The Patricia Lance Lecture 1997 Heredity and Strabismus

This highly distinguished invited lecture was delivered by Robin Wilkinson at the 54th Annual Orthoptic Association of Australia Scientific Conference in November 1997, Sydney, Australia.

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Abstract

Strabismus has long been thought to be hereditary. Studies of the increased prevalence of strabismus in the siblings of probands and studies of the higher concordance of strabismus in monozygotic as opposed to dizygotic twins support this observation. The genetic basis is not known. However, it does not appear to follow a simple Mendelian pattern of inheritance and is thought to be polygenic and multifactorial with environmental factors playing a part. The Strabismus Inheritance Study in Tasmania has been established to discover the gene(s) responsible for hereditary strabismus. The study will examine 300 affected sibling pairs and their nuclear families.

Key Words:
Hereditary strabismus, multifactorial inheritance, sibling pairs.

Introduction

Strabismus has long been noted clinically to have an apparent hereditary nature in some families. The higher prevalence of strabismus in the siblings of affected individuals (probands) together with a positive family history in many cases, have led clinicians to believe there is an underlying genetic predisposition to the disorder. In recent years there have been major advances made in the understanding of the genetic basis of many eye diseases, however the underlying genetic basis of strabismus is unknown. One of the major reasons for this lies in the fact that there are many different phenotypic expressions of strabismus. Strabismus can be congenital or acquired, constant or intermittent, manifest or latent, convergent, divergent or vertical. This variability of phenotypic expression is matched by the many different theories on the aetiology of strabismus. Worth theorised that the underlying basis of strabismus was in fact a defect affecting the fusion mechanism[1]. Chevasse on the other hand theorised that the underlying problem was an interference with the development of conditioned binocular reflexes leading to deviation of the eyes[2]. The more modern approach theorises that some patients may have a congenital lack of ability to develop central fusion[3] (eg congenital esotropia), whereas in others the development of strabismus is due to an interruption to the immature visual system which relies on the proper development of sensory and motor factors to produce binocular single vision[4].

Evidence That Squint Is Hereditary

In the general population the prevalence of strabismus is said to be from 4% to 5%[5,6]. There are several clinical indicators that lend weight to the hereditary nature of strabismus.

1.Prevalence of Strabismus in the Siblings of Probands

If the prevalence of strabismus amongst the siblings of probands is higher than in the normal

population then the defect is likely to have an hereditary component . Several studies have confirmed this. Czellitzer found that 15% of the siblings of affected individuals also had strabismus[7], while a large epidemiological study in America found that for any pair of siblings the odds of esotropia for one sibling more than doubled if the other sibling had esotropia. If one sibling had exotropia then there was only marginal evidence of association[8].

2.Parent/Offspring Correlation

Richter conducted a large study of siblings and their nuclear families and found that the incidence of squint amongst siblings increased if one or more parents were affected[9]. She found that if one or both parents of an index case were affected then about 30% to 50% of the siblings were also affected. If both parents were unaffected then only 20% to 30% of the siblings of a proband were affected. Thus the incidence of strabismus within a nuclear family increased if one or more parents were affected.

3.Presence of a Positive Family History

A familial trait is one which appears more frequently in the relatives of a proband than in the general population. Pratt Johnson reviewed 254 consecutive cases of simple concomitant squint and found that 65% of these probands had a positive family history of strabismus[10]. Schlossman and Priestly found a positive family history in 48% of patients with strabismus, while a Greek study by Chimonidou found a positive family history in 55%[11,12]. An interesting study in Western Australia, looking at children attending for follow up after squint surgery (this is a biased population in that the squints were all severe enough to require surgery), found that in those who had surgery before one year 72% had a history of squint in the parent generation and 24% in the grandparent generation. If the surgery was after two years, then 61% had a positive history in the parent generation and 30% in the grandparent generation[13].

4.Twin Studies

Twin studies are of great value when estimating the hereditability of a disorder. Monozygotic (identical) twins share exactly the same genes or DNA, whereas dizygotic (nonidentical) twins only share the same 50% genetic material that normal siblings do. If a pair of twins both have strabismus then they are said to be concordant for that trait. The influence of hereditary factors can be assessed by comparison of the concordance rates for monozygotic and dizygotic twins. If the concordance rate of a particular trait approaches 100% in monozygotic twins, while the same rate in dizygotic twins is lower, then the trait is said to have an hereditary component[14].

