Two other eye studies have also used the resources of the ATR in the study of ophthalmic conditions. These are the 'Genetic and Epidemiological Risk factors in Age-Related Macular Degeneration (AMD) Twin Study' and the 'GEM Study'. Recruitment arms of both of these studies were based at the Centre for Eye Research Australia at the Royal Victorian Eye and Ear Hospital in Melbourne.

The AMD Twin study commenced in 2003 with the aim to recruit twin pairs over the age of 50 for the study of AMD. The GEM Study commenced in 2004 with the aim to recruit twins over the age of 18 for the study of myopia and refractive errors. The ATR was the key resource for recruitment for both studies. Twin pairs from the AMD Twin Study were also eligible to be incorporated into the GEM Study. A total of 627 twin pairs were recruited into the GEM Study. A detailed description of recruitment protocols has been described elsewhere (Dirani et al., 2008a). Characteristics of the entire GEM cohort are described in Table 1.

TABLE 2

Heritability Study Results From the Australian Twin Eye Study (ATES) and the Genes in Myopia (GEM) Study for Various Ophthalmic Traits

Trait	Cohort	Heritability	Best fit model
Central corneal thickness	ATES	0.95	AE
Axial length	ATES	0.81	A
	GEM	0.94 (M), 0.92 (F)[a]	A
Anterior chamber depth	GEM	0.51 (M), 0.78 (F)[a]	ADE
Spherical equivalent	GEM	0.88 (M), 0.75 (F)[a]	ADE
Corneal astigmatism	GEM	0.50 (M), 0.60 (F)[a]	ADE
Retinal venular caliber	ATES	0.62	AE
Retinal arteriolar caliber	ATES	0.59	AE
Strabismus (eso-deviation)	ATES	0	CE
Strabismus (exo-deviation)	ATES	0.64	AE

Note: A = additive genetic effects; D = dominant genetic effects; E = unique environment effects.
[a]Heritability in males (M) and females (F) was calculated separately in this study.

Heritability Studies (Classical Twin Study)

Twins provide an excellent resource for the quantitative assessment of the contribution of genetic and environmental influences on any phenotype. Such studies, referred to as heritability studies, are based on the assumption that monozygotic (MZ) twins share 100% of their genes and environment whereas dizygotic (DZ) twins share environment but only 50% of their genetic variation on average. Thus, if one assessed phenotype concordance rates between twins, one would expect that MZ twins have a greater phenotypic concordance compared to DZ twins if a trait is attributable to genetic factors. The ATES has undertaken heritability studies using the ophthalmic phenotypes of central corneal thickness, axial length, strabismus, and retinal vascular caliber (Sun et al., 2009; Toh et al., 2005; Zhu et al., 2008). The GEM Study looked at refractive error, axial length, corneal astigmatism (CA), and anterior chamber depth (Dirani et al., 2006a, 2008b). Heritability study results for the ATES and GEM study are briefly summarized in Table 2 and discussed in more detail below.

Central Corneal Thickness and Glaucoma

Primary open-angle glaucoma is a progressive optic neuropathy associated with increasing loss of visual field where elevated intraocular pressure (IOP) can also present as a major risk factor. IOP in glaucoma is typically measured through the use of tonometry. Ocular tonometry measurements assume that corneal thickness is a constant, but in reality there is a wide range of corneal thickness in the general population. Hence, thin corneas can have an artificially low IOP reading, resulting in true IOP measures being underestimated. Conversely, thicker corneas can give high IOP and overestimations of true IOP measures. Given this, corneal thickness (CCT) is regarded as a confounder in glaucoma diagnosis. The ATES aimed to understand the driving factors for CCT by undertaking a heritability study to quantitate the contribution of hereditary and

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environmental factors on this trait (Toh et al., 2005). Using the classical twin model, the ATES collaboratively undertook a heritability study with the TwinsUK Adult Twin Registry. This study consisted of 262 MZ twins and 250 DZ twins with very high correlations for CCT in MZ twin pairs ($r^2 = 0.9$) as compared to DZ twin pairs ($r^2 = 0.27$). Heritability analysis suggested that CCT is 95% heritable with additive rather than dominant genetic effects at play. Environmental factors (non-genetic) appear to account for approximately 5% of the trait (Toh et al., 2005).

Ocular Axial Length and Anterior Chamber Depth

Refractive errors are a group of sight impairing disorders that include myopia (short sightedness) and hyperopia (long sightedness) and astigmatism. Refractive errors are influenced by many factors including curvature of the cornea, thickness of the lens, and position of the retina, but the most important factor associated with variable refraction appears to be the length of the eye (ocular axial length). The ATES and GEM studies have both made use of the classical twin model to better understand the genetic contribution to ocular axial length. In the ATES, it was shown that additive genetic factors influence ocular axial length, with heritability estimates of 81% (Zhu et al., 2008). In the GEM Study it was also shown that additive genetic factors also influence ocular axial length with heritability estimates reported as 94% for male MZ twins and 92% for female MZ twins (Dirani et al., 2006b). The GEM study also determined heritability estimated for anterior chamber depth, which is a subset of ocular axial length. It was shown that additive and dominant genetic factors were at play, with heritability estimates being 51% for males and 78% for females.

