Refractive Errors in Twin Studies

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It is estimated that 1.6 billion people worldwide have myopia, a refractive error, and this number is expected to increase to approximately 2.5 billion by the year 2020. It is now well established that both the environment and genetics play a role in the development of myopia. However, the exact contribution of each of these components to myopia development has yet to be completely determined. Twin studies (classical twin model) are commonly used to determine the weighting of genetic and environmental components in disease. Over the last century, twin studies have investigated the heritability of refractive errors in different sample populations and have collectively supported a genetic basis to refractive errors. However, different sample populations and methods of data collection have produced a wide range of heritability estimates ranging from .5 to .9. This article will review those twin studies that have investigated refractive error, particularly myopia, as well as biometric measures linked to refractive error, to compare heritability estimates and methodology designs.

Myopia and Other Refractive Errors

Myopia or 'short-sightedness' is a refractive error, whereby intersecting light rays focus in front of, rather than on the retina, thus producing a blurred image at distance fixation. The main ocular components that are seen to contribute to the development of myopia include corneal curvature, lens power, anterior chamber depth and in particular, ocular axial length (Curtin, 1988). The degree of myopia can be classified as low (–0.5 diopters sphere [DS] to –2.99), moderate (–3.00 DS to –5.99 DS) and high (worse than or equal to –6.00 DS; Curtin, 1985). Other refractive errors (ametropia) that also cause optical defocus include hypermetropia (intersecting light rays that focus beyond the retina), astigmatism (asymmetrically curved cornea) and presbyopia (age-related changes in the physiology of the natural lens). This article primarily aims to review the heritability of myopia, as most twin literature is based on this refractive error. However, it will also address the heritability of any ametropia (change in refraction) through the use of twin studies.

Prevalence of Myopia

Myopia affects approximately one in five Australians and almost 1.6 billion people worldwide (Kempen et al., 2004). The prevalence of myopia is comparable across Western countries (20%–25%; Wensor et al., 1999). However, it is much higher in urbanized areas of South East Asia where prevalence escalates to levels higher than 80% (Wu et al., 2001). It is estimated that 2.5 billion people (one third of the world's population) will suffer from myopia by the year 2020 (Kempen et al., 2004). The increase in prevalence of myopia has been termed a 'myopia epidemic' and this reflects findings from a collection of Singaporean studies that have shown a rapid increase in myopia prevalence from 26% in the late 1970s to 83% in the late 1990s (Wu et al., 2001). The rapidly increasing prevalence of myopia in selected areas of the world has become a significant public health problem. Consequently, the Vision 2020 initiative for the global elimination of avoidable blindness has included refractive errors as one of its five priority eye diseases.

Genetic and Environmental Risk Factors in Myopia

It is now well established that environmental risk factors, such as higher education, urbanization, higher socioeconomic status and extensive near work contribute to the development of myopia (Richler & Bear, 1980; Saw et al., 2002; Wong et al., 2000). However, all of these factors explain only a small proportion of the total variation in myopia (Saw et al., 2004). On the other hand, there is growing evidence to support a genetic basis to myopia. First, family correlation studies have collectively shown that children with myopic parents are four times more likely to develop myopia compared to children with nonmyopic parents (Garner et al., 1988; Wallman, 1994a, 1994b). Second, family linkage studies assessing higher levels of myopia (worse than or equal to –6.00 DS) have so far identified several loci on chromosome

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Xq28 (MYP1; Schwartz et al., 1990), 18p11.31 (MYP2; Young, Ronan, & Alvear, 1998; Young, Ronan, Drahozal, et al., 1998), 12q23-24 (MYP3; Young, Ronan, & Alvear, 1998; Young, Ronan, Drahozal, et al., 1998), 7q36 (MYP4; Naiglin et al., 2002), 17q21-22 (MYP5; Paluru et al., 2003; Stambolian et al., 2004) and chromosome 2q (Paluru et al., 2005). More recently, a family linkage study investigating low myopia (≤ –1.00 DS) has reported a myopia locus (MYP6) on chromosome 22q12 (Stambolian et al., 2004) Moreover, Hammond and co-workers (2004) performed the first genome-wide linkage analysis on 221 dizygotic (DZ) twins and identified a myopia locus (PAX6) on the short arm of chromosome 11p13 of significant linkage and also another three loci of significant linkage on chromosomes 3q26, 4q12 and 8q23 (Hammond et al., 2004). Third, twin studies have consistently reported higher within-pair correlations for myopia in monozygotic (MZ) twins (> 0.8) compared to DZ (< 0.4), further supporting a genetic basis to myopia (Hammond et al., 2001; Lyhne et al., 2001; Sorsby & Fraser, 1964). Additional evidence in support of a genetic basis to myopia also comes from the differences in myopia prevalence between different racial groups (Lin et al., 1988; Wensor et al., 1999; Zhao et al., 2002) as well as from the study of systemic disorders, such as Marfan's, Wagner-Stickler syndrome and Ehler-Danlos syndrome (Naiglin et al., 1999) which are associated with myopia. In summary, support for a genetic origin to the development of myopia has come from several sources, such as family linkage studies, familial aggregation studies, twin studies and epidemiological studies. This article will review twin studies that have investigated myopia and other refractive errors.