It should be noted that sometimes monozygotic twins show differences due to factors that are not genetic. For example, the effects of external factors during intrauterine life eg the conditions of fetal circulation, the effects of birth trauma/anoxia are not always the same for the two fetuses[15]. Several twin studies have been undertaken to investigate strabismus with the hope of differentiating hereditary and environmental factors, with varying results.

Waardenburg pooled his twin statistics with those in the literature and found a concordance rate in monozygotic twins of 81% , while dizygotic showed only 9%[16]. Richter, in a smaller study, found concordance in 12 pairs of monozygotic twins of 92% and in 27 pairs of dizygotic twins of 26%[9]. A Chinese study found concordance of 77% for monozygotics and 22% for dizygotics[17]. At the other end of the scale Reynolds found monozygotic concordance of 42% and dizygotic concordance of 20%[18]. A study by DeVries of 17 pairs of monozygotics found concordance for squint in 47%[19]. Obviously the statistics can vary enormously, and selection bias, small sample populations, and errors in assessing the true zygosity where monozygotic twins are in fact dizygotic can all lead to erroneous statistics for the concordance of strabismus. Another factor affecting the concordance is the quality of the clinical evaluation itself.

With consideration of these variable results Magli et al conducted a 5 year study of monozygotic twins and compared concordance with the same number of dizygotic twins. They concluded that there was a 72% concordance for monozygotic twins with esotropia as compared with 22% for dizygotic[20]. This lends definite supports to a genetic basis for strabismus.

5. Racial Genetic Variation

If racial differences occur for a given trait then this may provide supportive evidence that a trait is hereditary. It has been shown that there is a significantly lower rate of esotropia in blacks than whites. Eustace examined the prevalence of strabismus and refractive error in second generation West Indian children born in Birmingham and compared the data with previous data collected on white children and found that exotropia was four times more common in black children and that myopia was also more prevalent[21]. In summary, the clinical observation that there appears to be a genetic

component in the aetiology of strabismus is supported by the clinical data from several studies.

Genetics

In order to understand the possible genetic and molecular basis for the inheritance of strabismus and the pattern or model for inheritance, a basic knowledge of genetics and genetic terminology is necessary.

The human cell nucleus contains 46 chromosomes, arranged in 23 pairs based on their morphology on karotyping. The 23rd pair are the sex chromosomes XX in a female and XY in a male. Thus there are 22 pairs of autosomes and one pair of sex chromosomes. The cell nucleus also contains two different types of nucleic acid - RNA which contains the sugar ribose and is called ribonucleic acid and is found mainly in the nucleolus and the cytoplasm, and DNA which contains the sugar deoxyribose and is called deoxyribonucleic acid. It is found mainly in the chromosomes. Thus a chromosome is made up of DNA. Arranged linearly along the chromosomes are discoid elements called genes. These genes are the basis of the development of hereditary characteristics. A gene is in fact a tiny strand of DNA and its primary action is to control a specific cell function by governing the synthesis or manufacture of a specific protein. The DNA of each gene makes a specific RNA by a process called transcription, which then directs production of a protein by a process called translation. Thus DNA directs the synthesis of RNA and RNA is translated to protein[22].The location of a gene on a chromosome is called a locus. Each pair of chromosomes has two copies of a given gene and these corresponding copies of the gene at a given locus on a pair of chromosomes are called alleles. The clinical expression of a gene is called a phenotype. There are approximately 100,000 genes which code for specific proteins. Currently there is a world wide study 'The Human Genome Project' which aims to provide a map of all the human chromosomes and should be completed by the year 2000. A genetic defect or trait may be defined as any condition caused by an error in the genetic material DNA This error may occur as a result of a mutation. A mutation is a permanent change in the constitution of a gene which results in modification of its action. It may have a positive, negative or indifferent effect. If there is no effect of a given variation the term polymorphism may be applied. All genetic disorders may be grouped into three broad categories[23].

1.Chromosomal abnormalities: caused by structural rearrangement of the DNA in the chromosome, or an incorrect complement of chromosomes (eg. trisomy).

2.Molecular alterations: in gene structure: eg point mutation or deletion of a part or all of a gene.

3.Multifactorial abnormalities: where genetic and environmental factors play a part. In many traits multiple genes interact and hence the term polygenic is used.

