Risk Factors and Genetics in Common Comitant Strabismus
A Systematic Review of the Literature

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IMPORTANCE Understanding the development of common strabismus is important in locating “at-risk” populations and implementing optimal treatment. This systematic review will bring together reported genetic and environmental risk factors for common strabismus to reveal relationships between risk factors and guide future research.

OBJECTIVE To identify known environmental and genetic risk factors for comitant strabismus reported in the literature.

DATA SOURCES A systematic literature search was performed in Medline, Embase, BioSciences Information Service Previews, Web of Science, and the OMIM database during a 2-week period in July 2011 (including all available years) using the following key words: gene, genetic environmental factor, inheritance, risk factor, esotropia, exotropia, strabismus, squint, convergent strabismus, and divergent strabismus.

STUDY SELECTION No language restrictions were placed on the search. Exclusion criteria consisted of associated syndromes, strabismus not the primary outcome, poor study design or quality, and logarithm of the odds score less than 3.

DATA EXTRACTION AND SYNTHESIS A study quality and extraction tool was used. Analysis was performed descriptively because of the variant characteristics of the study designs.

MAIN OUTCOMES AND MEASURES Risk factor, twin, pedigree, and genetic studies.

RESULTS Forty-one articles fulfilled the inclusion criteria set out by the study, which highlighted 4 subcategories: risk factor, twin, pedigree, and genetic studies. Significant risk factors for strabismus reported by the studies included low birth weight, cicatricial retinopathy of prematurity, prematurity, smoking throughout pregnancy, anisometropia, hyperopia, and inheritance. Inheritance was further supported by twin and pedigree studies, which revealed the complexity of the inheritance pattern. At present the STBMS1 locus is the only gene location that has been supported; however, others have been reported.

CONCLUSIONS AND RELEVANCE Certain subgroups within the population are at higher risk of developing comitant strabismus and should be identified and monitored to allow for earlier detection. It is evident that a strong hereditary link is present particularly in intermittent and accommodative forms; however, further research is required to identify possible links between subtypes of strabismus. Further genetic research could also help to locate additional causative genes to aid the understanding of strabismus development.

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Since Hippocrates first observed the apparent inheritance of strabismus from parent to offspring, there has been increasing interest in identifying genetic and environmental risk factors that influence the development of strabismus. However, the interpretation and application to clinical practice of these studies are difficult because of conflicting results and variation in methods and primary outcomes.

At present, the reason for the development of comitant strabismus (CS) is unclear, although various hypotheses causing its occurrence have been proposed. To date, the term CS represents a variety of forms of strabismus that occur in childhood. Because additional research is required to further divide the various subtypes of CS into unlinked groups, subtypes were considered as 1 group in this study.

To our knowledge, no systematic review of the literature relating to the risk factors and inheritance in CS exists. Because of the nature of the studies that are performed in this area of research, the heterogeneity of the populations assessed, and various subtypes of CS, comparing and analyzing the results is difficult, although key to understanding the development of CS. This review will outline various environmental and genetic factors described in existing studies in an attempt to locate subgroups of the population at a higher risk of developing strabismus. Identifying risk factors for strabismus may allow for earlier diagnosis and management of amblyopia with a greater likelihood of successful treatment. Ascertaining potential risk factors may also enable greater understanding regarding the development of strabismus and determine areas of research that need further exploration.

Methods

A literature search was performed using key words (gene, genetic environmental factor, inheritance, risk factor, esotropia, exotropia, strabismus, squint, convergent strabismus, and divergent strabismus) in Medline, Embase, BioSciences Information Service Previews, and Web of Science during a 2-week period in July 2011 (including all available years). No language restrictions were placed on the search. We also searched the OMIM database and the Cochrane Library for randomized clinical trials and gene studies. Reference lists of included studies were reviewed for additional articles. All retrospective, prospective, and cross-sectional cohort studies and randomized clinical trials were included for review. The study selection and exclusion process can be viewed in the Figure. Exclusion criteria were defined as not relating to subject interest, reported associated syndrome, strabismus not the primary outcome reported, poor study design or quality, and genetic studies reporting of logarithm of the odds (LOD) score lower than 3. To assess study quality and extracted data, an adapted tool was applied. This tool has been specifically designed for implementation in observational studies for the assessment of information for systematic reviews. It was adapted to include the analysis of genetic and pedigree studies. The amended extraction tool is provided in the eFigure in Supplement. The process was undertaken by G.D.E.M and an independent review of study quality was performed by R.J.M to ensure articles were not overlooked.