The Classical Twin Model

Twins are described as either MZ in that they are genetically identical as they come from one fertilized egg (zygote), or DZ in that they arise from two separately fertilized eggs and thus share approximately half their genetic material (Hall, 2003). Genetic studies of twins offer the advantage of being able to model both the genetic and environmental components of disease. The most commonly used design in twin eye studies is the classical twin study model. Other twin research designs, such as the co-twin control design, longitudinal twin studies and the twin adoption design are also credible methods used to measure the heritability of disease; however, different methodological approaches are applied for each twin study design. For instance, the twin adoption design investigates phenotypes in twins reared apart and thus has better control for identifying genetic risk factors by minimizing the effect of shared environments that are seen in twin pairs that are reared together. However, twin pairs reared apart are not common and for this reason, twin adoption studies consist of a very small sample size and are not frequently conducted by researchers. A study by Knobloch and co-workers (1985) reported eye findings from 26 twin pairs (MZ twin pairs = 18, same-sex DZ twin pairs = 8) reared apart and found a greater similarity for refraction in MZ twin pairs compared to DZ twin pairs and thus supported a genetic influence to the development of refractive error. The assessment of extremely discordant MZ twin pairs is also an effective method of investigating unique environmental exposures that influence the development of disease.

The premise of the classical twin model is to compare intrapair correlations in MZ and DZ twin pairs. The MZ/DZ correlations can then be used to calculate crude heritability estimates for a continuous trait (Rende et al., 1990). A significantly higher disease correlation in MZ twins compared to DZ twins is a strong predictor of a genetic basis for the trait. This twin model relies on the 'shared environment assumption' in that it assumes the effects of environmental factors shared by twins are not influenced by zygosity.

Twin Analysis in the Study of Refractive Error

Most twin studies quantify the genetic component of trait variance through intrapair and interpair correlations of quantitative traits and concordance levels of binary traits. Also, they use model-fitting techniques, such as the 'threshold model' that has allowed for the calculations of heritability estimates of binary traits. However, more recently, the scope of twin analysis has advanced and different methods of analysis have been introduced. For example, assessing the association between birthweight and disease risk (fetal origin hypothesis) separately in DZ and MZ twins can provide information on the role of genetics. No significant differences in within-pair associations in both MZ and DZ twin pairs would indicate a nongenetic role in the association, and a significant difference in within-pair association would indicate a genetic role (Morley & Dwyer, 2005). Also, genetic linkage studies using DZ twins (sib-pair design) have given twin studies the scope to identify candidate genes. Association studies on the other hand allow assessment of an interaction of a candidate gene with environmental components in the study of common complex diseases, such as myopia. Furthermore, twin recruitment has advanced from observational clinical studies and retrospective studies of patient records to the use of population register (birth records), nationwide twin registers and media advertisements. The latter methods are more favorable due to more efficient twin identification and recruitment and also larger twin registers are more representative of the general population.

Myopia and Other Refractive Errors in Earlier Twin Studies

Methodological design issues have led to variation in the heritability estimate of refractive errors. These include small sample size, inadequate testing apparatus and possible misclassifications of twin zygosity.