Models of Inheritance

The discussion of the role of heredity and strabismus must necessarily include a model for its inheritance. The traditional Mendelian models fail to fit the observed pattern of inheritance for strabismus[24]. The three main Mendelian patterns are:

1. Autosomal dominant inheritance
2. Autosomal recessive inheritance
3. Sex linked inheritance

1.Autosomal dominant inheritance

An autosomal dominant disorder occurs when a trait is manifested when only one of the two copies of the gene (alleles) is abnormal. Autosomal dominant inheritance is characterised by:

1.Transmission from one generation to the next. Phenotypically normal parents do not transmit the phenotype to their offspring.

2.The risk of an affected individual having an affected offspring is 50%.

3. Males and females are equally affected.

4. All forms of transmission are observed eg from either male or female to offspring of either sex. With reference to heredity and strabismus, the clinical data on family studies does not support simple autosomal transmission in that often both parents are clinically normal.

2.Autosomal recessive inheritance

An autosomal recessive disorder means that each parent must have a copy of the abnormal gene and two abnormal copies are needed to produce a trait. Autosomal recessive inheritance is characterised by:

1.Individuals in one generation in a single sibship eg brothers and sisters are affected, and it does not occur in previous or subsequent generations.

2.The risk to offspring of a couple who are carriers is one in four or 25%.

3.Males and females are frequently affected.

4.Cosanguinity in parents can be an indicative factor (eg marriage between first cousins).

With reference to strabismus the clinical data on family studies does not support autosomal recessive transmission, in that just as parents may be unaffected, a certain proportion are affected.

3. Sex linked inheritance (X-linked dominant and X-linked recessive inheritance)

There is no evidence for the strabismus pattern being X-linked. This form of inheritance pattern implies differences in inheritance and transmission according to sex. On the contrary, clinical data have shown that males and females are equally affected. There is also no data to support a difference in transmission from either sex.

From the evidence above it is clear that strabismus does not follow a simple Mendelian pattern of inheritance and that we need to look to a different model to explain its familial aggregation.

The model which best fits hereditability of strabismus and in fact many other inherited disorders is called multifactorial inheritance.

Multifactorial Inheritance

The multifactorial model is now the most commonly held theory of the inheritance of strabismus. The term is used to explain the inheritance pattern in which both genetic and environmental factors are thought to play a part. The inherited genes are thought to work *additively* and there may be no single major error in the genetic information but rather a combination or additive effect from either or both parents, such that only when a threshold is reached and exceeded then the combined effect is seen as an abnormality. When a disorder is caused by the additive effect of more than one gene it is termed polygenic. In multifactorial inheritance the expression of a disorder in an individual is determined by:

1. How many of the gene factors responsible for that disorder are present in each parent.

2.What quantities of each factor are transmitted to each offspring[25].

3. Environmental factors.

Given the evidence that strabismus is hereditary with a polygenic multifactorial inheritance model it is important to assess both the contribution made by environmental factors and the genetic risk factors that contribute to the additive threshold effect that appears to cause the phenotypic expression of the trait.

Risk Factors

There are three main risk factors reported from clinical studies that are thought to contribute to the so called additive effect[14].

1.A positive family history and more specifically when either parent has esotropia.

2.If parents are normal but there is between them very low vergence ability.

3.If either parent has significant hypermetropia.

The first two points have been covered in earlier discussion. However refractive errors and their genetic significance may prove to be of vital importance in the inheritance of strabismus.

Refractive Errors

The refractive state of an eye is the result of a combination of different optical components such as corneal curvature, corneal thickness, depth of the anterior chamber, thickness of the lens, anterior and posterior lens curvatures and axial length. None of these components are constant and they vary between individuals so that total refraction may vary according to the combination and interaction of these components[26].

There are three main theories on the causes of refractive errors[27]:

1.The biological theory in which it is postulated that all errors of refraction are due to the way in which the components of the eye combine.

2.The use/abuse theory which explains the onset of myopia as an adaptation to the use of the eyes in prolonged closework.

3.The emmetropisation theory proposed by Van Alphen which postulates that the eye is self focusing and emmetropia is produced by cortical and subcortical control of the tonus of the ciliary muscle and ametropia by factors which interfere with this mechanism. This theory proposes that a stretch factor is exerted on the sclera by the ciliary muscle which originated from the scleral spur[28].

As with strabismus there is clinical evidence to support a genetic basis for refractive errors given that environmental factors can modify the effect.