Because of the variability and heterogeneous nature of the study designs, including the variability of multivariable analysis used in the included articles, analysis of the data involved locating key topics and performing a descriptive review of the relevant topics.

Results

Search Results

The search revealed 2769 citations, of which 342 studies directly related the interest area. Removal of duplicates left 219 studies, of which 38 fulfilled the inclusion criteria. The reference lists of included studies elicited a further 3 studies satisfying the inclusion criteria, giving a total of 41 studies included for review.

Included Studies

The search revealed 4 main areas of interest, risk factor studies (articles reviewing the effect of environmental or external factors [51.2%]), twin studies (14.6%), family studies (including inheritance patterns [22.0%]), and genetic studies (12.2%) where location of possible causative genes for strabismus were reported.

Risk Factors

Articles reporting risk factors including study type, risk factors assessed, and significant findings are summarized in Table 1. The majority of studies reported risk factors associated with any strabismus (not a specified type of strabismus)
Table 1. Characteristics and Risk Factors Assessed in Environmental Studies

<table>
<thead>
<tr>
<th>Source</th>
<th>Population</th>
<th>Study Design</th>
<th>Strabismus Population Size</th>
<th>Examination Age</th>
<th>Risk Factors Assessed</th>
<th>Significant Risk Factors*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abrahamsson et al</td>
<td>Population</td>
<td>Cross-sectional</td>
<td>343</td>
<td>3 y</td>
<td>D, MP</td>
<td>Assisted delivery, maternal smoking</td>
</tr>
<tr>
<td>Birch et al</td>
<td>Premature ET</td>
<td>Cross-sectional</td>
<td>70</td>
<td>2-3 y</td>
<td>R, D, BP, MP</td>
<td>ROP, anisotropia, hyperopia</td>
</tr>
<tr>
<td>Bremer et al</td>
<td>Premature</td>
<td>Cross-sectional</td>
<td>40</td>
<td>6 y</td>
<td>R, D, BP, MP</td>
<td>ROP, anisotropia, hyperopia</td>
</tr>
<tr>
<td>Goldstein et al</td>
<td>Infantile ET</td>
<td>Cross-control</td>
<td>23</td>
<td>Retrospective</td>
<td>23</td>
<td>BP, H</td>
</tr>
<tr>
<td>Hakim et al</td>
<td>Strabismic</td>
<td>Cross-sectional</td>
<td>95</td>
<td>16-60 mo</td>
<td>R, H</td>
<td>Anisometropia</td>
</tr>
<tr>
<td>Holmström et al</td>
<td>Premature Longitudinal</td>
<td>35</td>
<td>Up to 10 y</td>
<td>20 (57.1)</td>
<td>13 (37.1)</td>
<td>R, BP, H</td>
</tr>
<tr>
<td>Major et al</td>
<td>Infantile ET</td>
<td>Case-control</td>
<td>95</td>
<td>16-60 mo</td>
<td>278 (68.5)</td>
<td>128 (31.5)</td>
</tr>
<tr>
<td>Matsuo et al</td>
<td>Premature</td>
<td>Cross-sectional</td>
<td>38</td>
<td>Up to 10-12 y</td>
<td>21 (55.3)</td>
<td>17 (44.7)</td>
</tr>
<tr>
<td>Pennefather et al</td>
<td>Strabismic</td>
<td>Cross-sectional</td>
<td>95</td>
<td>Retrospective</td>
<td>270 (73.0)</td>
<td>100 (27.0)</td>
</tr>
<tr>
<td>Robaei et al</td>
<td>Premature</td>
<td>Cross-sectional</td>
<td>1320</td>
<td>Retrospective</td>
<td>1048 (79.4)</td>
<td>182 (13.9)</td>
</tr>
<tr>
<td>Snir et al</td>
<td>Premature</td>
<td>Cross-sectional</td>
<td>26</td>
<td>6 y</td>
<td>R, D, BP, MP</td>
<td>ROP, anisotropia, hyperopia</td>
</tr>
<tr>
<td>Torp-Pedersen et al</td>
<td>Population</td>
<td>Cohort</td>
<td>147</td>
<td>6 and 9 mo</td>
<td>68 (46.3)</td>
<td>79 (53.7)</td>
</tr>
</tbody>
</table>
| Vlachou et al                 | Strabismic   | Case-control  | 62 | Up to 18 y | 20 (83.3) | 4 (16.7) | BP | ...