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Nonetheless, earlier research, mainly in the form of single case studies and clinical observations, identified great similarities in refractive errors between MZ twin pairs (Blatt, 1924; Jablonski, 1922; Steiger, 1913), suggesting that genetics may play a role in the development of all refractive error. It has been recently suggested that the first classical twin study was conducted by Walter Jablonski who investigated refractive error in 52 twin pairs (Liew et al., 2005). Jablonski (1922) observed that the difference in refractive status of 28 MZ twin pairs was much smaller than that found in 24 DZ twin pairs. These findings were then reproduced by several other twin studies (Dahl, 1936; Glatzel, 1931; Law, 1935; Waardenburg, 1930). A summation of these early studies was reviewed by Karlsson (1974) who found that approximately 95% of MZ twin pairs were concordant (both twin members had a refractive error) for their refractive errors compared to only 29% of DZ twin pairs. Overall, most studies supported a genetic basis to refractive errors and formed the basis for larger twin studies to commence.

A much larger study by Sorsby and co-workers (1962) examined intrapair variances of 78 MZ twin pairs and 40 DZ twin pairs and demonstrated a significantly higher concordance rate for myopia in MZ twins (> .9) compared to DZ twins (< .25), thus supporting the earlier findings of a genetic involvement in refractive errors. Moreover, a number of ocular biometric measurements such as axial length and lens thickness were also measured and again a high correlation of 83.3% and 85.9% was noted, respectively for each of these components (Sorsby & Fraser, 1964). The heritability of the twin data from Sorsby and co-workers' (1962) twin study was recalculated by Goss and co-workers (1988), and a heritability of .87 was found and thus reiterated the strong genetic component to myopia. For several decades, the twin study by Sorsby and co-workers (1962) was regarded as the main reference to support a genetic origin to refractive errors, due to it having a large sample size, inclusion of ocular biometrics measurement and the series of statistical modeling of twin pair variances. However, other studies continued to provide evidence to support a genetic basis to refractive error (Awetissow, 1980; Nance et al., 1982).

Larger and more recent studies have also been undertaken whereby Lyhne and co-workers (2001) examined 114 twin pairs (53 MZ twin pairs, 61 DZ twin pairs) and observed a high heritability for both refractive error and ocular biometric parameters of .94. This added further support for an underlying genetic basis, not only for refractive error but also for ocular dimensions. It also suggested that dominant genetic effects were the most plausible explanation for the high heritability of refractive errors and its determinants. However, in this study, twins with high myopia (worse than –6.00 DS) were excluded from the study and so there was no information regarding the heritability of high myopia.

The largest twin study so far undertaken on refractive error has been by Hammond and co-workers (2001). They investigated 506 female twin pairs aged between 50 and 79 years and found that the correlation for refraction was almost double that in MZ twin pairs (> .8) compared to DZ twin pairs (< .5; Hammond et al., 2001). The large sample size (n = 506) used in this study provided good statistical power to measure refractive components of disease. Also, the use of multivariate modeling rather than the analysis of bivariate data (yes/no) used in this twin study allowed for more variables to be measured and ultimately increased its statistical credibility. This elegant twin study has now justifiably become the main source of reference for the genetics of refractive errors in twins. However, there have been limitations with all the twin studies so far undertaken including; gender selection, postal questionnaires, small sample size, restricted age range and the absence of ocular biometric measures. For example, it has previously been shown that heritability for refraction is lower in females compared to males (Lyhne et al., 2001; Teikari et al., 1991) thus heritability estimates of refraction in both genders would be useful. In addition, age needs to be accounted for as individuals over the age of 50 years may undergo hyperopic shifts typically seen in presbyopia or myopic shifts associated with nuclear cataract development (Panchapakesan et al., 2003). Finally, obtaining biometric measurements such as axial length are important, as these measurements represent a quantitative trait in determining refractive error status (refer to Table 1 for a list of twin studies that have reported heritability estimates for myopia).

Concordance of High Myopia

Twin studies have generally reported a high heritability of low/moderate myopia ranging from .5 to .9. There have been fewer reports on the heritability of high myopia in twin studies as its prevalence is less in Western populations (2%–3%) compared to the prevalence of low/moderate myopia at 20% (Kempen et al., 2004). When heritability estimates in high myopia (worse than or equal to –6.00 DS) have been

