Genetic epidemiological study of strabismus and congenital cranial dysinnervation disorders in Rawalpindi district

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Genetic epidemiological study of strabismus and congenital cranial dysinnervation disorders in Rawalpindi district

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In the name of Allah, The most Compassionate,
The most Merciful

Declaration

I hereby declare that I have worked on my thesis “Genetic epidemiological study of strabismus and congenital cranial dysinnervation disorders in Rawalpindi district” independently. All the work presented in this thesis is my own effort and composition. No part of this thesis has been previously presented for any other degree.

Faiza Batool

Dedication

Dedicated to my

Father, Raja Rehman Akhtar

and

Uncle, Tanveer Akhtar Shirazi

For believing in me and without whom I would never have accomplished such worthy tasks

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Alhamdulillah, I praise and thank **Allah** SWT who has sent down the disease and the cure, and has made for every disease, the cure.

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Faiza Batool

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Abbreviations	Full form
CCDDs	Congenital cranial dysinnervation disorders
CFEOM	Congenital fibrosis of the extra ocular muscles
CN	Cranial nerve
CNS	Central nervous system
CS	Concomitant Strabismus
DRS	Duane's retraction syndrome
DS	Diopter sphere
ET	Esotropia
EOM	Extraocular muscle
IOOA	Inferior oblique overaction
KPK	Khyber Pakhtunkhawa
LIO	Left inferior oblique
LIR	Left inferior rectus
LSO	Left superior oblique
LSR	Left superior rectus
MGJW	Marcus gun jaw winking syndrome
PCT	Prism cover test
PD	Prism diopter
RE	Refractive error
RIO	Right inferior oblique
RSR	Right superior rectus
VA	Visual acuity
XT	Exotropia

Abstract

Strabismus is an ocular alignment disorder, can affect people of all ages, however congenital forms are common among children. It is characterized by the direction of misalignment and may be latent or manifest, with a variety of etiologies. Its timely diagnosis, classification and treatment are important in pediatric population to limit the occurrence of amblyopia. It is important to understand the development of common strabismus to identify 'at risk' populations and implement appropriate treatment. Data on the epidemiology and genetic and phenotypic attributes of strabismus for the metropolitan population of Rawalpindi district are not available. In this context, the present study is a hospital based cross-sectional epidemiological study carried out to determine the prevalence pattern, and clinic-epidemiological and genetic attributes of strabismus in Rawalpindi population. A total of 498 subjects diagnosed with strabismus were recruited from an orthoptics clinic and classified into five subtypes i.e., Esotropia (n=229) > Exotropia (n=158) > Mixed (n=80) > Syndromic (n=19) > Vertical (n=12). The age of the participants has a significant influence on the prevalence of disorder irrespective of their gender. Children in the age range >3-6 were more represented in this cohort. The left eye is more vulnerable to esotropia (n=58), and the action of inferior oblique muscle was found to be the most common insult (n=101). Refractive error was an important determinant of strabismus with astigmatism (24%) being most common among patients with esotropia. Sporadic cases constituted 75% of all patients. Consanguinity, caesarian delivery, positive family history and premature birth were significant risk factors. This study is a pilot epidemiological approach to investigate relative pattern and incidence of strabismus subtypes and may bridge the gaps in the current knowledge of the cause and consequences of the disease. This will also be helpful for health management authorities to plan and build optometry centers for such patients. Further research on molecular genetic level could help to identify hereditary links in strabismus subtypes and locate causative genes to aid the understanding of strabismus development.

Chapter 1

Introduction

1.1 Strabismus: a common congenital ocular alignment disorder

Strabismus, from Greek "Strabismos", also called squint or crossed eyes is an ocular disorder characterized by misalignment of one eye with respect to other eye resulting in the failure of two eyes to concentrate on the object of interest simultaneously (Azam et al., 2019). It is also defined as any heterotropia at distant or near distance, with or without spectacles (Tang et al., 2016). It includes misalignment in primary position (straight ahead gaze) as well as eccentric gaze. The term probably dates to the geographer "Strabo" whose ugly-looking squint was famous in Alexandria (Nelson et al., 1987). During normal conditions, six eye muscles in each eye regulate all movements of the two eyes (Kumar and Roopashree, 2020).

A deviation of fewer than 10 prism diopters in the presence of demonstrable binocular vision is called microstrabismus (Bothun et al., 2022). Pseudo-strabismus is a bogus impression of deviation which may be due to telecanthus or distinguished epicanthal folds that cover nasal sclera or closely set eyes or eye lid asymmetry (Bommireddy et al., 2020). In most cases, strabismus occurs during infancy or early childhood, adults also develop the condition secondary to other ailments such as trauma, cranial nerve palsies, thyroid dysfunction, surgical procedures, or other neurologic diseases (Martinez-Thompson et al., 2013). At birth, visual functions are poor but upon appropriate stimulation, develop rapidly over the first few months of life (Birch and Connor, 2017). There is certain evidence that suggests trauma during the period of brain development is likely to be an important determinant of strabismus. This critical period begins with the rapid multiplication of cells at midgestation and ends

with the myelination of neuronal cells, a process that is not complete until 3 to 4 years after birth. Although this interval spans the onset of most types of strabismus (Mohney, 2001; Mohney, 2003), the method and timing of the insult may be important determinants in the type of strabismus that develops.

1.2 Impact of strabismus

Eyes are highly developed sensory organs through which we perceive almost 80% of information (Jabeen et al., 2022). With the advancement in the evolutionary process, these structures moved from temporal sides to frontal portion of head resulting in the fusion of image from the two eyes and giving the ability of stereopsis. Stereopsis or depth perception is a binocular discrepancy between the images discerned by the two eyes. Measure of the level of depth perception is called stereoacuity. The efficiency in stereoacuity can be reduced by various factors such as the presence of strabismus, refractive error, or amblyopia (Bommireddy et al., 2020). In mammals, the neural substrate for stereopsis is neurons in the visual cortex of brain whose maturation depends on the proper alignment of two eyes early in life (Donahue, 2007). Ocular misalignment is not just a superficial imperfection but has myriads of biological and psychosocial effects. For instance, disruption of binocular vision, reduced stereoacuity, abnormal retinal correspondence, reduced self-esteem (Ye et al., 2014), social prejudice (Jabeen A et al., 2022), an abnormal head posture and reduced eye contact (Bommireddy et al., 2020). Amblyopia is a permanent loss of visual acuity in an otherwise structurally healthy eye. It is often accompanied by one or more amblyogenic

factors such as strabismus, refractive error, or cataract, is one of the most important causes of unilateral blindness in adults (DeSantis, 2014). In children with immature visual systems, the critical period for developing strabismic amblyopia is as early as 1–2 months of age and 90% of the cases are reportedly caused by strabismus and/or anisometropia (Buffenn, 2021). Its prevalence varies between 2%–5% in the United States (Pescosolido et al., 2014). Symptoms of the condition may also change with time, and if left untreated ocular misalignment that seemed well managed at early stage may become more apparent and frequent as the patient grows to older ages (Davidson and Quinn, 2011).

1.3 Prevalence of strabismus

Prevalence rates of strabismus in various populations is influenced by its definition. Recent studies often define strabismus as the deviation present either for near or distance fixation. Therefore, both constant and intermittent deviations are included in the calculation of prevalence. Prevalence of strabismus varies in different ethnic groups, geographical regions, age groups, sex, and squint types, etc. Global prevalence of strabismus is 0.14% to 5.65% (Agaje et al., 2020). The condition affects between 5 and 15 million people in the United States (Azam, 2019). Prevalence of strabismus reported by various studies lies between 1% and 5%. A comparative multi-ethnic cohort study of the UK found the prevalence rate is higher for white British (2.1%) than Pakistani children (1.3%) (Bruce and Santorelli, 2016). Various population-based studies revealed the occurrence of strabismus varies between 0.5% in

urban New Delhi to 2% in rural South India (Bruce and Santorelli, 2016). Such a low reported prevalence can be attributed to the varying definition used in New Delhi. In most of their studies, strabismus is a constant deviation i.e., present for both near and distance fixation. A review study carried out by Hassan Hashemi and colleagues revealed that the pooled prevalence of strabismus, exotropia (XT), and esotropia (ET) was 1.93%, 1.23%, and 0.77%, respectively (Hashemi et al., 2019). Dominant refractive error can also be the reason for the difference in strabismus prevalence such that the higher prevalence of XT than ET in Asians can be due to the higher prevalence of myopia in this population. Contrarily, subjects suffering from ET need more accommodation to compensate hyperopia they are more likely to have hyperopia. With respect to age, higher prevalence in the low age group followed by decreasing trend thereafter may be attributed to decreased prevalence of hyperopia with age and early detection of the disease at lower ages (Chen et al., 2015).

1.4 Status of strabismus in Pakistan

According to population census 2017, the estimated population in Pakistan of people of all ages is 207 million. Children under the age of 20 years account for 45% of the total population (PBS, 2017). Estimated prevalence of blindness among Pakistani children is 10 per 10,000. Country wide approximate prevalence of strabismus is 5.4%. The national prevalence of 5.4% suggests that there are 7.02 million patients with strabismus in a population of 130 million (Abbas et al., 2005). Community based data on the prevalence of strabismus found that the condition prevails 13.5% in NWFP (Sethi

et al., 2001), 12.4% in Bahawalpur (Farrukh et al., 2015), 11.4% of all vertical deviations in Rawalpindi population (Abbas et al., 2005), 8.3% in Lahore (Iqbal et al., 2021), 6.2% in Karachi (Fahim, 2019), 3.9% in Rawalpindi (Asif et al., 2017), and 1.3% in tehsil Laki Marwat (Ullah et al., 2020). Most common refractive error and strabismus subtype in these studies is Hypermetropia and esotropia, respectively. A review of the literature shows that prevalence with respect to type of squint and age groups varies in different parts of the country.

1.5 Classification of strabismus

Strabismus is classified in a variety of ways such as onset of the condition, phenotypic appearance, time of appearance, laterality of eye, gaze position, direction of deviation, and in relation to accommodation. Summary of classification is given in Table 1.

1.5.1 Congenital or acquired (idiopathic)

According to etiology-based strabismus classification scheme for pediatricians, congenital or early onset misalignment of eyes is called physiologic strabismus (Mocan et al., 2022). Congenital means “present at birth”. Birth is a premature event in relation to the visual system. Normal ocular alignment is a learned process that should be completed by around 4-6 months of age (Mocan et al., 2022). All esotropes were noted to resolve by 2 months and almost all exotropes (97%) were resolved by 6 months of age (Sondhi et al., 1988). Congenital esotropia or infantile esotropia includes children

with intact mental health and with a constant non-accommodative esotropia that developed by first few months of life. Intermittent exotropia was defined as an acquired deviation that was either intermittent or, if constant, not associated with dissociated strabismus (Mohney, 2007).

1.5.2 Latent or manifest

Manifest squint or tropia is seen when no fusional control is present. There is obvious deviation of one eye whilst the other eye takes the fixation. On the other hand, in latent squint or phoria fusional control is present with normal ocular alignment and deviation is only seen when binocularity of vision is interrupted by cover-uncover test (Bommireddy et al., 2020).

Nearly all individuals exhibit phoria to some degree. The fusion mechanism holds the condition in check, which is the binocular system's drive to fixate the same object with both eyes via vergence eye movements (motor fusion), resulting in sensory fusion. In people with a large near phoria or weak vergence system, the effort to prevent diplopia during sustained near work may cause significant headache and eye strain (Borsting et al., 2003) (Fig. 1).