Abbreviations: Accom, accommodative; BP, birth and pregnancy; BW, birth weight; D, demographic; ellipses, information not given; ET, esotropia; XT, exotropia; FH, family history; GA, gestational age; H, hereditary; MP, maternal and paternal; R, refractive; ROP, retinopathy of prematurity.

* Significant risk factors after multivariable analysis.

and only 5 studies reported by type (esotropia and exotropia). Significant differences shown in studies that report by type are summarized in the eTable in Supplement.

Fifteen publications reported risk factors relating to pregnancy and birth. Of these, 6 describe risk factors relating to only premature infants with birth weights of less than 1251 g to less than 1701 g.

Retinopathy of Prematurity | Univariate analysis revealed that increasing severity of retinopathy of prematurity (ROP) was significantly related to increased risk of strabismus in 5 of 6 studies. Multivariate analysis was performed in 4 studies, all of which ROP severity only remained significant for 1. Once cicatricial ROP was adjusted for, severity of ROP was no longer significant.

The overall effect of ROP, compared with those without ROP, significantly increased the risk for strabismus even after multivariate analysis, with stage 1 ROP (odds ratio [OR], 2.6; 95% CI, 1.3-5.99) remaining independently significant.

Birth Weight and Gestational Age | In premature populations, birth weight and gestational age were not significantly related to strabismus after multivariate analysis, although O’Connor et al reported that birth weight 1000 g to 1500 g compared with more than 1500 g was a significant risk factor (OR, 2.5; 95% CI, 1.02-9.4).

In cross-sectional studies, infantile esotropia (IET) and black race, gestational age, and birth weight have been reported to be significantly related to strabismus. After multivariate analysis, 2 of the 3 studies found gestational age to be no longer significant, with the remaining study finding an association with esotropia when gestational age was between 33 and 36 weeks (OR, 1.39; 95% CI, 1.07-1.81). Birth weight continued to be significantly related to strabismus after multivariate analysis although Torp-Pedersen et al reported this significance only when related to esotropia.

Other Birth and Pregnancy Risk Factors | Two studies compared hospital delivery with delivery elsewhere; VanderVeen et al found a significant decreased risk for those born in the hospital (OR, 0.35; 95% CI, 0.16-0.74). Further risk factors included delivery mode (including Caesarean section), Apgar score at 1 minute, respiratory abnormalities at birth, jaundice, infection (including septicemia), and admittance to intensive care. When adjusted for various factors (including birth weight), in a population of only IET, all became insignificant except assisted delivery (OR, 1.7; 95% CI, 1.2-2.5) and Apgar score at 1 minute (OR, 4.9; 95% CI,
1.1-22.3).\textsuperscript{20} When reviewing all articles for any remaining significant birth and pregnancy factors, only head circumference of 38 cm or more was significant (OR, 1.39; 95% CI, 1.11-1.74)\textsuperscript{26} after multivariate analysis.