Table 1

Heritability Values for Myopia From Twin Studies

Study	No. of twin pairs	Age	Heritability (h^2)
Sorsby et al. (1962)	MZ = 78, DZ = 40	4–14	.87
Nakajima (1968)	MZ = 39, DZ = 10	12–17	.83
Kimura (1965)	MZ = 33, DZ = 16	15–20	.80
Hu (1981)	MZ = 49, DZ = 37	7–19	.61
Lin and Chen (1987)	MZ = 90, DZ = 36	7–23	.25
Teikari et al. (1991)	MZ = 54, DZ = 55	30–31	.58
Angi et al. (1993)	MZ = 19, DZ = 20	3–7	.11
Lyhne et al. (2001)	MZ = 53, DZ = 61	20–45	.89–.94
Hammond et al. (2001)	MZ = 226, DZ = 280	49–79	.84–.86

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undertaken, several have shown greater heritability compared to low/moderate myopia (better than or equal to –5.99 DS; De Jong et al., 1993; Guggenheim et al., 2000; Hoffman & Carey, 1942; Weber, 1941) while other twin studies have reported a reduction in heritability for high myopia (Karlsson, 1974; Lin & Chen, 1987; Meyer-Schwickerath, 1949). For example, Otsuka (1956) assessed refraction in 182 MZ twins and reported that MZ twin pairs with high myopia had levels of discordance of up to 5.50 DS in their refractive status compared to a 1.75 DS difference in MZ twin pairs with low/moderate myopia (Otsuka, 1956). This reduced level of concordance for refraction in high myopia was due to comorbidities, such as anisometropia (Bucklers, 1953; Burns, 1949) or the absence of myopia in one twin member (Gedda et al., 1981; Hoffman & Carey, 1942; Orth, 1954).

The discordance seen in the high myopes may also be as a result of different intrauterine environments, comorbidities, or the possible misclassification of twin zygosity.

Hypermetropia and Twin Studies

There has been less twin research investigating the genetic component to hypermetropia. More emphasis has been placed on myopia due to several factors, such as the difference in myopia prevalence seen between different ethnicities (genetics/environment), the retinal pathology associated with severe forms of myopia, the association of myopia with genetic disorders (Marfan's syndrome), the environmental risk factors associated with myopia (education level) and the strong correlation between myopia and ocular biometrics (axial length). Nonetheless, the existing twin studies assessing refractive error have a supported a genetic component to hypermetropia (Hammond et al., 2001; Nance et al., 1982; Teikari et al., 1990). These studies should be used as the basis to explore the genetic and environmental risk factors associated with the development of hypermetropia.

Astigmatism in Twin Studies

Astigmatism is a refractive error that is usually seen with either myopia or hypermetropia but is rarely seen on its own. Thus it is difficult to assess the heritability of astigmatism. Nonetheless, over the last century, twin studies have attempted to investigate the heritability of astigmatism (Hammond et al., 2001; Teikari et al., 1989; Valluri et al., 1999). Teikari et al. (1989) investigated the refraction of 72 female twin pairs aged between 30 and 31 years via postal surveys. They found that concordance for astigmatism in MZ twin pairs was not significantly different from that found in DZ twins, implying there was little genetic influence in astigmatism. The method of data collection used in this study relied solely on spectacle wearers who were willing to send their latest prescription. Potential participants with uncorrected astigmatic errors and those who failed to send their prescription were not represented in the study and therefore this may represent a highly selective sample. Other twin studies also found no significant difference in concordance for astigmatism in MZ twins compared to DZ twins (Teikari et al., 1988; Valluri et al., 1999). However, the use of questionnaires in data collection in these studies can lead to inaccurate information on the heritability of refractive error due to the increase rate of missing data, the possibility of the wrong twin replying and the inability to correctly identify their own refractive status. Finally, the most recent and largest twin study by Hammond and coworkers (2001) reported findings that are contrary to previous reports in that the correlation for astigmatism was almost four times larger in MZ twin pairs compared to DZ twin pairs, thus suggesting a major role for a dominant gene in this phenotype. The latter study also supported earlier twin studies that showed a significantly higher correlation for astigmatism between MZ twin pairs compared to DZ twin pairs (Nance et al., 1982; Sorsby et al., 1962).