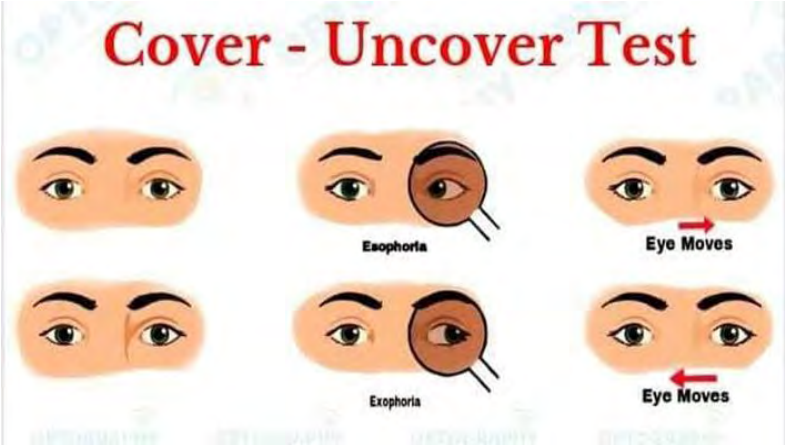


Fig. 1 (A) Heterophoria

Source: Optography.org/heterophoria (Khatun R, 2021)

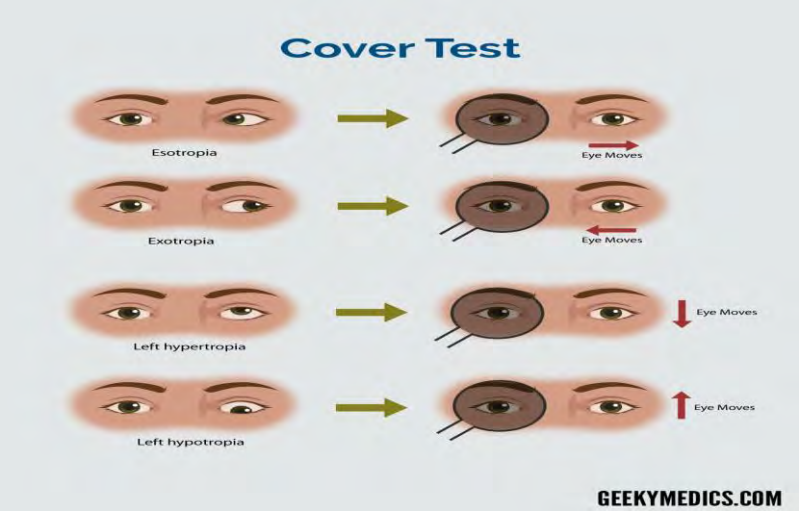


Fig. 1 (B) Heterotropia

Source: https://geekymedics.com/strabismus/

1.5.3 Gaze position

There are two forms of strabismus: comitant and incomitant. If the angle of deviation remains the same in all directions of gaze irrespective of which eye is used for fixation, it is called comitant. It includes the most common types of strabismus, including esotropia, exotropia, hypertropia, monofixation syndrome and micro strabismus (Azam et al., 2019). It occurs in approximately 3% of otherwise healthy, neurologically intact children (Mohney, 2007), however, much higher frequency is observed in children with neurologic disorders like Down syndrome and cerebral palsy (Aslan et al, 2013). Onset is usually between 3 months of age to 6 years (Mohney et al., 2003). Contrarily, incomitant strabismus, also called complex or paralytic strabismus, angle of ocular deviation vary in different directions of gaze (Oystreck and Lyons, 2012), indicating a neurological, orbital, or extra-ocular muscle pathology (Salchow, 2017). Of 12 cranial nerves (CN), three CN (CN 3, CN 4, CN 6), if not innervated properly, are found to be responsible for incomitant strabismus (Bommireddy et al., 2020).

1.5.4 Constant or intermittent

Ocular misalignments that are present all the time are called constant (Bommireddy et al., 2020). If there is an inconsistent expression of misalignment, it is called intermittent. It can be more prominent at the end of the day or with fatigue.

1.5.5 Unilateral or alternating

In a unilateral state, strabismus is limited to one eye only. While in alternating conditions, fixation can be taken by either eye, however, laterality of the strabismus alters.

1.5.6 Direction of deviation

Convergent (esodeviation) (Fig. 1.2) or divergent (exodeviation) (Fig. 1.3) strabismus in relation to the fixing eye are horizontal deviation. They are the most common types of strabismus (Davidson and Quinn, 2011) whereas vertical deviation includes upward (hyper deviation) and downward (hypo deviation) deviation with respect to fixing eye. The magnitude for such deviation can roughly be estimated by Corneal light reflex test. For asymmetrical ocular alignment, a decentered light reflex is an indication of deviation in the opposite direction.

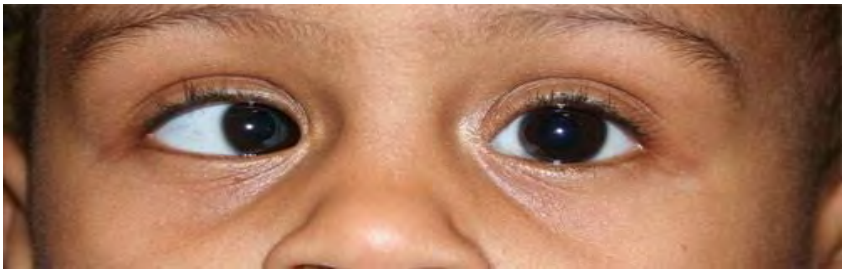


Fig. 2 Esotropia in the right eye

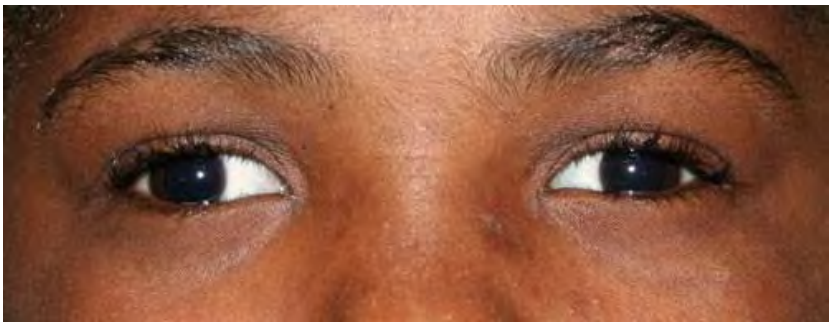


Fig. 3 Exotropia in the right eye

Source: https://aapos.org/glossary/strabismus

1.5.7 In relation to accommodation

Strabismus, more noticeable with accommodative effort and associated with hypermetropia is called accommodative. The use of glasses to correct refractive errors can improve or reduce the condition (Fig. 1.4). If correction of refractive error does not improve angle of deviation it is called non-accommodative. Amy E Greenberg classified accommodative esotropia as those patients with an acquired constant or intermittent deviation that was corrected or reduced 10 pd or more after wearing hyperopic spectacles full-time for at least three weeks whereas partially accommodative esotropia designated those with a residual deviation of 10 pd or more (Greenberg et al., 2007). Acquired nonaccommodative esotropia comprises those children whose deviation developed later than six months of age and is not associated with accommodative effort (Mohney, 2007).

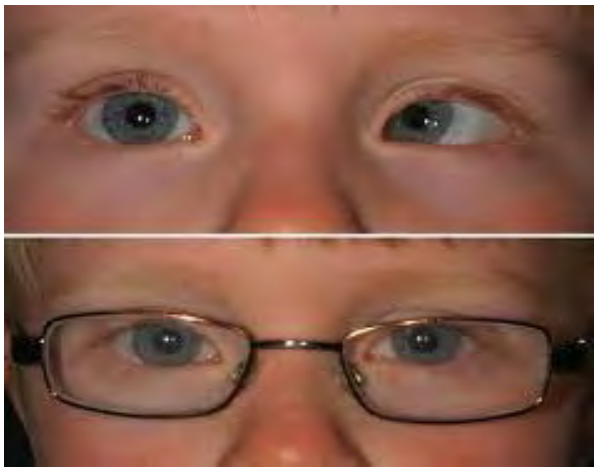


Fig. 4 Comparison of) alignment without (upper) and with correction (lower

Source: Rogers and Longmuir, 2011

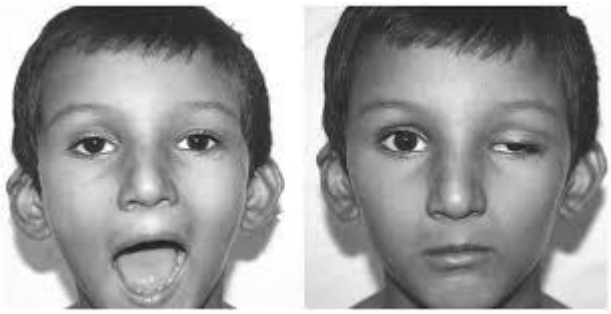
1.5.8 Syndromic strabismus

These forms of strabismus have distinctive misalignment patterns. Most of the time, these Strabismic syndromes are limited to the ocular motility system but can also be a feature of systemic syndromes. Examples Duane syndrome (DS) (Fig. 1.5), Mobius syndrome, Brown syndrome, (CFEOM), monocular elevation deficiency (double elevator palsy) and chronic progressive external ophthalmoplegia. A variety of etiologies exist for the specific entities within this group, which include aplasia of cranial nerves, tendon dysfunction, CNS lesions, intra-uterine anomalous innervation and dysinnervation amongst others (Wright, 2012). These forms are either strictly congenital, strictly acquired, and some can be both.

(A) **(B)** **(C)**

Fig. 5 Duane retraction syndrome, Type 1. Left eye adduction normal **(A)**. Front gaze normal **(B)**. Left eye abduction limited and widening of palpebral fissure **(C)**

Source: Awadein et al., 2021



(A) **(B)**

Fig. 6 Ptosis with Marcus-Gunn jaw wink syndrome. Eye opens when the mouth opens **(A)**. Eye blink when mouth closes **(B)**

Source: Sthapit and Saiju, 2015

Table 1 Classification summary

Disorders of ocular muscles, binocular movement, accommodation, and refraction

ICD-10 #	Major type	Subtype
H50.0	Convergent concomitant strabismus	Esotropia alternating/monocular, except intermittent
H50.1	Divergent concomitant strabismus	Exotropia alternating/monocular, except intermittent
H50.2	Vertical strabismus	• Hypertropia • Hypotropia
H50.3	Intermittent heterotropia	Intermittent: • esotropia • exotropia alternating/monocular
H50.5	Heterophoria	• Alternating hyperphoria • Esophoria • Exophoria
H50.8	Duane syndrome	
H52.0	Hypermetropia	
H52.1	Myopia Excl.: degenerative myopia (H44.2)	
H52.2	Astigmatism	

Source; ICD-10: Version 2019

1.6 Etiology of strabismus

The causes of manifest (tropia) and latent (phoria) misalignment of the visual axes are not completely understood yet. But it is likely that both genetic and environmental factors contribute. There are various causes of strabismus in children, some of which can be sinister and are potentially eye or life threatening. Refractive errors are common amongst Asian population and are significant risk factor in causing strabismus. Myopic children had a 5.23-fold high risk of developing exotropia as compared to those without significant ametropia. In addition, a very strong association exists between hyperopia and esotropia in a dose-related effect manner (Tang, et al., 2016). Various recognized risk factors for primary strabismus include prematurity (gestational age, <36 weeks), parental strabismus history (Chen et al., 2021) low birth weight, pregnancy or delivery complications, assisted delivery and neonatal ill health during first week of life or admission to NICU (Linghamet al 2020) can increase the risk of isolated strabismus. Several risk factors for secondary strabismus, usually associated with neurodevelopmental or neurological disorders are maternal smoking during pregnancy, low birth weight for gestational age and sex, maternal ill health, and perinatal and neonatal illnesses (Bommireddy et al., 2020), intracranial tumors, head trauma, infection, and disorders of the immune system (O'Dowd, 2013).

1.7 Mechanism of strabismus development

There are several tissues or systems involved in the mechanism of the development of strabismus. Five components with a potential role in the determination of the position of eye include extraocular muscles (EOM), cranial nerves (CN

3=Oculomotor nerve, CN 4=Trochlear nerve, CN 6=Abducens nerve) orbital connective tissues, fusion centers in the midbrain and hindbrain and visual cortex (Demer, 2010). Malfunction of either of these components can lead to acquired or congenital strabismus. There are six EOMs that regulate eye movements in various directions. These include two oblique and four recti muscles. Moreover, abnormality in the optical input like weak EOM hinders the process of binocular fusion and may cause squint. Motor nerves that are hypoplastic or are not routed properly to the EOMs may cause congenital cranial dysinnervation disorders (CCDDs), often called congenital fibrosis of the extraocular muscles (CFEOM) (Jolene et al., 2021). A cyclic pathway of EOM innervation is shown in figure 7.