Maternal and Paternal Influence

Ten articles contained information relating to maternal and paternal influences (Table 1).

Smoking | Studies of the premature populations,\textsuperscript{26} a strabismus cohort,\textsuperscript{29} and an IET group\textsuperscript{20} found no significant difference between maternal smoking and not smoking during pregnancy. Four studies, however, found that the amount of cigarettes smoked by the mother during pregnancy was an important influencing factor and smoking more than 10 cigarettes\textsuperscript{12,22,27} a day gave rise to a significant increased risk (OR, 1.8-2.0), even after multivariate analysis or additional adjustments. Further reports\textsuperscript{14,22} suggest that smoking throughout pregnancy increases the risk of their child developing strabismus compared with mothers who had never smoked/had ceased smoking during the first or second trimester of pregnancy. Secondary smoking was only significant for esotropia when the mother also smoked,\textsuperscript{14} although this association was not supported by Robaei et al.\textsuperscript{24}

Other Maternal and Paternal Characteristics | Maternal age, occupational lead exposure, parental education, and tea, coffee, and alcohol consumption during pregnancy revealed no significant increased risk.\textsuperscript{14,15,18,20,24,27,29} However, Chew et al\textsuperscript{12} found that 30- to 34-year-old pregnant mothers compared with 20- to 24-year-old pregnant mothers had an increased risk (OR, 1.43; 95% CI, 1.19-1.70) for both esotropia and exotropia. Paternal age had a significant effect in 3 studies,\textsuperscript{12,24,29} although for 2, this was only significant for esotropia. Increased consistent hyperemesis gravidarum during pregnancy was also significant (OR, 1.6; 95% CI, 1.1-2.3), although it was only reported in 1 study, which did not allow for multivariate analysis.\textsuperscript{22}

Demographic and Social Factors

Ethnicity | Three studies found significant relationships between white ethnicity\textsuperscript{20} and increased risk of CS, confined to esotropia in 2 studies.\textsuperscript{12,24} After multivariate analysis, 2 studies produced significant conflicting results.\textsuperscript{12,22} Further studies found no significant risk of race at any stage.\textsuperscript{24,11,21,28}

Sex | The majority of studies reported no effect of sex.\textsuperscript{11,12,20,24,28} In 1 study of IET, the risk was significantly increased in males (OR, 4.01; 95% CI, 1.22-13.17),\textsuperscript{18} although this was not supported in a second study.\textsuperscript{20}

Socioeconomic Status and Housing | Socioeconomic status and housing produced conflicting results regarding their influence on strabismus development.\textsuperscript{13,23,24} Chew et al\textsuperscript{12} reported that socioeconomic status was significantly related to exotropia (P = .09) with univariate analysis. However, Vlachou et al\textsuperscript{22} found after multivariable analysis that socioeconomic status, including parental vocation and address, was not a significant risk for strabismus.

Refraction

Anisometropia | In studies that defined anisometropia by 1-diopeter (DS) difference, anisometropia was found to be significantly related to increasing risk of strabismus,\textsuperscript{10,11,16,21,23,24} remaining significant even after multivariate or stepwise regression. Birch et al\textsuperscript{10} also reported that effects of anisometropia were more significantly related to strabismus when hyperopia was less than +3.00 DS when compared with hyperopia more than +3.00 DS (OR, 7.79; 95% CI, 4.46-8.43) for less than +3.00 DS vs OR, 1.49; 95% CI, 1.32-1.60 for more than +3.00 DS). VanderVeen et al\textsuperscript{28} (defining anisometropia as a 2-DS difference between eyes) found no effect of anisometropia after multivariate analysis.

Hyperopia | The effect of hyperopia more than +3.00 DS was associated with a significant increase in strabismus when compared with those with minimal refractive errors (< +3.00 DS).\textsuperscript{9,16,21,24} In all studies, esotropia and exotropia were combined into 1 group. Refractive errors in monozygotic twins with strabismus also show high concordance and are discussed in the Twin Studies subsection.