Spherical Equivalent (SE) and CA

The GEM Study undertook additional detailed heritability studies into the traits of SE, which is a quantitative measure of refractive errors in general, and CA (Dirani et al., 2006b, 2008b). The GEM study showed that additive and dominant genetic factors were at play for SE, and CA. For SE, heritability estimates were 88% for males and 75% for females suggesting this is a highly heritable trait. Conversely, heritability estimates for CA were 50% for males and 60% for females suggesting a less heritable trait.

Retinal Vessel Caliber and Cardiovascular Disease

Assessment of retinal vascular caliber (retinal arteriolar caliber and retinal venular caliber) can give insights into the early structural changes in the microcirculation and the relationship of these measures with cardiovascular disease, diabetes, and hypertension. In the ATES, heritability estimates were calculated for retinal arteriolar caliber and retinal venular caliber for the TEST and BATS cohorts separately (Sun et al., 2009). For retinal arteriolar caliber, additive genetic effects accounted for 59.4% of the variance seen in TEST and 56.5% in BATS. For retinal venular caliber, additive genetic effects also accounted for 61.7% of the variance in the TEST samples and 64.2% in the BATS samples. Hence, the ATES was able to show that retinal vascular caliber, in general, is a heritable trait (Sun et al., 2009).

Strabismus

Strabismus (also known as heterotropia or squint) is a complex ocular disorder characterized by the misalignment of one or both eyes. Strabismus can be classified as eso-deviation (inward turning eye/s) or exo-deviation (outward turning eye/s). The ATES, in collaboration with the TwinsUK Adult Twin Registry, has recently reported a genetic study attempting to quantify the genetic and environmental contributions of strabismus using a classical twin study (Sanfilippo et al., 2012). This report is the first of its kind and was able to show that additive genetic effects account for 64% of the variance seen for eso-deviation with unique environment accounting for the remaining for 36%. In contrast, exo-deviation was not shown to be influenced by genetic factors, but instead common environment accounts for 54% of the variance and unique environment 46%.

Genetic Studies

The classic twin studies described above provide the necessary foundations to implicate a genetic basis in a number of ophthalmic traits. Thus, the Australian twin cohort studies from the ATES and GEM studies have been utilized in a number of genetic studies to investigate the nature of the hereditary influences on ophthalmic traits, including intraocular pressure, iris color, optic disc size, and refractive error. These studies have come in the form of genetic linkage studies, candidate gene-based studies, and genome-wide association studies. A brief summary is provided in Table 3, with a more comprehensive discussion below.

Linkage Studies

Following on from the heritability studies, genome-wide linkage studies have been performed in the ATES cohort for the traits of ocular axial length and retinal vascular caliber. Linkage analysis was performed on 142 twin pairs from the BATS arm of the ATES for ocular axial length defined as a quantitative trait (Zhu et al., 2008). The maximum multipoint logarithm (base 10) of odds (LOD) score reported was 3.4 on chromosome 5q, which represents a novel locus for ocular axial length. The exact nature of the gene underlying this linkage result is yet to be determined. A second linkage study was performed, again using the BATS samples, for retinal vascular caliber (Sun et al., 2009). No statistically significant genome-wide LOD scores were reported for retinal venular caliber or arteriolar vascular caliber in the BATS cohort. Maximal LOD scores were suggestive and reported on chromosome 8p23.1 for retinal arteriolar caliber (LOD = 2.24) and 2p14 for retinal venular caliber (LOD = 2.69).

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TABLE 3

Summary of Genetic Studies From the Australian Twin Eye Study (ATES) and the Genes in Myopia (GEM) Study Into Various Ophthalmic Traits

Trait	Cohort	Analysis type	Gene or locus
Primary open angle glaucoma	ATES	GWAS[a]	*TMCO1, CDKN2B*
	ATES	GWAS[b]	*GAS7, TMCO1*, rs423660
Central corneal thickness	ATES	GWAS[a]	*ZNF469, FAM53B, FOXO1*
Optic disc size	ATES	GWAS[a]	*ATOH7*
Iris pigmentation	ATES	GWAS[a]	*SEMA3A, TRAF3IP1, SLC24A4*
Eye color	ATES	GWAS[b]	rs7219915, rs9894429, rs12452184, rs1003719 rs2252893, rs2835621, rs2835630, rs7277820
Myopia	ATES	GWAS[b]	Chromosome 15q25
	GEM	Candidate gene screen	*HGF*
Hypermetropia	GEM	Candidate gene screen	*HGF*
Ocular axial length	ATES	Genome-wide linkage	Chromosome 5q
Retinal arteriolar caliber		Genome-wide linkage	Chromosome 2p14
Retinal venular caliber	ATES	Genome-wide linkage	Chromosome 8p23
	ATES	GWAS[b]	*RASIP1*, rs10774625, rs17421627

Note: [a]Genome-wide association study (discovery cohort).
[b]Genome-wide association study (replication cohort).