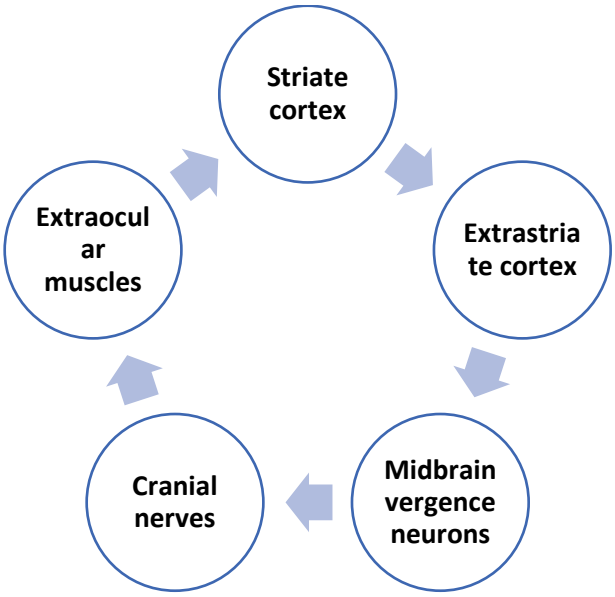


Fig. 7 Visual-Motor pathway

Source: Ye et al., 2014

1.8 Inheritance patterns of strabismus

The hereditary nature of strabismus was recognized very early. Mendelian inheritance is shown by several syndromic forms. However, such inheritance patterns are not very common among families displaying isolated strabismus (Ye et al., 2020). In such cases, a multifactorial or co-dominant inheritance pattern appears to be the most reasonable explanation. A multifactorial comprise both genetic and exogenous factors. Various family studies showed contrasting results about mode of inheritance for non-syndromic starabismus (Ferreria et al., 2002). Furthermore, X linked inheritance pattern evaluated by few studies, is not acceptable for strabismus due to significant male to male transmission and almost equally affected male and female (Ferreria et al., 2002). The mode of comitant strabismus inheritance may be autosomal dominant or autosomal recessive (Ye et al., 2014).

1.8.1 Heritability and Genetic analysis

Transmission of strabismus from parents to child was first observed by Hippocrates (Hippocrates, 1886). The heritability of concomitant strabismus is also supported by Twin studies, which reveal a high concordance rate among monozygotic twins i.e., 73% to 82% and 35% to 47% among dizygotic twins (Matsuo et al., 2002). Despite the long history, the genetic factors in the various forms of strabismus and the molecular mechanism that underlies the disease is obscured. In families with isolated strabismus, genetic loci on chromosomes 4, 6, 7, 12, 16 and 19 have been identified, but no causal gene has been identified in these regions (Ye et al., 2020). However, 11 genes (*PHOX2A, ROBO3, KIF21A, SALL1, TUBB3, HOXB1, SALL4, CHN1, HOXA1,*

TUBB2B, MAFB), of which six encode transcription factors (underlined), have been identified for a subgroup of strabismus associated with congenital cranial dysinnervation disorders (Ye XC et al., 2014).

GWAS of common strabismus form reported three Mendelian loci 7p22.1, 4q28.3 and 7q31.2 (Fujiwara et al., 2003; Shaaban et al., 2009). A recent study identified a *NPLOC4–TSPAN10–PDE6G* gene cluster as being associated with an increased risk of strabismus (Plotnikov et al., 2019). Gong et al., found a nonsynonymous mutation in paired box 3 (*PAX3*) gene in the two affected individuals with strabismus (Gong et al 2017). Additional loci for esotropia and exotropia have also been identified at 8q24.21 and 14q21.3 locus, respectively (Shaaban et al., 2009). A summary of genes and loci is given in Table 2.

Table 2 Strabismus susceptibility and risk loci

(A) Comitant strabismus genetics

Classification	Disorder	Inheritance	OMIM #	Map location	Locus	PMID
Susceptibility to strabismus		AR and AD	185100	7p22.1	STBMS1	14519848 (Parikh et al., 2003; Rice et al., 2009)
Susceptibility to strabismus		AD		4q28.3		18824738 (Shaaban et al., 2009)
Susceptibility to strabismus		AR		7q31.2		18824738 Shaaban et al., 2009)
Infantile esotropia and esotropic Duane retraction syndrome		Recessive		16p13.12-p12.3		21541264 (Khan et al., 2011)
Risk allele	Esotropia			21q22.2		
				17q25		
Risk allele	Strabismus					
Comitant strabismus		Imprinting		6q26		19597570 (Shaaban et al., 2009)
Comitant strabismus		Imprinting		12q24.32		19597570 (Shaaban et al., 2009)
Comitant strabismus		Imprinting		19q13.11		19597570 (Shaaban et al., 2009)

(B) Incomitant strabismus genetics

Classification	**Disorder**	**Gene or map location**	**Inheritance**	**OMIM #**
Congenital cranial dysinnervation disorders	CFEOM1	*KIF21A*	AD or de novo	135700
	CFEOM2	*PHOX2A*	AR	602078
	CFEOM3	*TUBB3*	AD or de novo	600638
Duane syndrome – isolated	DURS1	8q13	De novo	126800
	DURS2	*CHN1*	AD	604356
	DURS3	*MAFB*	AD or de novo	617041
Duane syndrome with associated anomalies	Duane-radial ray	*SALL4*	AD	607323

AD=Autosomal dominant, AR=Autosomal recessive

Source: Whitman and Engle, 2022; Ye XC et al., 2014

1.9 Consanguinity and strabismus

Consanguineous marriages can cause those birth defects which have genetic basis and thus can be inherited (Stoll et al., 2005). It is a relationship between two biologically related individuals who share at least one common progenitor (Tadmouri, et al 2009). There is a significant correlation between inheritance and strabismus. There are studies that have suggested a greater frequency of horizontal deviation amongst parental cousin marriage (Fujiwara et al., 2003). For Hypermetropia associated with esotropia, the rate is significantly higher among first degree relatives (Jayaraj, 2022). In addition, patients with non-accommodative acquired ET had the highest mean of inbreeding coefficient (α) (Bagheri et al., 2015). These results show that recessive form of inheritance plays an important role in the etiology of comitant strabismus.

1.10 Genetic counseling

Genetic counseling is defined as the process of assisting people to acknowledge and adapt to the medical, psychological, and familial implications of genetic contributions to disease (Resta et al., 2006). A useful patient reported outcome (PRO) in genetic counseling is empowerment, that enables a person from a family afflicted by a genetic condition to feel that they have some control over and hope for the future (Allister et al., 2011). For infantile esotropia, accommodative esotropia, and Duane syndrome, identification of family members at risk and the genetic counseling would alert parents to watch for signs of strabismus or to have their infant examined and treated early for strabismus, possibly preventing amblyopia, and promoting binocular

vision (Paul and Hardage, 1994). Identification of correct inheritance pattern for each strabismus type will help enabling the use of genetic counseling.

1.11 Management and treatment of strabismus

During the past few decades, great advancements in the management, treatment, diagnosis, and prevention of strabismus have been made. The management of strabismus depends on the cause. Isolated strabismus can be treated by refractive error correction with spectacles or contact lenses, and amblyopia therapy with patching or use of atropine. Some other unconventional interventions include the use of prisms in glasses, behavioral eye exercises and the use of intramuscular botulinum A neurotoxin (Modi and Jones, 2008; Kushner, 2011). Surgical correction of ocular alignment is a well-tolerated procedure, with minimal post-operative discomfort is commonly recommended. Primary goals are to prevent amblyopia and achieve binocular vision with functional depth perception (stereopsis), and secondarily to achieve better cosmesis (Astle et al., 2011). Yilmaz et al., studied the effect of prism cover test on the post-operative outcomes in patients of strabismus. They found that the surgical outcomes with and without prism cover test led to a successful motor alignment in 80% of cases (Yilmaz et al., 2015). Hatt and colleagues studied the importance of deviation measurement in patients of intermittent exotropia, and they urged upon the repeatability of prism cover test measurement to get an accurate measurement and detect any significant change in deviation (Hatt et al., 2012). Kamal et al compared the adjustable versus non-adjustable sutures in pediatric horizontal strabismus surgery. While ascertaining no significant difference in the manipulation of two techniques, they

concluded that adjustable suture technique was associated with better success rates (Kamal et al., 2016). A case series about the use of botulinum toxin in patients of alternate strabismus who have undergone at least one-month trial of prismatic correction for phoric angle found botulinum toxin effective (Georg, 2018). Saunte et al., noticed botulinum toxin action in patients of intermittent exotropia and found a significant reduction in the deviation and an improvement in the reading symptoms (Saunte et al., 2015). Most of the surgeons use these treatments in combination.

1.12 Study objectives

The aims of conducting this research include the following:

- To recognize the clinical characteristics, phenotypic variations of strabismus types and deduce its most prevalent forms for the best preservation of visual function.
- To elucidate the prevalence of the strabismus and potential risk factors to determine the burden of disease in Rawalpindi and nearby areas.
- To analyze the relative importance of genetic and environmental factors.
- To observe the role of parental consanguineous marriage and family history in causing strabismus.
- To observe and compare anomaly types with sociodemographic variables.

Chapter 2

Materials And Method

2.1 Study area and population

2.1.1 Rawalpindi district

Rawalpindi is a city in the Punjab province of Pakistan, Its existence dates to 18th century. The city lies on the Potohar Plateau 9 miles (14 km) southwest of Islamabad, the national capital. Britain's army raised the city status from a small town to the third largest city in Punjab by 1921 (Mazumder and Rajit, 2003). Rawalpindi features a humid subtropical climate (Climate: Rawalpindi). The weather conditions fluctuate due to the proximity of the city to the foothills of Himalayas. Neighboring cities include Gujar khan, Muree, Attock, Abbottabad, Haripur, and Islamabad. The city covers an area of 5285 km^2. As per the record of Pakistan Bureau of Statistics 2017, rural population predominates over urban population and female population exceeds male population (Pakistan Bureau of Statistics, 2017).

Healthcare facilities are adequately established in the city both in public and private sectors. There are certain well reputed Ophthalmology hospitals and clinics that offer their multispecialty ophthalmic practice both for rich and poor.

Demographic variables of Rawalpindi are listed in Table 3.

Table 3 Demographic variables of Rawalpindi district

Variable	Estimate
Area	22,254km^2
Population-2017	10,006,624
25Population-1998	6,659,528
Urban Population	4,134,521
Rural Population	5,872,103
Male	4,999,414
Female	5,005,714
Sex Ratio	99.87%
Literacy Ratio (10+ years)	64.01%
Male	71.17%
Female	56.67%
Population Density	449.66 per km^2
Average Household Size	5.94
Average Annual Growth Rate (1998-2017)	2.16%
Tehsils	7

Source: Pakistan Bureau of Statistics (2017)

2.1.2 Al-Shifa Trust Eye Hospital, Rawalpindi

Al-Shifa Trust was established in 1985 by Lt Gen (R) Jahandad Khan and started functioning in 1991. The hospital is located on Jhelum Road, near Ayub Park, Rawalpindi. It is a charitable organization that aims for the prevention and control of blindness by providing standard and sustainable eye care services. Hospital based tertiary eye care services constitute one of its essential components. It has specialized departments in various fields of eye like oncology,

optometry, diagnostics, low vision, retina. There are three types of outpatient departments (OPD) in the setting, zakat, general and private (Malik et al., 2019). A summary of patients visiting the hospital is given in Table 4.

Table 4 summary of patients visited the hospital during 2021 –2022

Variables	**Annual influx of patients**
Total OPDs	1,034,093
Total Pediatric Patients	94,524
Total Pediatric Surgeries	5,811

Source: Al-Shifa Trust Annual Report FY 21-22

2.2 Ethical and consent approval

The study protocol was approved by the Institutional Review Board of Quaid I Azam University, Islamabad in September 2023. It was also approved by the Office of the Clinical and Academic Director of the Al Shifa Eye Hospital, Rawalpindi. A memorandum of collaboration (MOU) was signed by both institutes. The study protocol, its aims and objectives were fully demonstrated to each eligible patient and their family. An informed consent was obtained from the parents or legal guardians of the study participants. They were assured of the confidentiality of their personal information and their right to refuse or withdraw at any stage was respected.

2.3 Study design and duration

This was a hospital-based cross-sectional study conducted from October 2022 to March 2023 in the Department of Ophthalmology & Optometry, Al Shifa Trust Eye Hospital, Rawalpindi, Pakistan. Furthermore, stratified sampling technique was used to collect the data.

2.4 Inclusion/Exclusion criteria

Inclusion criteria was patients up to 20 years of age irrespective of their gender, caste, or language, congenital or spontaneous onset of the condition and no history of squint surgery. All patients who complained about onset after traumatic injury or eye surgery and those who refused to give consent were excluded from the study. Patients with pseudo strabismus or latent squint and microtropias (>10pd) were also kept out. In addition, affected children accompanied by their distant relatives were not part of this study.

2.5 Data collection and proforma design

Patients of both genders under the age 20 years, meeting the inclusion criteria were included in the study. Sociodemographic and clinical findings were recorded on a predesigned comprehensive proforma. Proformas were validated for content and face validity by circulating them to subject experts. The first section of proforma was devoted to demographic details of the index such as name, age, origin (Rural/Urban), language, caste, and area of residence. Information

regarding the eye condition and systemic functions was noted in the next sections. Parental age, family history of disease and consanguinity information constituted the last part of proforma.