Other Refractive Risk Factors | Spherical equivalents in myopia were related to increased risk of strabismus particularly when myopia was less than −3.00 DS.\textsuperscript{24} Of 2 studies assessing astigmatism, 1 combined results with other refractive errors, making individual effect difficult to assess,\textsuperscript{22} and multivariate analysis was not performed in the other study but an effect was found using univariate analysis.\textsuperscript{24}

Hereditary

Seven studies investigating the effect of inheritance found a significant increased risk for developing strabismus.\textsuperscript{9,10,16,18,20,21,29} Two studies (1 with a premature population and the other, an IET population) reported a significant 4-fold increased risk of strabismus if there was a family history compared with children with no family history of strabismus, after multivariate analysis.\textsuperscript{20,22} However, another study reported this significance only with maternal family history (OR, 6.42; 95% CI, 1.39-29.7).\textsuperscript{29} A cross-sectional study by Chew et al\textsuperscript{12} examined the association between siblings for both esotropia and exotropia using a model that included risk factors identified in a previous study. They found that when another sibling was affected, the risk of developing esotropia doubled (OR, 2.6; 95% CI, 1.2-3.2); however, this did not apply for exotropia.\textsuperscript{30} Matsuo et al\textsuperscript{30} reported that heredity was significantly higher in accommodative/partially accommodative esotropia (P = .03) and intermittent/constant exotropia (P < .001) than IET.

Family Studies

Six studies considered inheritance of strabismus throughout families\textsuperscript{31-36 (Table 2), 2 of which recruited probands with esotropia; 1, IET; and 4 combined both exotropia and esotropia. True concordance of the type of strabismus has been difficult
to assess because of missing information in a large number of the pedigrees; however, in 1 study, in those who could be assessed, 80% had concordance.32 This was further supported by a later study that found that in 53.9% of families only 1 type of squint occurred (esotropia or exotropia) compared with 46.1% that had both.35 X-linked inheritance was evaluated by 6 studies but quickly rejected as the mode of inheritance for strabismus because of a similar number of affected males and females and significant male to male transmission.31-36 Recessive and dominant models also produced conflicting results.35-36 The majority of studies propose a polygenic inheritance where multiple factors, genetic and environmental, are involved because inheritance patterns cannot be fully explained by simple mendelian models.31-33,36

Dominant inheritance with esotropia when compared with exotropia has been reported in 1 study by Schlossman and Priestley.34 Additionally, Maumenee et al,33 when recruiting patients with IET, found that the majority of probands (113 of 173) were isolated cases within pedigrees.

Twin Studies
Nine studies included twins, of which 6 identified a concordance difference between monozygotic and dizygotic twins.30,37-42 Zygosity was determined by the Nichols and Bilbro33 method in 5 and by obstetrician or genetics in 4.35,37,41,42 Concordance was universally accepted as both twins having a squint in the same direction. Table 3 shows the characteristics of these studies.

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Pedigrees (% Incidence)</th>
<th>Included Relatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dufier et al32</td>
<td>181 (65.4)</td>
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<tr>
<td>Maumenee et al13</td>
<td>173 (15.8)</td>
<td>Minimum all second degree</td>
</tr>
<tr>
<td>Richter36</td>
<td>697 (29.6)</td>
<td>Third degree</td>
</tr>
<tr>
<td>Schlossman and Priestley43</td>
<td>88 (47.5)</td>
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</tr>
</tbody>
</table>

* Consisted of only infantile esotropia pedigrees.