Twin studies have established that refraction as a whole and its major individual components axial length and the powers of the cornea and lens, are genetically determined. Sorsby found concordance for monozygotic twins to be 71% for refractive errors while for dizygotic twins it was negligible[29]. Hereditability was high for corneal curvature, posterior lens surface and axial length.

A study by Young and Leary found that there was a significant child-parent refractive error correlation[30]. This is especially true for myopia where studies have found that when both parents are myopic the prevalence of myopia in the offspring is at least three times higher than when neither parent is myopic[31].

A study by Hegmann et al looked at three different groups and their nuclear families;

1. 118 families with esotropia.
2. 27 families with exotropia.
3. 163 random families.

They examined the clinical data in relation to the implication that hypermetropia and myopia are a primary factor in the aetiology of strabismus. They found results consistent with the general clinical observation that hypermetropia tends to occur with esotropia and myopia tends to occur with exotropic patients. They concluded that the correlation between hypermetropia and esotropia, and myopia and exotropia was statistically significant and suggested that there were gene differences among the refactive errors and that these may be directly implicated in the aetiology of strabismic phenotypes[32].

Finally a British study by Anker looked at a sample population of 829 infants with a positive family history of strabismus and screened them between the ages of 6 months and three years for refractive errors. They concluded that infants with a positive family history of strabismus are four times more likely to develop significant hypermetropia and that 20% of these hypermetropes will develop a strabismus.[33]

Thus it appears that refractive errors and their inheritance are in some way related to strabismus and its inheritance.

Environmental Factors

A large multidiciplinary study in America examined data to identify risk factors for strabismus in a group of children followed from gestation to age seven years[34]. They found the following factors to be significant:

1. The risk of strabismus increased with low birth weight.
2. The risk of esotropia increased with increasing maternal age until 34 years.
3. Maternal cigarette smoking during pregnancy increased the risk of offspring developing strabismus.

A study in the USA has shown that a dietary intake of Omega 3 fatty acids during the first months of life was important. It showed that at 36 months children fed with human milk containing omega 3 fatty acids had better random dot stereopsis and letter matching skills than formula fed children (the latter being a poor source of this nutrient)[35]. A further study showed that Omega 3 fatty acids played an essential role in retinal development[36].

Thus it can be seen that while there is evidence of a genetic predisposition to strabismus there have been shown to be risk factors and environmental factors that cause an additive effect and a threshold is reached whereby the defect expresses itself clinically as strabismus.

The Strabismus Inheritance Study

The Strabismus Inheritance Study (SIST) commenced in Tasmania in February 1997. The aim of the study is to identify the genes responsible for hereditary concomitant strabismus.Given the clinical evidence that there is a definite hereditary component and that the model which best fits this inheritance pattern is multifactorial, the study will examine in detail 300 affected sibling pairs and their nuclear families, looking at the penetrance of the phenotype in each family and also at possible environmental factors. The study will compare parent/offspring similarities for several clinical measures as well as collecting DNA for analysis.

The SIST team is comprised of three orthoptists who have designed the clinical protocols and who clinically examine all participants. The genetic investigation and laboratory supervision will be managed by an ophthalmologist, and a molecular geneticist.

The study has compiled a list of over 250 sibling pairs in Tasmania from case records in private practices and from public hospital records and will target these families initially.

Methodology

Polygenic inheritance complicates genetic mapping because no single gene locus is responsible for producing a trait. The SIST study has adopted the affected sibling pair method of analysis. This method has been shown to be the method of choice where multifactorial inheritance is the model. The aim is to compare the DNA of a large number of affected sibling pairs looking for genetic markers. Genetic markers are patterns of DNA sequences with a known location on a chromosome and these are mapped and compared, looking for identical segregation of a genetic marker with a disease phenotype that is not simply random segregation.

The closer together two genes are located on a chromosome when they are compared the higher the chance of their being inherited together.

The initial genetic mapping will target a major subgroup of strabismus - congenital esotropia. Investigation will then be carried out on other major subgroups, which may or may not be linked to the same gene.

Two recent ophthalmic genetic discoveries offer an interesting insight into the search for the strabismus gene and where the initial search may be best directed. The location of one of the gene mutations responsible for primary open angle glaucoma has proven to be the same gene responsible for juvenile glaucoma located on chromosome 1. The location of the gene mutation responsible for 16% of age related macular degeneration is known to be on chromosome 2 and is the same gene responsible for the more severe early onset Stargardt's macular dystrophy.