Genome-Wide Association Studies

Australian twins have been utilized in a number of genome-wide association studies, either as discovery or replication cohorts, that have identified single nucleotide polymorphisms or genes associated with a number of ophthalmic traits. The Australian twins from the TEST and BATS studies have been utilized as discovery cohorts in genome-wide association studies to identify statistically significant single nucleotide polymorphisms (SNPs) in genes associated with four traits, including optic disc size (*ATOH7*), central corneal thickness (*ZNF469*, *FAM53B*,*FOXO1*), primary open angle glaucoma (*TMCO1*, *CDKN2B*), and iris patterns (*SEMA3A*, *TRAF3IP1*, *SLC24A4*; Burdon et al., 2011; Larsson et al., 2011; Lu et al., 2010; Macgregor et al., 2010). Findings from all these studies have been replicated in independent cohorts.

Additionally, the Australian twins have been utilized as replication cohorts in genome-wide association studies to identify genes and single nucleotide polymorphisms associated with primary open angle glaucoma (GAS7, TMCO1, rs423660), eye color (rs7219915, rs9894429, rs12452184, rs1003719, rs2252893, rs2835621, rs2835630, rs7277820), and retinal venular caliber (*RASIP1*, rs10774625, rs17421627; Ikram et al., 2010; Liu et al., 2010; Thorleifsson et al., 2010; van Koolwijk et al., 2012).

The Australian twins from both the ATES and GEM study are also part of the newly formed Consortium of Refractive Error and Myopia (CREAM) that brings together 31 cohorts representing four continents and 55,177 individuals, with the aim to identify genes and gene variants associated with myopia and its related sub-phenotypes. This consortium has so far undertaken a meta-analysis to confirm an association of myopia with a locus on chromosome 15q14 (Verhoeven et al., 2012). The Australian twins have also been utilized as a replication cohort to identify a second myopia locus at chromosome 15q25 but this result was not able to be replicated when using the extended cohort from CREAM (Hysi et al., 2010; Verhoeven et al., 2012).

Candidate Gene Studies

Australian twins from the GEM study have also been incorporated into studies investigating candidate genes for myopia and refractive errors. Twins from the GEM study were used as part of a larger cohort that assessed genetic associations between the genes transforming growth beta-induced factor (*TGIF*), retinoic acid receptor alpha (*RARA*), hepatocyte growth factor receptor (*cMET*), and hepatocyte growth factor (*HGF*) and the traits of myopia, ocular refraction, ocular axial length, corneal curvature, and anterior chamber depth (Pertile et al., 2008; Schache et al., 2009; Veerappan et al., 2009a, 2009b). These studies showed that the *TGIF*, *RARA*, and *cMET* genes are not likely to be associated with these ophthalmic traits. These studies also reported novel findings, suggesting that two SNPs within *HGF* (rs12536657, rs5745718) are associated with hypermetropia, and an additional five SNPs (rs1743, rs4732402, rs12536657, rs10272030, rs9642131) are associated with low/moderate myopia. Other studies have also reported positive associations with SNPs in HGF and mild/moderate myopia (rs3735520; Yanovitch et al., 2009). Additional SNPs in HGF have also been reported as positively associated with high myopia (rs2286194, rs3735520) in case–control cohorts of Caucasian and Chinese ethnicity, but the results in the Chinese cohort was not replicated in a second independent study (Han et al., 2006; Wang et al., 2009; Yanovitch et al., 2009).

From these linkage, genome-wide association and candidate gene-based studies it is clear that Australian twins are a valuable resource for the discovery of novel genes and gene variants associated with ophthalmic traits.

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Conclusion

This review has provided a broad overview of recent ophthalmic studies that have utilized the ATR for recruitment purposes. Although there is still a large amount of work left in identification of genes and genetic influences on ophthalmic traits, the currently identified genes and gene loci lead the way to the next wave of work. This may involve further dissection of the hereditary influences using epigenetic studies or through the analysis of copy number variations. Ultimately, functional studies will be required in order to clarify the exact role that these genes and gene variants play in the eye. Clearly, twins have played an important role in increasing our understanding of the eye with the ATR being an invaluable resource for studies into the genetic and environmental influences on ophthalmic phenotypes.

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