A detailed three generation pedigree was constructed for all participants according to the information provided by their parents/guardians. Photographs clearly depicting the phenotype were also taken and preserved.

2.6 Identification and classification of strabismus types

All the subjects were keenly evaluated under the supervision of expert optometrist. A crucial step in the assessment of strabismus that helps to formulate a differential diagnosis is history taking. This included information about onset of the condition (sudden or gradual), associated symptoms, past medical history, past ocular history, and family history (Bommireddy at al., 2020). Tools used for examination were ETDRS (chart to access visual acuity), occluder and Snellen chart for distance target and picture stick for near target, to perform cover test (Malik et al., 2019). The visual acuity of every patient was checked both for near and distance and with and without spectacles. Orthoptic assessment included Cover test, Hirschberg's test, krimsky, Prism Cover test (PCT) whenever possible, examination of extra ocular muscles and fundus. Suppression of eye was further confirmed by worth 4 dot test. The anterior segment of eye was examined by slit lamp. Cyclopentolate 0.5% -1% eye drops were used for cycloplegic refraction of each patient. Myopia, hyperopia, and astigmatism refractive errors were defined when the refractive error was >-0.5 diopter sphere (DS), >+0.50 DS and >1.0 DS, respectively. Emmetropia was defined as optically normal eye with refractive error -0.5 to +0.5DS (Bashir et al., 2022). Based on the

clinical presentation of both eyes, strabismus types were identified. In the presence of other systemic abnormalities, classification of isolated and syndromic was applied. Summary of subtypes of strabismus is presented in Fig. 8.

2.7 Analysis of data

All the information of each subject collected during the survey on the structured proforma was keenly entered into MS Excel Sheet and scrutinized and reassessed by two other persons. Data were analyzed and compared with respect to different variables and association between anomaly type, gender, risk factors was observed. Furthermore, statistical analysis for demographic characteristics, family history of disease, parental consanguinity and delivery complication was performed. Chi-square test ($p< 0.05$) were applied to check the distribution of different variables using GraphPad Prism (version 5.00).

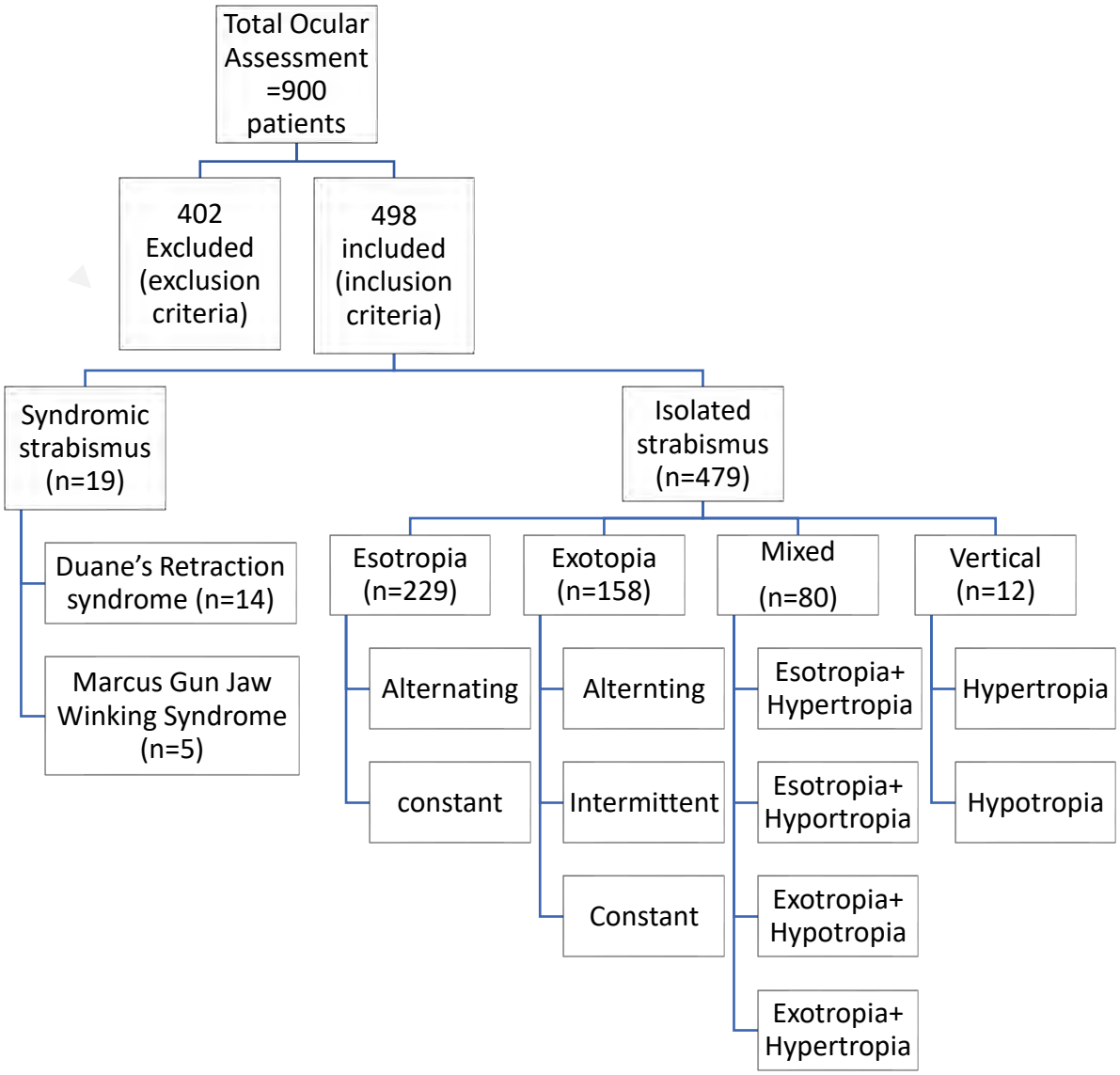


Fig. 8 A flow chart presenting the summary of subtypes of strabismus

Chapter 3
Results

A total of 498 subjects with manifest strabismus were recruited during the study from a tertiary care setting in Rawalpindi.

3.1 Demographic attributes of recruited subjects

All the participants were categorized based on their demographic characteristics, which included age, gender, origin, family type, ethnicity, and language.

The distribution of male and female, among all the studied subjects was 52.5% (n=260) and 47.8% (n=238), respectively (Table 5). In addition, there was uneven distribution of subjects from rural and urban origin. 51% of the subjects were of rural origin and 49% were from urban areas. The regional distribution of these subjects assumes the order of Punjab, excluding Rawalpindi (n=196, 39%), Rawalpindi (n=160, 32%), KPK (n=103, 21%), Kashmir (n=32, 6%), Gilgit Baltistan (n=4, 1%) and Baluchistan (n=3, 1%).

With respect to the age of the subjects, five groups were established. i.e., Up to 3, >3-6, >6-9, >9-12, >12 years. Age group >3-6 years had the highest representation 37% (n=184) of subjects, followed by >6-9 years with 23% (n=112) index cases. The highest age group, >12 years consisted of least number of patients (9%).

Only two classes of family type were recognized, i.e., nuclear and extended. The nuclear family type was defined as a mother and father of the subject and their offspring's. The extended family type is expansion of nuclear type by grandparents and/or other relatives. There was remarkable prevalence of subjects from Extended family type, 61% (n=273), as shown in Table 5. The Nuclear family type comprised 39% (n=172) patients only.

Different groups of subjects were established based on caste systems like Awaan, Rajpoot, Pathan, Mughal, Abbasi, Jut, and Gujar. Awaan were predominant among studied

subjects with 15% (n=74), representation followed by Rajpoot (n=58), Pathan (n=43), Mughal (n=23), Abbasi (n=18), Jut (n=17), Gujar (n=17) and others (less common castes).

There was diversity of languages among subjects. Majority (35%) were Punjabi speakers. The two other predominant groups include Urdu (31%) and Pushto (19%). The rest of languages were included in others group that comprised 16% (Table 5).

Table 5 Demographic distribution of subjects according to gender

Demographic variables	Gender		Total	Percentage
	Male	Female		
Origin (n=498)				
Rural	128	126	254	51
Urban	132	112	244	49
χ^2=0.68; df=1; p=0.408, non-significant				
Province				
Punjab	103	93	196	39
Rawalpindi	84	76	160	32
KPK	52	51	103	21
Kashmir	16	16	32	6
Gilgit Baltistan	3	1	4	1
Baluchistan	2	1	3	1
χ^2=1.28; df=5; p=0.937, non-significant				
Age range (years				
Up to 3	51	51	102	21
>3-6	95	89	184	37
>6-9	62	50	112	23
>9-12	33	23	56	11
> 12	19	25	44	9
χ2=3.12; df=4; p=0.538, non-significant				
Family type (n=445)				
Nuclear	89	83	172	39
Extended	147	126	273	61
χ^2=0.19; df=1; p=0.665, non-significant				
Paternal age ranges (n=468)				
Up to 25	31	31	62	13
>25-30	68	61	129	28
>30-35	76	66	142	30
>35-40	46	46	92	20
>40	23	20	43	9
χ^2=0.44; df=4; p=0.979, non-significant				

Maternal age ranges (n=467)				
Up to 20	18	20	38	8
>20-25	70	67	137	29
>25-30	80	71	151	32
>30-35	56	39	95	20
>35	20	26	46	10
χ^2=3.60; df=4; p=0.464, non-significant				
Paternal education				
Illiterate	33	37	70	14
Matric	125	111	236	47
Graduate	77	64	141	28
Higher level	25	26	51	10
χ^2=1.31; df=3; p=0.727, non-significant				
Maternal education				
Illiterate	64	58	122	25
Matric	100	84	184	37
Graduate	66	59	125	25
Higher level	30	37	67	14
χ^2=1.84; df=3; p=0.606, non-significant				
Caste system				
Awaan	36	38	74	15
Rajpoot	34	24	58	12
Pathan	29	14	43	9
Mughal	12	11	23	5
Abbasi	3	15	18	4
Jut	7	10	17	3
Gujar	11	6	17	3
Others	128	120	248	50
χ^2=16.37; df=7; p=0.022, **significant***				
Language				
Punjabi	91	82	173	35
Urdu	80	74	154	40
Pushto	53	40	93	19
Others	36	42	78	16
χ^2=2.01;df=3;p=0.5, non-significant				

3.2 Frequency of strabismus types in relation with gender

The present study showed that overall male subjects were more frequent compared to the female. But when these subjects are classified based on strabismus types, it is found that male participants outnumbered only for esotropia (n=130) as shown in Table 6. For all other strabismus types, female proportion is higher. However, the overall distribution of strabismus types between the two genders is statistically non-significant. While comparing the combined proportion of strabismus types with each other, esotropia constitute 46% (n=229) and lies at the top, followed by exotropia 32% (n=158), mixed type 16% (n=80) that includes subjects with at least two types of squint conditions simultaneously. For example, esotropia+hypertopia, esotropia+hypotropia, exotropia+hypertropia and exotropia+hypotropia, syndromic type 4% (n=19) that embrace Duane's retraction syndrome and Marcus-Gunn jaw wink syndrome (MGJW). The vertical squint type comprised both hypotropia and hypertropia and contributed least number 2% (n=12) to the overall proportion.

Table 6 Distribution of strabismus types with respect to gender

Anomaly type	**Gender**		**Total**	**Percentage**
	Male	**Female**		
Esotropia	131	98	229	46
Exotropia	78	80	158	32
Mixed	38	42	80	16
Vertical	5	7	12	2
Syndromic	8	11	19	4
Sum	**260**	**238**	**498**	**100**
χ^2=4.83; df=4; p=0.306, non-significant				

3.2.1 Distribution pattern of strabismus types with respect to gender

In this study, five subtypes of strabismus i.e., Esotropia, Exotropia, Vertical, Mixed and Syndromic were observed. Subjects included both male and female. This bar chart illustrates the relative distribution of strabismus types between the two sexes. Esotropia shows preponderance of all other types and constitute more males (n=131) than females (n=98). For all other anomaly types, male and female subjects' contribution is relatively equal. The chart shows a steep gradient of number of patients from esotropia to exotropia, mixed and vertical type. The proportion of syndromic cases (n=19) is slightly greater than patients with vertical strabismus (n=12) (Fig. 9).