There is no candidate gene for strabismus, but it would appear sensible to look at congenital infantile esotropia initially, as it is arguably the most severe form of strabismus in that it appears in the first six months of life and binocular single vision is rarely if ever achieved. It is also phenotypically a very distinct subgroup of strabismus.

Tasmania, and in particular the north - west coast of Tasmania, provides an excellent population for such a genetic study, in that many families have lived in the area for generations and can be traced back to common ancestors in many cases. This is called the 'founder' effect and provides a gene pool with less external genetic influences and an ideal population to target initially, as far fewer families with the identical genetic disorder may be needed by the laboratory. It is hoped that by early next year a pilot genome search for genetic markers in congenital esotropia may be commenced.

Clinical Examination

Much of the difficulty in studying the hereditability of strabismus lies in the use of varying definitions and measures of strabismus. The study aims to clinically examine, refract and classify every member of each nuclear family. One of the strengths of the study lies in the fact that the same team will examine every family and strict criteria are adhered to for examination and classification.

A comprehensive history is obtained from each family member with particular attention given to the factors outlined previously as risk and environmental factors. The questionnaire looks at all the siblings and the maternal history during pregnancy, birth details, milestones and strabismus history of those affected. This history is sent to each family prior to the clinical appointment and then thoroughly checked by a member of the team on the day.

Clinical examination is then carried out on all members of the nuclear family wherever possible. The following factors are investigated by the same examiner:

1. Visual acuity using the logMar chart where possible.
2. Near and distance cover test with prism bar measurements.
3. Ocular motility.
4. Investigation of binocular vision.
5. Stereoscopic acuity using the Randot and Titmus tests.
6. Measurement of prism fusion range.
7. Measurement of the AC/A ratio (heterophoria and gradient method)
8. Fixation.
9. Refraction using an autorefractor.

Cycloplegic refraction is carried out on those aged 10 years and under.

A comprehensive classification has been designed wherein each strabismus is classified into a very specific subgroup. One of the difficulties has been to classify the strabismus in the subgroup it belonged to *before* treatment as this is the relevant classification genetically. This is essential for the laboratory once genome studies are commenced given that more than one gene is thought to be responsible for strabismus and there are so many different types of strabismus. It may well eventuate that some subgroups will be traced to the same gene or that previously apparently unrelated subgroups may prove to be genetically linked. However, initially, it is essential to classify each subgroup so that they are phenotypically identical within the group.

This comprehensive examination will provide valuable information on the penetrance and phenotypic expression of a gene in each family. Strict guidelines have been established to define the range of normality and thus where abnormality begins. The entire examination takes approximately one hour per family, and the family is required to attend for one visit only.

DNA Collection

DNA is typically isolated from blood samples for genetic analysis. While this is the ideal and more robust method of collection this has only

been used in adults in the SIST study. Buccal mucosal swabs are a non-invasive method of DNA collection. The DNA is contained in cells which are plentiful in the mucosal lining of the mouth. The sampling is obtained with plastic cyto brushes which are gently rubbed on the inside of the cheeks and stored in a fixative until sent to the laboratory. The main disadvantage of this method of DNA sampling is that the yield of DNA is not as high as with blood samples and the yield drops if the DNA is not extracted within three weeks. Blood samples can be kept indefinitely. The yield from 1 ml of blood is about 100 micrograms of DNA and the average yield from one buccal swab per patient is approximately 50 micrograms per swab in total. However this yield will be sufficient given that current genome searches require much less DNA than in the past. Mucosal DNA can be immortalised to make it more stable long term, however this is cost prohibitive given that it is a relatively easy procedure to repeat, and the study is dealing with a relatively young population.

The study is now piloting an updated DNA collection kit, using smaller cyto brushes and small containers called epindorfs which are easier to transport and easier to process, giving a higher DNA yield and only requiring two swabs per person.

Clinical Observations To Date

Having completed the first year of what is anticipated will be a three year study by the SIST team, it is relevant to look at an overview of 70 affected sibling pairs and their nuclear families, 8 of these being families with monozygotic twins. Several observations are of clinical interest.

1. Monozygotic Twins

As previously mentioned, if a trait shows a high concordance in monozygotic twins it provides evidence the trait is hereditary. This study has examined 8 pairs of monozygotic twins to date and found 100% concordance for strabismus, subgroups, and refractive errors.