Significantly higher concordance rates in monozygotic twins were noted in all studies except 1.47 Podgor et al39 reported significance with esotropia (P = .03) but not exotropia; however, in a Chinese population, Wei39 noted that concordance was more common in exotropia than esotropia. In the Reynolds and Wackerhagen study,38 the difference became significant when a more rigid criterion of angle concordance (difference in angle size within 10 prism diopters) was used. The most common phenotypes with concordance, noted by Matsuo et al,39,37 were accommodative/partially accommodative esotropia and intermittent exotropia. Three further studies also reviewed only monozygotic twins, 1 study found only 47% had concordance,44 and 1 study noted that although the direction of the strabismus was concordant, associated features of strabismus remained discordant in the majority of twins.41 Two studies reported the squint occurring earlier or resulting in a greater deviation in the lighter or second-born twin and this was not significant.40,41

Studies that also looked at concordance in refractive error found higher concordance in monozygotic twins than dizygotic.38,44 de Vries and Houtman44 reported that 82.4% had identical refractive errors, of which 41.2% had spherical correction of 2 or more and/or cylindrical correction of 1 or more in both twins. Reynolds and Wackerhagen35 noted a significant difference only in cylindrical equivalents that were within 0.5 of each other (6/6 vs 0/0).

Genetic Studies
Burdon et al45 attempted to locate genes by noting the association between IET and albinism based on the possibility that the misrouting of fibers at the chiasm in IET may be similar to albinism; however, no established albinism genes were found in any of the 21 IET pedigrees.

Genome-wide searches and linkage analysis have been used to locate genes, raising the possibility of several gene loci, the most significant being 7p22.1,46 now named the “recessive STBMS1 locus.” Furthermore, Rice et al47 found a pedigree in which STBMS1 was the locus for strabismus, which fit a dominant rather than a recessive model. Possible susceptibilities on chromosomes 4 and 9 have been located; however, these loci were only supported when levels of penetrance were varied.46

Table 2. Number of Pedigrees in Each Study and the Percentage of Incidence of More Than 1 Affected Member

<table>
<thead>
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</tbody>
</table>

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Genome-wide screening in 55 pedigrees with the proband having various forms of CS found significant loci 4q28.3 in the dominant model (heterogeneity LOD = 3.32) and 7q31.2 in the recessive model (heterogeneity LOD = 3.33 and 3.80 at 125.2 cM and 107.8 cM).48 The STBMS1 locus in these families was only suggestive using the recessive model proposed by Parikh et al46 and probands with esotropia (heterogeneity LOD score = 2.53). Later exploration of parent-of-origin genomic imprinting revealed the most significant loci being on chromosome 12q24.32 with almost complete maternal imprinting,49 with possible imprinting at 7q31.2, allowing for complete penetrance.48 The possibility of other strabismus loci on chromosomes 6, 12, and 19 was also revealed, using a model-maximized LOD score, by experimenting with various genetic model parameters, including using single-locus models for both recessive and dominant models, to produce the highest LOD score possible.49

Discussion

Comitant strabismus represents a variety of childhood misalignments of the eyes and it is evident from the studies reviewed that the risk factors for the various types of CS are complex and likely to be a combination of genetic and environmental factors. Comparing ORs for the different risk factors showed that the greatest independent risk factors were anisometropia (OR, 7.79; 95% CI, 4.46-8.43),30 maternal inheritance (OR, 6.42; 95% CI, 1.39-29.7),29 and critical ROP (OR, 5.89; 95% CI, 1.27-27.33).23 Other risk factors reported ORs between 1.50 and 3.00.

Retinopathy of prematurity, particularly cicatricial, and low birth weight were the main causative factors for strabismus relating to birth and pregnancy. The specific effect of cicatricial ROP may be related to the frequent asymmetric development between the eyes leading to low vision in 1 eye50 and, as a result, secondary strabismus.

Birth weight is unlikely to be an influencing factor on its own because of its strong relationship with ROP50,52 and abnormal neurological development.53,54 However, it is reported that an immature development occurs in individuals with low birth weight during which a process of “catch up” arises leading to cardiovascular and metabolic disorders55 and could also lead to abnormal development of the eyes after birth. Head circumference of 38 cm or more56 could be an indication for other problems that lead to strabismus developing, such as chromosomal abnormalities and hydrocephalus.