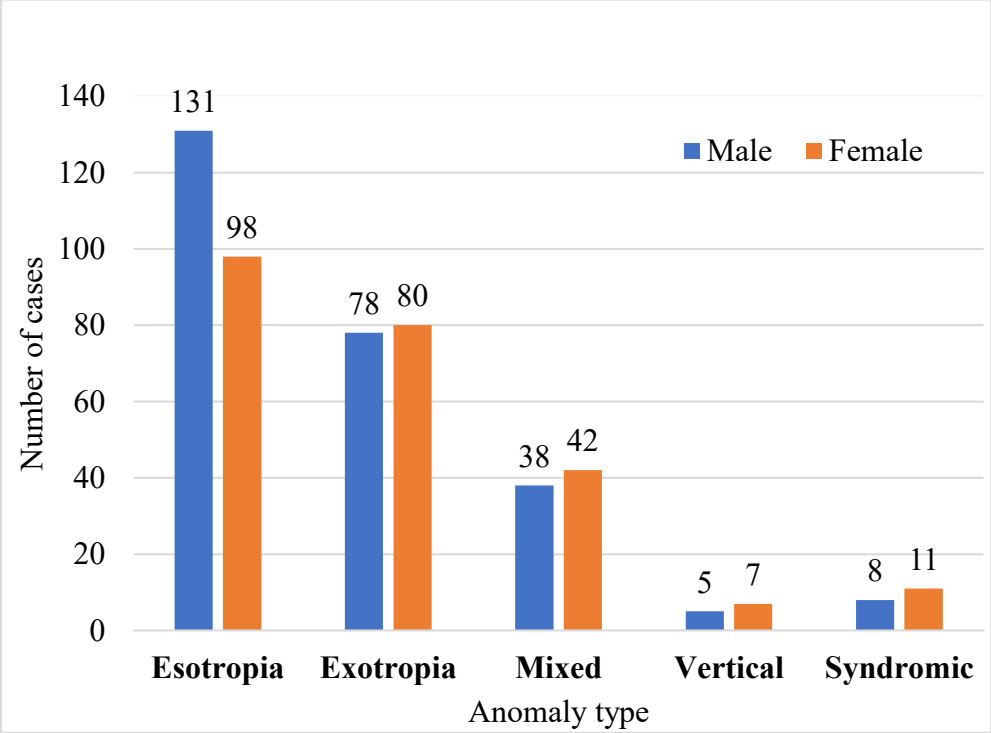


Fig. 9 Strabismus types vs gender

3.3 Demographic variables and disease distribution

The two most prevalent subtypes of strabismus encountered in this study were esotropia and exotropia with overall prevalence 46% and 32%, respectively. They were compared with various sociodemographic variables and their distribution was analyzed using a Chi-square test. The results show that the difference in distribution for both subtypes is non-significant and are shown in Table 7.

Table 7 Association of disease with sociodemographic factors

Sociodemographic variables	Anomaly type		Total
	Esotropia	Exotropia	
Origin			
Rural	123	70	193
Urban	106	88	194
$\chi 2$=3.31, df=1; p=0.069, non-significant			
Family type			
Nuclear	74	55	129
Extended	129	90	219
$\chi 2$=0.08, df=1; p=0.778, non-significant			
Maternal age ranges (n=467)			
Up to 20	19	9	28
>20-25	65	47	112
>25-30	66	48	114
>30-35	45	32	77
>35	18	11	29
$\chi 2$=1.13, df 4; P=0.810, non-significant			
Maternal education			
Illiterate	61	31	92
Matric	83	61	144
Graduate	49	47	96
Higher level	36	18	54
$\chi 2$=5.96, df=3; p=0.113, non-significant			

3.4.1 Strabismus prevalence rate by age of onset

Manifest strabismus was seen in 498 cases. The children with eye syndromes, infantile esotropia and/or family history of the condition show onset before 1 years of age. Certain types of strabismus were noted to occur after 1 year, instantaneously and spontaneously. Although isolated strabismus can occur at any age, all strabismus syndromes were congenital. Our data shows that age up to 12 months to 48 months is critical period for developing horizontal strabismus and very few cases are seen after this age. The difference in the distribution of strabismus types with respect to their age of onset is found significant in Table 8. Thus, strabismus is found as a disease of early childhood.

Table 8 Strabismus types and age of onset

Age ranges (months)	**Esotropia**	**Exotropia**	**Mixed**	**Vertical**	**Syndromic**	**Total**
Up to 12	139	103	61	7	19	329
>12-24	18	7	7	1	0	33
>24-36	32	20	5	1	0	58
>36-48	16	9	5	3	0	33
>48-60	9	12	1	0	0	22
>60	15	7	1	0	0	23
Sum	**229**	**158**	**80**	**12**	**19**	**498**
$\chi 2$=34.58, df=20; P=0.023; **Significant***						

3.4.2 Strabismus prevalence rate by age of diagnosis

Table 9 shows the age of participants at the time of data collection. We encountered patients of various ages. Our data shows maximum number of patients for almost all strabismus types lie in the range of >3-6 years of age. Patients with two or more types of squint in one eye (mixed type) are noted to be diagnosed later in life. This might be attributed to the complexity of eye condition. The subjects are widely distributed among various age groups and this distribution is found highly significant.

Table 9 Strabismus types and subjects' age of diagnosis

Age groups (years)	**Esotropia**	**Exotropia**	**Vertical**	**Mixed**	**Syndromic**	**Total**
Up to 3	49	38	1	8	6	102
>3-6	93	56	2	28	5	184
>6-9	54	34	3	18	3	112
>9-12	19	15	4	13	5	56
> 12	14	15	2	13	0	44
Sum	**229**	**158**	**12**	**80**	**19**	**498**
$\chi 2$=33.42, df=16; p=0.007; **Highly significant****						

3.4.2.1 Distribution of subjects with respect to age of diagnosis

The current ages of all the included subjects were distributed into five consistent age ranges. The bar chart, plotted between the age ranges of study participants and their gender, depicts that larger number of male and female patients fall in the range of >3-6. The two groups above and below this range constitute almost equal proportions. However, higher age ranges account for the lesser number of patients of both genders (Fig. 10).

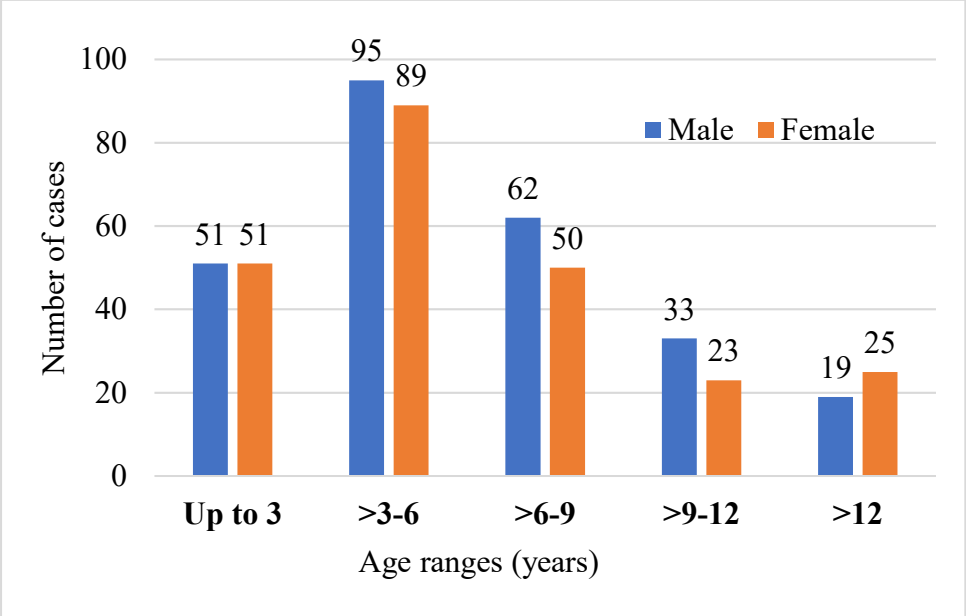


Fig. 10 Strabismus types vs age of diagnosis

3.5.1 Laterality of deviated eye in relation to strabismus types

Strabismus is a function of eye movement and alignment. The condition might be limited to only one eye (constant), or it may alternate from one eye to the other (alternating). Accommodative esotropia happens when one or both eyes cross to focus on the object. Our data shows that various strabismus forms can affect any one eye. While comparing the laterality, left eye is more likely to be affected by esotropia (n=58) than the right eye (n=41). On the other hand, the right eye is more prone to be affected by almost all other squint types. The relative proportion for exotropia, mixed strabismus, syndromic and vertical types in left and right eye were found to be 3%, 5%, 2%, 1% and 4%, 11%, 1% and 1%, respectively. Detail is shown in Table 10

Table 10 Laterality of deviated eye in strabismus subtypes

Anomaly type	Bilateral		Left eye only		Right eye only			
	No. of cases	%age	No. of cases	%age	No. of cases	%age	Total	%age
Esotropia	18	4	58	12	41	8	117	23
Alternating Esotropia	112	23					112	23
Alternating Exotropia	65	13					65	13
Intermittent exotropia	58	12					58	12
Exotropia			13	3	22	4	35	8
Esotropia accompanied with hypertropia			7	1	18	4	25	5
Exotropia accompanied with hypertropia			6	1	18	4	24	5
Exotropia accompanied with hypotropia			7	1	9	2	16	3
Esotropia accompanied with Hypotropia			4	1	11	2	15	3
Duane retraction syndrome			9	2	5	1	14	3
Marcus gun jaw wink syndrome			3	1	2	1	5	1
Vertical			5	1	7	1	12	1
Sum	**253**	**51**	**112**	**22**	**133**	**27**	**498**	**100**

3.5.2 Laterality of deviated eye in relation to gender

This table show comparison of affected/deviated eye among male and female subjects. Although there are no remarkable differences of affected eye among the two sexes, male proportion slightly exceeds in all cases which might be attributed to their overall higher number. Thus, male and female are equally likely to have either right eye, left eye or both eyes affected. Table 11 shows the difference in their relative distribution is statistically non-significant.

Table 1 Affected eye and gender of subject

Affected eye	**Gender**		**Total**	**%age**
	Male	**Female**		
Bilateral	129	124	253	51
Right only	73	60	133	27
Left only	58	54	112	23
Sum	**260**	**238**	**498**	**100**
$\chi 2=0.54$, df=2; p=0.763; non-significant				

3.5.2.1 Distribution pattern of affected eye between male and female subjects

The figure chart 11 delineate information about the distribution of affected eye between male and female subjects. There is balanced distribution for both genders for each affected eye however, their combined proportion descends in the order of bilateral (51%), right (27%) and left (23%) affected eye.

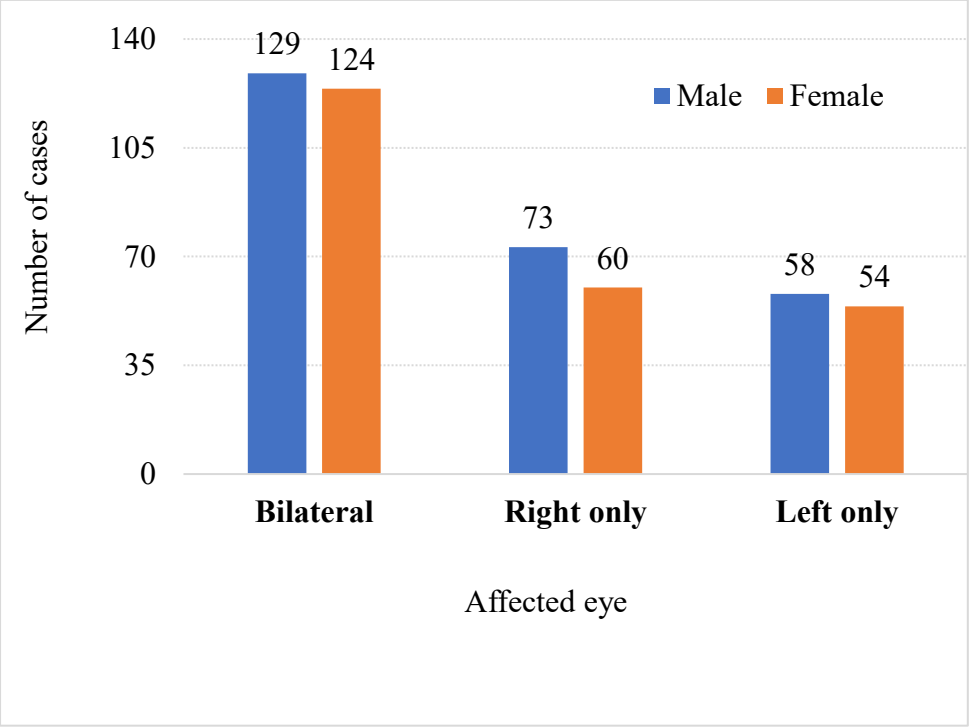


Fig. 11 Affected eye vs gender

3.6 Relationship between dominant hand and dominant eye

It is important to know about the dominant eye to perform activities that require focus on target. The non amblyopic eye, actively taking fixation is called dominant eye (Perdziak et al., 2016). The fact that Right and Left hand are not equally efficient, in a similar way ocular dominancy may exist. In the present study, hand dominance was determined by the writing method. According to our observation, maximum subjects 46% (n=53) with right dominant hand had right eye dominant. There were 7% (n=8) subjects who showed left handedness and possessed left dominant eye. An interesting phenomenon found in this area of study was that there were appreciably high number of subjects 42% (n=49) with right dominant hand and left eye dominant. Furthermore, there were few cases, 5% (n=6) of left hand and right eye dominant (Table 12).