Discordant Refraction in MZ Twins

The majority of twin studies support a genetic basis to refractive error, however, there are several reported cases of MZ twins that are discordant for refractive error. Earlier studies have reported differences in refraction ranging from 2.25 DS to 5.5 DS (Burns, 1949; Halbertsma, 1930; Waardenburg, 1930) and even up to 26 DS between twins in an MZ twin pair (Orth, 1954). The discordance observed in these MZ twins is mainly due to the presence of strabismus and myopic retinopathy occurring in only one of the twin pair. Therefore it is important that these conditions be accounted for when assessing heritability estimates of refraction. Other possible hypotheses that may explain extreme discordance for disease in MZ twin pairs include different intrauterine environments, skewed X-chromosome inactivation (Watkiss et al., 1994), incomplete genetic penetrance, variable expressivity due to environmental exposures and intrapair epigenetic variation. For example, a more recent hypothesis suggests that post-genomic events such as changes in the regulation of DNA methylation may be a contributing factor to explain the discordance seen in MZ twin pairs (Petronis et al., 2003).

Children/Adolescent Twin Studies in Myopia

Most twin studies that have investigated refractive error have examined adult twins, primarily to ensure complete refractive development and also to account for refractive errors acquired during adulthood. The ages of subjects assessed in most twin studies ranges from 30 to 31 years (Sorsby et al., 1962), 25 to 45 years (Lyhne et al., 2001) and 49 to 79 years (Hammond et al., 2001). There have only been two twin studies that have used younger twins to assess the heritability of refractive errors (Angi et al., 1993; Chen et al., 1985a, 1985b). The first twin study by Angi and co-workers

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(1993) examined 39 twin pairs aged between 3 and 7 years and found no significantly higher correlation for refraction in MZ twins (.73) compared to DZ twins (.69). The age group used in this twin study was extremely young and there is strong evidence to suggest that refractive errors, particularly myopia progress into early teenage years with most refractive errors developing after the age of 7 years (Curtin, 1985). Also, the time of onset of refractive errors may differ between twins. Although this study provided valuable information on the development of refractive errors in twins, incomplete refractive development in children makes it difficult to accurately calculate correlations for MZ and DZ twin pairs. The second twin study by Chen and coworkers (1985) examined a total of 357 same-sex Taiwanese twins aged between 10 and 15 years and found a higher concordance for myopia in MZ twins with similar reading habits (.92) compared to DZ twin pairs (.62) with similar reading habits. Although, this twin study used retinoscopy (objective test of refraction) as the sole measure of refractive error, it clearly demonstrated an increase in concordance of refraction in MZ twin pairs. In both studies, it would be of interest to reexamine their twins to ascertain whether those co-twins who were recorded as unaffected, went on to develop myopia at a later stage (longitudinal study) and how these findings may effect intrapair correlations.

Summary

Irrespective of the different methods of twin recruitment and twin analysis, most twin studies examining refractive error over the last century have reached the same consensus in that genetics plays a major role. However, a small sample size (Chen et al., 1985a, 1985b; Hu, 1981; Lin & Chen, 1987; Sorsby et al., 1962; Waardenburg, 1930), gender and/or age preference (Angi et al., 1993; Hammond et al., 2001; Teikari et al., 1991; Valluri et al., 1999), noncycloplegic refraction (Hammond et al., 2001; Teikari et al., 1989; Valluri et al., 1999) and the use of postal surveys (Teikari et al., 1989; Teikari et al., 1991) may have over or under estimated the heritability estimate in a number of these studies. Furthermore, future twin studies can benefit from previous twin studies in developing better and more powerful twin methodologies (see below) to better estimate the correlations for continuous traits in MZ and DZ twin pairs using multivariate twin modeling.

Future Directions

In light of the existing twin studies investigating refractive errors, more twin literature is required investigating other refractive errors (particularly hypermetropia and presbyopia). In addition, the measurement of biometric markers aside from refraction (axial length measurements), differing degrees of refraction, age and sex comparisons, longitudinal twin studies and the exploration of gene–environment interaction would also be useful. For example, examining refractive error in twins of different ages will provide the researcher with important information on the change of intrapair correlations with age (environmental component) and the change in the prevalence of refractive error over time, providing that the twin data is representative of a population. Also, the use of twins to aid in the identification of disease loci through the use of genome-wide linkage analysis as previously performed by Hammond and coworkers (2004) will also be most beneficial. Furthermore, quantifying the role of epigenetic effects and intrauterine environments in discordant twins is essential in better understanding twinning and gene expression (Evans & Martin, 2000). It is important to try and resolve the extent of the genetic/environment component in the range of refractive errors, as this will undoubtedly provide researchers with better direction to identify risk factors and hence offer improvements in treatment options.

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