Effects of smoking throughout pregnancy compared with smoking only in the early stages of pregnancy imply that changes during later stages of fetal development cause strabismus. This period corresponds to specialization of areas within the brain, including the oculomotor and sensorimotor systems and the myelination of the optic nerve.56 If development during this period is disturbed by toxic exposure or as a result of fetal hypoxia linked to smoking, abnormal development and strabismus may result.

The association of CS with hypermetropia relates to the effects of accommodation and convergence seen in a number of subtypes of CS. Occasionally, a high accommodative convergence to accommodation ratio may also be seen.57 The additional effect of anisometropia could be related to a distorted image in 1 eye causing difficulties in fusing images and maintaining binocularity. This inability to obtain binocularity during development could explain why CS persists in these individuals even after prescribing refractive corrections.58 A similar idea could be applied to astigmatism; however, this requires further exploration.

Findings from family studies highlight difficulties in assessing inheritance patterns for CS because they cannot be contained to a simple mendelian pattern. Further complications occur with varying forms of CS and the discovery that several forms of strabismus exist in 1 family. Concordance has been explored partly by Maumenee et al33 in pedigrees with IET but is limited because other forms of strabismus that could be linked were not assessed. Future studies should expand various subgroups of strabismus to compare key features.

Concordance levels in monozygotic vs dizygotic twins reveal that although strabismus is not solely inherited (monozygotic twins did not produce 100% concordance) it does have strong genetic elements. However, the accuracy of studies was weakened by use of the Nichols and Bilbro method,43 which does not provide 100% accuracy in identifying monozygotic twins. These studies report that accommodative esotropia or esotropia had the greatest genetic link when compared with exotropia, implying that development of constant exotropia may be a result of mainly environmental factors and findings of ocular and/or systemic disease.59 Discordant twins were also found, although not significantly, to have a stronger association with ocular and systemic conditions.37 Further classification of the types of CS could provide additional information on which types are more influenced by environmental factors.50 Strong concordance noted in twins with strabismus and refractive error, especially cylindrical correction, suggests that inherited refractive errors could cause increased susceptibility for CS.

This review has identified STBMS1 at location 7p22.1 as the only current defined locus for CS; however, other loci are possibly involved, for example, on chromosomes 7 and 4.48 The location of current genes is the basis for future research. Understanding the role of these genes could help to understand mechanisms behind development that at present are still unknown. Although the location of STBMS1 has been identified as a gene locus for strabismus, there is a need for extended research because it is evident that it is not expressed in all pedigrees.

There are several limiting factors to this systematic review. The exclusion of articles where strabismus development was not the primary outcome may have limited this review, although many of these articles did not produce further analysis relating to strabismus but rather the primary outcome such as amblyopia, refractive errors, additional systemic problems, and development of ROP.56,60-62 To capture all the relevant literature, varying study designs were included for review. This may affect the quality of our results because of the inability to control for confounding variables and possible sampling bias. In addition, because we were unable to undertake quantitative analysis, results may be biased by...
subjectivity and prevent repeatability; however, by following a set systematic progress, attempts were made to reduce these factors. Finally, it is evident from Table 1 that all articles included for review have relatively large sample sizes. This suggests that there may be the possibility of publication bias, in that small studies may not have been published if they were not significant.

Conclusions
It is evident through this review that there are population subgroups who appear to be at higher risk of developing strabismus; these groups include infants of mothers who smoked throughout pregnancy, premature infants with ROP (in particular cicatricial ROP), individuals born with low birth weight but not premature, and those with a family history of strabismus (particularly accommodative esotropia). It is apparent, through the various studies, that genetics play a key role in the development of strabismus. However, at present, current research has revealed only a few loci for strabismus and further research is required to understand the genetic association with strabismus and phenotypes of strabismus that are associated with different gene loci. Identifying correct inheritance patterns for each type of strabismus will enable the use of genetic counseling. Better understanding of the causes of strabismus will allow those groups who are susceptible to strabismus to be identified, examined early on, and monitored, ensuring that the implementation of treatment, if required, is not delayed, allowing for better visual outcomes.
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