Table 12 Dominant hand vs dominant eye

Dominant hand/ Dominant eye	**Number of cases**	**%age**
Right hand and right eye	53	46
Right hand and left eye	49	42
Left hand and left eye	8	7
Left hand and right eye	6	5
Sum	**116**	**100**

3.7 Frequency of weak extraocular muscles

There are six types of extraocular muscles identified to have role in controlling eye movements in up, down, right, left, and oblique gazes. Optimum strength of these muscles is crucial for proper alignment of both eyes during focus on the target object. We observed frequency of these weak muscles by H-Test and Bielschowsky three-step head tilt test: n=52 (42%) for right inferior oblique (RIO), n=49 (40%) for left inferior oblique (LIO), n=5 (4%) for right superior oblique (RSO), n=4 (3.3%) for left superior oblique (LSO), n=2 (2%) for right inferior rectus (RIR), and left inferior rectus (LIR), n=6 (5%) for right superior rectus (RSR) and n=3 (2%) for left superior rectus (LSR). 88 (72%) patients had inferior oblique over action (IOOA). Of these, 54 patients had unilateral IOOA and 17 had bilateral IOOA. The overall higher frequency of EOM shows that their function is underrated in most strabismic patients. The results are recorded in Table 13.

Table 13 Frequency of weak muscles compared to affected eye (n=123)

Extra-ocular muscles	**Right eye**		**Left eye**		**Total**	
	No.	%age	No.	%age	No.	%age
Inferior oblique	52	42	49	40	101	82
Superior oblique	5	4	4	3	9	7
Inferior rectus	2	2	2	2	4	3
Superior rectus	6	5	3	2	9	7
Sum	**65**	**52.8**	**58**	**47.2**	**123**	**100**

3.7.1 Frequency of weak extraocular muscles in the right and left eye

Extraocular muscles were not functioning at their optimum strength in most of strabismus patients. A comparison of frequency of these muscles in the two eyes has shown that right eye muscles were weak in slightly more cases. In addition, Inferior oblique muscle action was most affected in both eyes. There is an abrupt fall of frequency from Inferior oblique to other types of muscles as shown in Fig. 12.

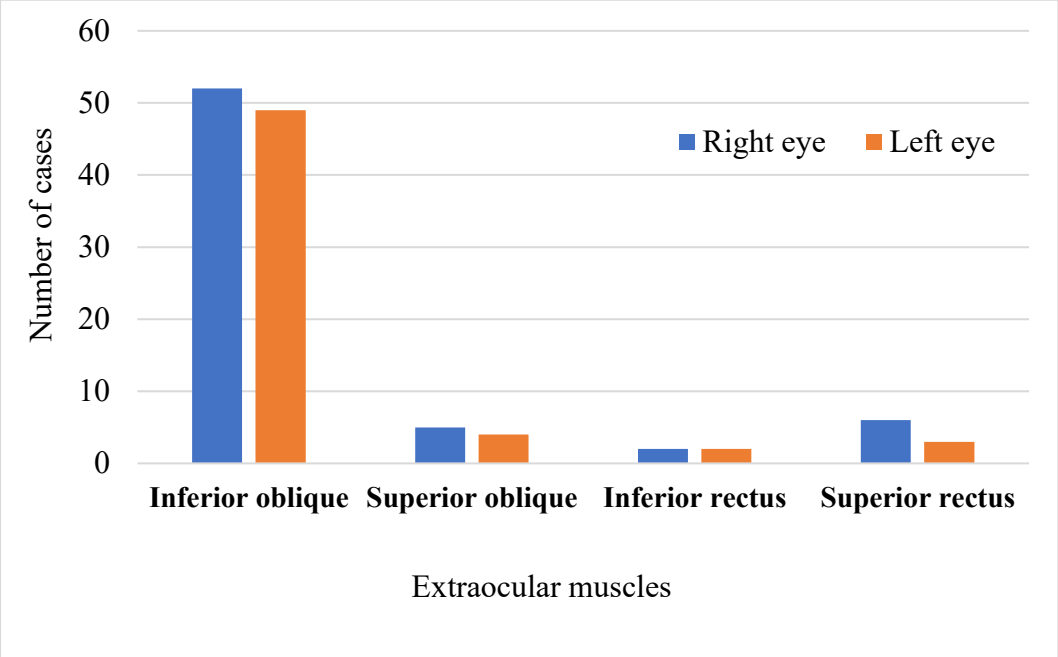


Fig. 12 Frequency of extraocular muscles vs affected eye

3.8.1 Distribution of refractive error among strabismus types

Out of total 498 cases with strabismus, cycloplegic refraction was performed for 450 cases and assessed using tropicamide and cyclopentolate given 5 minutes apart. Study subjects were distributed into four groups based on absence or presence of threshold refractive error (RE) and type of RE. These groups include Astigmatism, Hypermetropia, Emmetropia and Myopia. The refractive error might be present in both eyes or only one eye and may result in amblyopic strabismus. In our study, the highest prevalence (n=109, 24%) of astigmatism associated with esotropia was observed. Hypermetropia (n=94, 21%) was the second most common RE which is also associated with esotropia. A compelling finding in this area was that there were no cases (n=0) of vertical squint with myopia. In addition, among all refractive error types, myopia had the least prevalence. Details are shown in Table 14.

Table 14 Distribution of refractive error among strabismus subtypes (n=450)

Refractive error	**Esotropia**	**Exotropia**	**Vertical**	**Mixed**	**Total**	**%age**
Astigmatism	109 (24%)	82 (18%)	3 (1%)	41(10%)	235	52
Hypermetropia	94 (21%)	5 (1%)	2 (1%)	17 (4%)	118	26
Emmetrope	10(2%)	48(11%)	5 (1%)	14 (3%)	77	17
Myopia	9 (2%)	7(2%)	0	4 (10%)	20	4
Sum	**222**	**142**	**10**	**76**	**450**	**100**

$\chi 2=96.38$, df=12; $p<0.0001$; **Significant*****

3.8.2 Distribution of refractive error among male and female subjects

Table 15 presents analogy of refractive error types between male and female indices. Our data shows high prevalence of refractive error among male subjects nearly in all cases. Majority of male, 26% (n=119) and female, 26% (n=117) subjects are affected by astigmatism. Hypermetropia was the second most common type of refractive error, with male contributed more than females, 16% and 10%, respectively. Myopia was found to be the least common type of refractive error. Only about 4% of subjects suffered from myopia. The difference in distribution is statistically non-significant.

Table 15 Association of gender with refractive error

Gender	No of children	Types of Refractive Error							
		Astigmatism		Hypermetropia		Emmetrope		Myopia	
		Cases	%	Cases	%	Cases	%	Cases	%
Male	239	119	26	71	16	37	8	11	2
Female	211	117	26	47	10	39	9	9	2
Sum	**450**	**236**	**52**	**118**	**26**	**76**	**17**	**20**	**4**

χ^2=3.661, df=3; p=0.301; non-significant

3.8.1.2 Refractive error distribution with respect to gender

The following bar chart gives a picture of variation in the distribution of subjects based on RE. There is almost equal distribution of male and female subjects in all four groups. Maximum number of patients suffered from astigmatism (52%). Hypermetropia (26%) follows astigmatism and very few patients were noted to have myopia (4%). Emmetropes had RE 0.5DS or less in both eyes (Fig. 13).

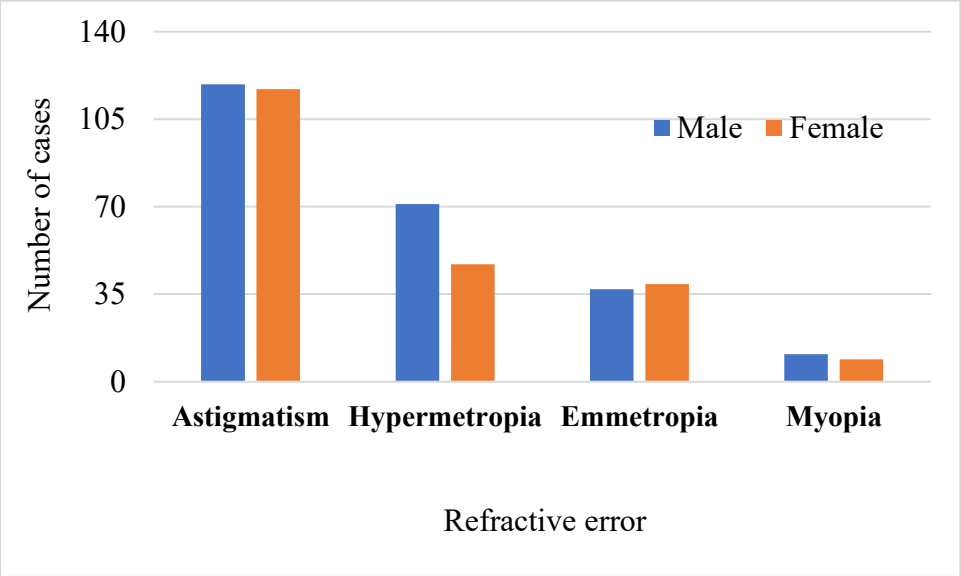


Fig. 13 Types of refractive error vs gender

3.9.1 Risk factors associated with strabismus

In this study, we noted factors that may cause or increase the chances of developing strabismus. These include prenatal or early age trauma, age and health of mother and eye conditions of the subject. Our findings show that, of all the factors, consanguinity was most frequent. 51% (n=252) subjects had parents who were blood related. Maternal debilitated health conditions during pregnancy for example hypertension, gestational diabetes, abnormal presentation of child at birth, uterine bleeding, and hyperemesis gravidarum among others were also found common (41%). Most subjects were born in hospital therefore home delivery contributed 11% (n=55) of all cases. Of all hospital-based deliveries, 38% (n=189) had caesarian delivery. Positive family history is observed for 25% (Table 16).

Our study found that susceptibility to strabismus increased by delicate health conditions immediately after birth or during early age (before 1 year). For instance, Neonatal intensive care unit (NICU) stay (17%), birth trauma (13%) which includes hypoxia at birth, reduced fetal heartbeat, delayed or absent cry, reduced Apgar score or neonatal septicemia, seizure disorder (5%), infection (typhoid, jaundice, pneumonia etc. (8%) and unstable mental state (cerebral palsy, Down syndrome, psychological disorder (3%). 14% of subjects, born before 37 weeks of pregnancy, majority due to pregnancy complications. Anisometropia can act as cause or effect of strabismus. In addition to subject related risk factors, high maternal age can also be an element of risk.

Analogy of these risk factors with strabismus types indicate that they all increase chances for developing strabismus. There was a total of 19 cases with syndromic strabismus, 12 cases had parents with consanguineous marriages. Table 16 shows the distribution of risk factors for various strabismus types is statistically significant.

Table 16 Distribution of risk factors with respect to strabismus subtypes

Risk factors	Strabismus types					
	Esotropia	**Exotropia**	**Vertical**	**Syndromic**	**Total**	**%age**
Consanguinity	111 (44%)	90 (36%)	39 (16%)	12 (5%)	252	51
Pregnancy complication	91 (45%)	65 (32%)	41 (20%)	7 (3%)	204	41
Caesarian delivery	89 (47%)	61 (32%)	31 (16%)	8 (4%)	189	38
Positive family history	49 (40%)	48 (39%)	22 (20%)	4 (3%)	123	25
NICU stay	46 (56%)	22 (27%)	14 (17%)	0	82	17
Associated eye condition (Ptosis, Nystagmus, Coloboma)	19 (25%)	29 (38%)	19 (25%)	10 (13%)	77	16
Prematurity (less than 37 weeks)	33 (49%)	23 (34%)	9 (13%)	2 (3%)	67	14
Birth trauma	23 (35%)	26 (40%)	14 (22%)	2 (3%)	65	13
Maternal age at childbirth ≥ 35	29 (47%)	17 (27%)	10 (16%)	6 (10%)	62	12
Home delivery	25 (46%)	16 (29%)	10 (18%)	4 (7%)	55	11
Reduced visual acuity in one eye (anisometropia)	25 (56%)	8 (18%)	11 (24%)	1 (2%)	45	10
Infection/fever	18 (47%)	13 (34%)	5 (13%)	2 (5%)	38	8
Seizure	10 (42%)	9 (38%)	5 (21%)	0	24	5
Neurological disorder	11 (65%)	3 (18%)	0	3 (18%)	17	3
Sum	**579**	**430**	**230**	**61**	**1300**	**100**

$\chi 2=63.79$, df=39; P=0.007; **Highly significant****

3.9.2 Distribution of risk factors according to gender

The table below gives the difference in the distribution of risk factors between the two genders. In most cases the difference is nonsignificant, that is both sexes are affected almost equally. Despite this, pregnancy complications, caesarian delivery and neurological disorder are a bit more common for male subjects. Details are shown in Table 17.