2. Presence of a Positive Family History

In the 62 families of affected sibling pairs (ie excluding monozygotic twins) there was a positive family history of strabismus in 74% of families.

With regard a positive history: 39% were positive on the mothers side, 16% on the fathers side and 19% on both sides.

This is a higher incidence of a positive family history than in previous studies of consecutive concomitant squint mentioned earlier (65% being the highest). One possible reason for this is the fact the study is looking at families with a higher penetrance, that is, with two affected siblings. Another reason is the detailed history taken by the SIST team, as quite often a definite family history is revealed with more detailed questioning.

3. Is Strabismus Phenotypically the Same in Families?

In the 62 families under discussion some interesting variations occurred within families. Only 60% of families had sibling pairs from an identical subgroup while 40% had affected pairs who fell into different subgroups. Of the 60% with identical subgroups there were 14 pairs of congenital esotropes. The 40% with different subgroups had a variety of combinations of subgroups including those thought to be unrelated eg congenital esotropia with fully accommodative and intermittent divergent squint with convergent microtropia.

Thus it appears that familial strabismus is not phenotypically the same in every family and can be expressed in a variety of subgroups within a nuclear family.

4. Risk Factors

The parents were examined for risk factors thought to contribute an additive effect in the inheritance of strabismus. By far the most significant risk factor in this group of affected sibling pairs was the positive family history of 75% previously mentioned. The incidence of parental strabismus was 26%. The risk factor of a low vergence range in either parent appeared in 23% of families where the limit of 40pd of convergence and 16pd of divergence was taken to be the normal range,and 25pd of convergence to 10/12 pd of divergence or below these limits taken as a reduced vergence range.

There was an overall incidence of parental refractive error of 49% where 2 diopters of hypermetropia and 1 diopter of myopia were taken to be significant. Interestingly, the breakdown shows more parental myopia than hypermetropia with 30% being myopic and 19% being hypermetropic.

Thus it appears the above risk factors do play a significant role in the inheritance of strabismus.

Significance Of SIST

The discovery of the genes responsible for strabismus and the investigation of the nuclear families and their clinical status will provide new and valuable information that will assist in the management and treatment of strabismus.

1. The discovery of the gene(s) will lead to a better understanding of the pathophysiological processes involved in the development of strabismus. This is absolutely essential if we are to progress in the understanding and management of strabismus.

2. An understanding of the underlying genetic basis of strabismus and the genes involved may lead to reclassification of strabismus, as previously apparently unrelated phenotypes are shown to have the same genetic basis. This may lead to the adoption of different management procedures.

3. Genetic identification of the molecular basis of strabismus may give rise to new therapeutic interventions eg medication, or changes to diet or environment to minimise or negate the effects of the trait.

4. The ability to accurately predict its occurrence will lead to earlier intervention.

5. Improved and more economical screening techniques may be adopted once high risk individuals are more readily identified.

Conclusions

Strabismus has been shown by the clinical research data available to have an hereditary component. However the pattern of inheritance does not fit a simple Mendelian model but rather is thought to be polygenic and multifactorial with environmental factors playing a part. The Strabismus Inheritance Study aims to identify the genes responsible for hereditary concomitant strabismus. It is the first study of its kind in the world and the information obtained on the genetic inheritance of strabismus and the familial phenotypic penetrance of strabismus has the potential to change the way we classify, interpret and manage strabismus in the future.

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References

1.Worth C. Squint, its causes pathology and treatment. 6th ed.London: Balliere,Tindall and Cox. 1929.

2. Chavasse FB. Worth's Squint. The binocular reflexes and the treatment of strabismus. 7th ed.Philadephia:.P.Blakiston's Son and Co Inc. 1939.

3. Pratt-Johnson JA. Fusion and suppression:development and loss. J Pediatric Ophthalmol Strabismus 1992; 29: 4-10.

4. Von Noorden G. Binocular vision and ocular motility. Theory and management of strabismus.5th ed. Mosby St Louis. 1995: 132-145.

5. Chew E, Remaley N, Tamboli A, Zhao J, Podgar M, Klebanoff M. Risk factors for esotropia and exotropia. Arch Ophthalmol Oct 1994; 112: 1349-1355.