Table 1 Distribution of risk factors with respect to gender

Risk factors	Gender		Total	%age
	Male	Female		
Consanguinity	131	121	252	51
Pregnancy complication	111	93	204	41
Caesarian delivery	104	85	189	38
Positive family history	61	62	123	25
NICU stay	49	33	82	17
Associated eye condition (Ptosis, Nystagmus, Coloboma)	35	42	77	16
Prematurity (less than 37 weeks)	35	32	67	14
Birth trauma	23	42	65	13
Maternal age at childbirth ≥ 35	28	34	62	12
Home delivery	26	29	55	11
Reduced visual acuity in one eye (anisometropia)	29	16	45	10
Infection/fever	18	20	38	8
Seizure	14	10	24	5
Neurological disorder	12	5	17	3
Sum	**676**	**624**	**1300**	**100**

$\chi 2=19.45$, df=13; p=0.110; non-significant

3.10 Distribution of subjects according to familial/sporadic cases

This table presents analogy between subjects of various strabismus types and familial/sporadic cases. Familial cases include those subjects who had at least two affected members in their family whereas sporadic cases had only one affected member in their whole family i.e., subject. Our data shows an overall high proportion of sporadic cases (n=374) compared to familial cases (n=124) i.e., 1/4th of the total subjects. This difference, however, is statistically non-significant. A consistent decreasing trend of family history from esotropia to vertical squint both for familial and sporadic cases which is in line with their corresponding number of cases, as shown in Table 18. More of the syndromic cases were sporadic.

Table 18 Distribution of subjects with respect to familial/sporadic cases

Anomaly type	**No. of subjects**	**Familial/Sporadic nature**	
		Familial	**Sporadic**
Esotropia	229	50 (46%)	179 (78%)
Exotropia	158	48 (30%)	110 (70%)
Mixed	80	20 (25%)	60 (75%)
Syndromic	19		
strabismus		4 (21%)	15 (79%)
Vertical	12	2 (17%)	10 (83%)
Sum	**498**	**124 (25%)**	**374 (75%)**

$\chi 2$=4.27, df=4; p=0.370; non-significant

3.11 Isolated or syndromic nature of strabismus patients

This table also shows comparison of isolated and syndromic cases with strabismus types. Isolated cases include those subjects who had only one physiological abnormality and only one organ is involved i.e., eye. On the other hand, syndromic cases include all those subjects who had more than one physical or physiological abnormality and it may or may not (Eye syndromes) involve more than one organ. Our study shows a greater number of isolated cases, 80% as opposed to syndrome 20%. Furthermore, the proportion of isolated cases is higher for all strabismus types except syndromic strabismus. This type includes particularly those eye syndromes that usually accompany strabismus as one of their clinical symptoms. These cases are purely syndrome (100%). Application of chi-square test on this data shows that it is highly significant**.** The distribution pattern is shown in Table 19.

Table 19 Distribution of subjects according to Isolated/syndromic nature

Anomaly type	**No. of subjects**	**Isolated/syndromic presentation**	
		Isolated	**Syndromic**
Esotropia	229	188 (82%)	41 (18%)
Exotropia	158	133 (84%)	25 (16%)
Mixed	80	69 (86%)	11 (14%)
Syndromic strabismus	19	0	19 (100%)
Vertical	12	11 (92%)	1 (8%)
Sum	**498**	**401 (80%)**	**97 (20%)**

$\chi 2=82.88$, df=4; $p<0.0001$; **Highly significant*****

3.12 Strabismus patients and affected members in their family

In the present study, total affected members that is subjects and their other family members were found to be 569. Among these cases, the number of affected male members (n=296) exceeds affected females (n=273). The majority of affected members suffered from esotropia (n=259), thenceforth, exotropia (n=179), mixed type (n=95), syndromic strabismus (n=22) and vertical (n=14). This trend is given in Table 20.

Table 20 Affected members in families of subjects

Anomaly type	Affected male in family	Affected female in family	Total affected
Esotropia	147	112	259
Exotropia	86	93	179
Mixed	46	49	95
Vertical	6	8	14
Syndrome	11	11	22
Sum	**296**	**273**	**569**

$\chi 2=4.46$, df=4; p=0.347; non-significant

3.13.1 Sibships with the disease among subject's families

The study showed that a total of 81% of families had only one affected sibship for all strabismus types. Families with two, three or more affected sibships are less common. Strabismic syndromes are found to rarely run in families (Table 21).

Table 21 Sibships distribution in subject's families

Anomaly type	Sibship with the disease			Total
	1	2	≥3	
Esotropia	192	29	8	229
Exotropia	123	28	7	158
Mixed	65	13	2	80
Vertical	11	0	1	12
Syndrome	16	2	1	19
Sum	**407**	**72**	**19**	**498**

$\chi 2=5.70$, df=8; p=0.681; non-significant

3.13.2 Disease segregating generations among subject's families

The number of disease segregating generations was also determined. Our data shows that out of 498 cases, 89% had only one generation with affected member/members. This category predominates for all strabismus types. Families with two affected members were common for exotropia (n=23). There were very few families (1%) with three or more affected generations as shown in Table 22.

Table 22 Distribution of Disease segregating generations among subject's families

Anomaly type	Disease segregating generations			Total
	1	2	≥3	
Esotropia	210	16	3	229
Exotropia	134	23	1	158
Mixed	73	7	0	80
Vertical	11	1	0	12
Syndrome	16	3	0	19
Sum	**444**	**50**	**4**	**498**

$\chi 2=8.41$, df=8; p=0.394; non-significant

3.14 Maternal parity order and strabismus types

In this study, parity order of all indices was noted. We found a descending pattern in the number of subjects with respect to their parity order. 31% of subjects observed parity order 1. This is followed by 29%, 19%, 11% and 9% for order of parity 2,3,4 and ≥5, respectively. The pattern of distribution is given in Table 23.

Table 23 Parity order distribution for various strabismus types

Anomaly type	Parity order					Total
	1	**2**	**3**	**4**	**≥5**	
Esotropia	72	68	42	27	20	229
Exotropia	54	46	32	12	14	158
Mixed	22	22	16	13	7	80
Vertical	4	5	1	1	1	12
Syndrome	4	4	4	3	4	19
Sum	**156**	**145**	**95**	**56**	**46**	**498**
	(31%)	**(29%)**	**(19%)**	**(11%)**	**(9%)**	**(100%)**

$\chi 2=10.74$, df=16; p=0.826; non-significant

Chapter 4
Discussion

Visual impairment is a global public health problem. About 80% of the visual impairment is preventable (WHO, 2013). Physical, psychological, and intellectual development of children highly depends on their Visual experience. Uncorrected refractive error and strabismus causes visual impairments that can have both short and long-term consequences in children (Resnikoff et al., 2008). Therefore, it is essential that these conditions should be diagnosed and managed promptly and properly. Otherwise, they can cause complications of amblyopia and permanent reduction of visual acuity. About 15% of Pakistani population suffers from blindness only due to refractive insults (Al-Tamimi et al., 2015).

Strabismus is a common childhood ocular alignment disorder throughout the world. In Pakistan, a high prevalence of 5.4% has been reported among children under the age of 15 years that approximately constitute 45% of the total population (Azam et al., 2019). Such a high prevalence highlights the need to accelerate research and its practical application in this area. The present study was carried out on children, average age 6.5 years, with manifest strabismus, in a tertiary care center, Rawalpindi. Most patients were from the local city, however, approximately 30% of patients were from far flung areas which indicates poor health resource management in these regions. A total of 498 subjects, meeting the inclusion criteria were enrolled in the study, irrespective of the heterogeneity in their demographic attributes.

In this study, the distribution of subjects with respect to their gender and origin was found to be unequal. Frequency of male participants superseded female subjects. Likewise, there were more patients with rural backgrounds. There are variations in the intergender differences in the studies that report prevalence of strabismus and its various subtypes. A review study carried out by Hashemi et al., 2019 found intergender differences as insignificant in the prevalence of

strabismus, XT and ET and attributed these differences due to unique characteristics of the study population and sample size. In this study, a relatively high proportion of subjects from rural areas may be due to differential access to health care facilities, low literacy rate and their low socioeconomic status.

There is less similarity among studies that describe the relationship between strabismus types and socioeconomic variables. According to a study conducted on preschool children in Singapore, high paternal education is associated with low strabismus onset whereas, Sydney Myopia study (SMS) and Baltimore Pediatric Eye Disease Study (BPEDS) found no association between paternal education and strabismus (Cotter et al., 2011). Similarly, in the current study, the relationship between strabismus types and parental education, age, language, and caste system were found to be non-significant. Regardless of these fore mentioned factors, several studies found the role of ethnic-racial differences. For example, prevalence of strabismus types among children of white ethnicity and African American and East Asian population differs from each other (Matsuo and Matsuo, 2005; Group M-ePEDS, 2008).

Of all the four subtypes of common comitant strabismus recognized in the present study, esotropia and exotropia were found to be the most dominant types in terms of their prevalence. Esotropia was found to be the most prevalent (46%). In addition, more males were affected with esotropia than females. This finding is inconsistent with many studies that reported higher prevalence of esotropia in western countries especially among white people and Caucasians (Hashemi et al., 2017; Hashemi et al., 2019) while in black people and Asians, exotropia has a higher prevalence (McKean-Cowdin et al., 2013; Hashemi et al., 2017). Furthermore, pure vertical misalignments were found least common in our study. Syndromic type included Duane retraction

syndrome (DRS) and Marcus-Gunn jaw wink syndrome (MGJW). DRS type 1 had the highest presentation. This finding is in line with Kekunnaya et al. (2017). There are several reasons for the variations in the prevalence of strabismus subtypes such as ethnicity, genetics, environmental factors, and even other unknown factors. Dominant refractive error also plays part in determination of dominant strabismus type.

Despite advancement of research about strabismus, no consistent association could be established about strabismus trend change with age. Several studies on pediatric group, for example, children aged 6–72 months (Group M-ePEDS, 2008), 36–72 months (Chen et al., 2016), and 30–72 months (McKean-Cowdin et al., 2013) have shown a higher gradient for older children. A study conducted by Kvarnström et al. (2002) on children aged 1–12 years concluded that age has pronounce influence on the difference in the prevalence of strabismus. In his study, the peak prevalence of strabismus was seen in children up to 4 years of age followed by a decreasing trend thereafter. This finding is comparable to the present study which was carried out on children whose age ranged from neonates to 20 years. It found a significantly high number of strabismic subjects, for all strabismus subtypes, belonging to age group >3-6 years. These findings may be attributed to decreased prevalence of hyperopia with age and early detection of the disease at lower ages. However, there are certain studies that do not accord with these findings for example, Hashemi et al. studied subjects aged 3 to 93 years and proposed no significant difference in the prevalence of strabismus with age (Hashemi et al., 2017). The results of this study and several other studies indicate that age affects the prevalence of strabismus and other factors like genetic and environmental may also be responsible for the difference in the distribution of strabismus.

In this study, the age of onset of strabismus was also compared with the subtypes of the disease. There was statistically significant association between strabismus subtypes, (esotropia followed by exotropia) and early onset. These results of the present study are common to Singh et al. findings who reported significantly high onset of esotropia before 6 months of age (Singh et al., 2021). Such an early onset may be due to birth trauma, complicated delivery, admittance to neonatal intensive care unit (NICU) or other illnesses that required medical interventions.