6. Graham P. Epidemiology of strabismus. British J Ophthal 1974; 58: 224-231.

7. Czellitzer A. Wie verebt sich Schielen? Arch Rassen.Ges Biol 1923; 14: 377.

8. Podgor M, Remaly N, Chew E. Associations between siblings for esotropia and exotropia. Arch Ophthal June 1996; 114: 739-744.

9. Richter S. Untersuchungen iiber die Hereditat des Strabismus concomitans. Abhandlungen aus dem Gebiete der Augenheilkunde 1967; 23: Leipzig.VEB Georg Thieme.

10.Pratt-Johnson J. Early case finding and the heredity factor in strabismus. Canad J Ophthal 1967; 2: 50-53.

11.Schlossman A, Priestly BS. Role of heredity in aetiology and treatment of strabismus. Arch Ophthalmol 1952; 47: 1-20.

12.Chimonidou E. Palmeris G. Koliopoulos J. Velissaropoulos P. Family distribution of concomitant squint in Greece. Brit Jnl of Ophthal 1977; 61: 27-29.

13.Bremner M. Letters To The Editor: Hereditary Strabismus. Med Jnl of Aust Sept 6 1993; 159.

14.O'Hara M. Nelson L. Heredity of strabismus. Duanes Foundations of Clinical Ophthalmology Hagerstown 1990; 3 : 59: 3.

15. Francois J. Heredity in ophthalmology. C V Mosby St Louis. 1961: 77.

16. Waardenburgh P J. Squint and heredity. Doc Ophthalmol 1954; 7-8: 422-493.

17.Wei NF. Chung-Hua Yen KO Tsa Chi.(Chinese J of Ophthal) 1987; 23 :282-283.

18.Reynolds J .Wackerhagen,C. Strabismus in monozygotic and dizygotic twins. Am Orth Jnl. 1986; 36:113-119.

19.De Vries B, Houtman W. Squint in monozygotic twins. Doc Ophthalmologica 1979; 46: 2: 305-308.

20.Magli A, Calabro S, Tonna G.Oculo-motor and sensorial anomalies in esotropic monozygotic and dizygotic twins.Transactions ,5th International Orthoptic Congress.Lyon LIPS 1983;195-200.

21.Eustace P. Myopia and divergent squint in West Indian children.Br J Ophthalmol 1972 ;56: 559-564.

22.Drack A, Basics of inheritance. Foundations of Clinical Ophthalmology 1996; 3 :51: 1-17.

23.Cross H. The hereditibility of strabismus.Am Orth Jnl 1975; 25:11-17.

24.Wang M, Nelson l, Donoso L. Molecular genetic basis of eye disease. Foundations of Clinical Ophthalmology1996; 3: 55: 1-44.

25.Grutzner P, Yazawa K. Heredity and strabismus. Surv of Ophthalmol 1970;14: 6 : 441-456.

26.Francois J. Multifactoral or polygenic inheritance in ophthalmology. Dev Ophthal 1985; 10:1-39.

27.McBrien N. Barnes D.A review and evaluation of the theories of refractive error development. Ophthal,Physiol Opt1984; l4 :3:201-213.

28.Van Alphen G. On emmetropia and ametropia. Ophthalmologica Suppl 1961;142 :1-92.

29.Sorsby A, Fraser G R. Statistical note on the components of ocular refraction in twins.J Med Genet 1964; 47-49.

30. Young F A.Leary G A. The inheritance of ocular components.Am J Optom 1972;49: 546-555.

31. Yap M, Wu M, Liu Z, Lee F, Wang S. Role of heredity in the genesis of myopia. Ophthal Physiol Opt 1993;13:316-319.

32. Hegman J, Mash A, Spivey B. Genetic analysis of human visual parameters in populations with varying incidences of strabismus. Am J Hum Genetics 1974;26:549-562.

33. Anker S, Atkinson J, Bobier W, Tricklebank J, Wattam-Bell J. Infant vision screening programme:screening for refractive errors in infants with a family history of strabismus. Br Orth Jnl 1992; 49: 12-14.

34.Chew E, Remaly N, Tamboli A, Zhao J, Podgar M, Klebanoff M. Arch Ophthalmol 1994;112:1349-1355.

35.Birch E, Birch D, Hoffman D, Hale L, Everett M, Uauy R. Jnl Paediatr Ophthalmol Strabismus 1993; 30: 33-38.

36. Uauy R, Birch D, Birch E, Tyson J, Hoffman D.Paed Res. 1990; 28:5:485-492.