Management of squint, for example treatment of amblyopia, anisometropia or squint surgery requires marked distinction of the deviated or suppressed eye and fixating eye. The present study highlights the importance of scientific research of the laterality of affected eye. We found a high proportion of strabismic patients, approximately 50% had only left eye affected with esotropia. While exotropia is found more commonly affecting the right eye compared to left eye. These results do not accord with Junejo and Hassan, who found more esotropia in the right eye (Junejo and Hassan et al., 2019). However, a study on the laterality of amblyopia shows a condition more prevalent in the left eye than the right eye (Repka et al., 2010). The difference in the two eyes to be affected with any form of strabismus may be due to laterality predilection of amblyopia, neurological disorder, laterality in the development of refractive error or combination of these conditions.

In the present study, several risk factors for various types of strabismus were identified and that provide evidence that it is a complex disorder with genetic and environmental causes. Consanguinity was found to be the predominant factor (50% approx..) for all subtypes of strabismus which draw attention to the autosomal recessive inheritance. This finding is also supported by Doctor et al., (2022). In addition, assisted delivery and family history were the

leading causative factors in this study. These factors were reported as significant by several studies (Tejaswi et al., 2020; Zhang et al., 2021). Another strong risk factor reported in this study was refractive error. Both astigmatism and hypermetropia were highly associated with esotropia whereas, higher number of exotropes were emmetropes. Myopia is found to be least prevalent. However, Faheem et al., reported myopia as most common and astigmatism, least common RE among primary school children (Ullah et al., 2020). Besides he found higher prevalence of RE among girls but in this study intergender difference was statistically non-significant. There is great discrepancy about the most prevalent type of RE among strabismic patients, but one fact supported by most of the studies is association of hypermetropia with esotropia (Tang et al., 2016; Kangari et al., 2023).

Positive family history has a strong association with the incidence of strabismus. This was defined as the presence of manifest strabismus, of the same or different subtype in blood relatives. The disease history was investigated for first, second, and third-degree relatives of subjects. In the current study, 25% of patients had two or more other members in the family, affected with strabismus. It is found to be a potential risk factor in various studies. $P< 0.001$ observed by Zhang et al., (2021). In another study, family history was found to be more common for esotropia (Çakır et al., 2022). However, Cotter et al., (2011) reported that positive family history was solely associated with increased risk of exotropia. Thus, this factor should be investigated during the clinical examination of the patient.

In this study, the isolated and syndromic nature (occurrence in association with other anomalies) of the disease was studied. We observed almost 80% of strabismus cases occur in isolated, acute state. These patients were otherwise completely normal which renders pathology of

disease unknown. Similarly, a ten year review carried by Chong et al., (2021) compared isolated and non-isolated strabismus patients and found isolated cases significantly higher (Chong et al., 2021).

The literature review during this research revealed that the true candidate gene/genes of isolated strabismus has not been elucidated yet. Various susceptibility loci, and risk variants are discovered associated with the condition. In Pakistan, most of the studies are focused on the prevalence and surgical management of the condition. The disease is even more common in our country due to prevailing trend of consanguineous marriages and lack of awareness about early treatment. Iqbal et al., found association of horizontal deviation and RE with consanguinity (Iqbal et al., 2018). Moreover, there are very few studies from Pakistan that could illustrate concordance patterns of disease among twins and in families with a positive family history. Thus, there is dire need to conduct studies like this that provide a foundation for further molecular studies and highlight the areas that needed to be explored. Advance genetic research is intensely required to unveil transmission patterns and in turn provide genetic counseling to afflicted families. Recently, a variant in the *GPR56* gene in Pakistani population is discovered to cause malformation in brain area responsible for eye movements (Zulfiqar et al., 2021). This gives insight into the mutation of *GPR56* gene. Such studies would aid in creating genetic profile and elucidating genetic heterogeneity among Pakistani population. Owing to the high heterogeneity in Pakistani population, it is expected that novel genes and mutations may be discovered in other strabismus families.

Conclusion

Strabismus is a neurogenic disorder that affects sufferers biologically and psychologically. Early diagnosis and treatment of the condition is crucial to avoid long term dire consequences. In this study, high occurrences of infantile esotropia and astigmatism were found. There are several risk factors found to be associated with the condition, however, no definite cause has been recognized yet. There is paucity of twin and family studies to disclose concordance among strabismus types within a family. Therefore, keen attention should be given to the mechanism of developing strabismus, the role of family history and consanguineous marriage. Furthermore, the genetic basis of the common comitant strabismus, still to be revealed, demands such studies in this area. This study helps in understanding various epidemiological aspects of strabismus and paves a way to its molecular analysis.

Chapter 5
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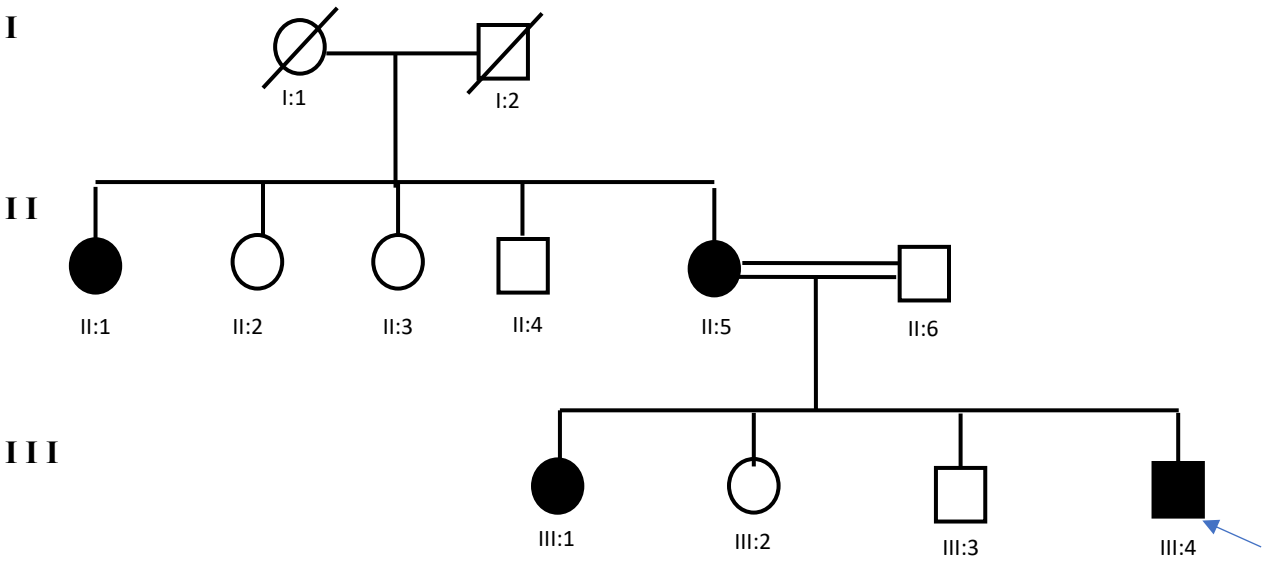
Annexure I

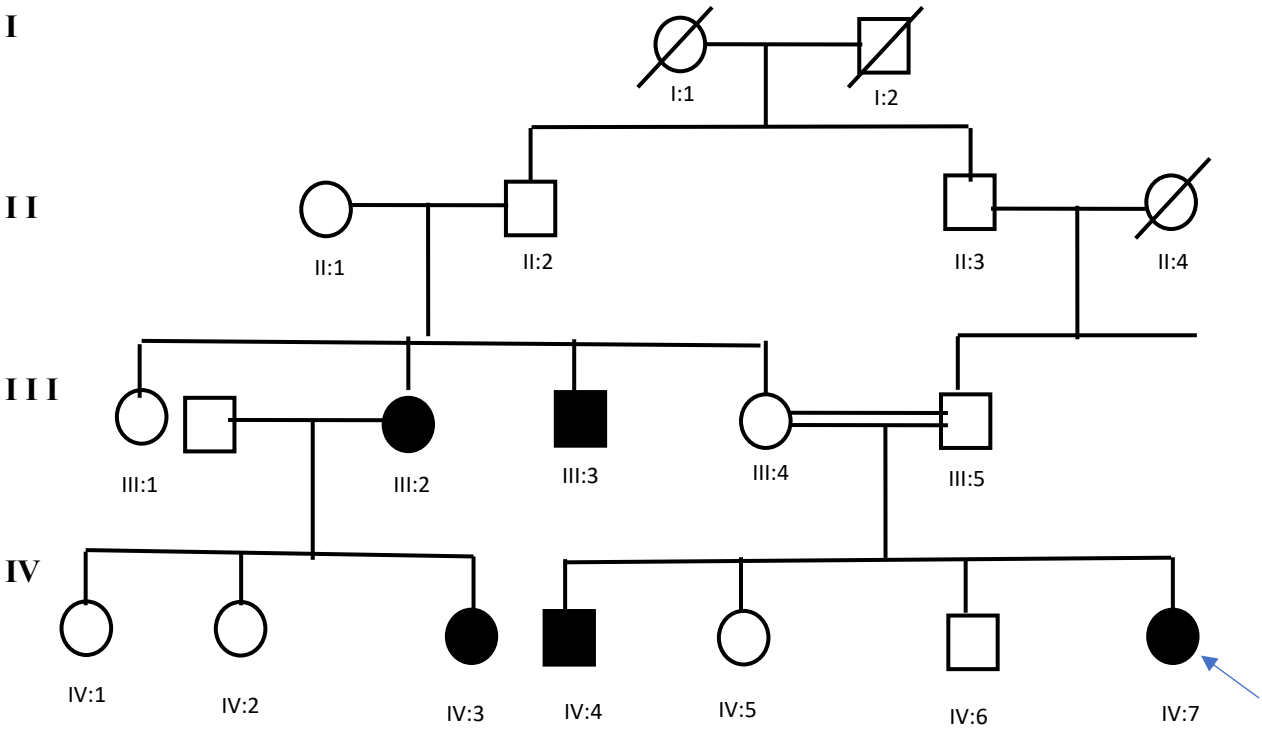
Representative pedigrees



Pedigree 1. A three-generation pedigree of a family with exotropia

Autosomal dominant inheritance predicted

100% concordance of strabismus subtype



Pedigree 2. A four-generation pedigree of a family with exotropia

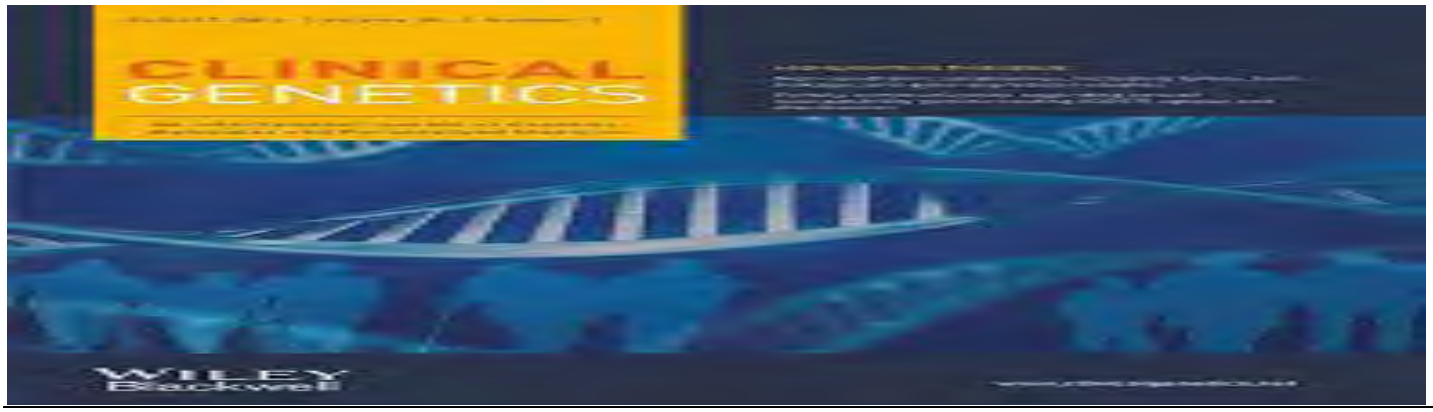
Autosomal recessive inheritance predicted

100% concordance of strabismus subtype

Annexure II

Proforma for data collection

Genetic study of strabismus, Congenital Cranial Dysinnervation Disorders (CCDDs) and Associated Anomalies



Demographic study of affected person:

Name: ----------

Gender: Male/female

Current age: ----------

Home address: ----------

Present Height: ---------- ft

Present Weight: ---------- kg

Cell No: ----------

Phone: Home: ----------

Family Background:

Province: Punjab / Sindh/ Baluchistan/ KPK

District: ----------

Origin: (R/U)

Language: Urdu /Punjabi/ sariki/ blochi/sindhi

Cast: major: ---------- minor: ----------

Socio-demographic:

Educational status: ----------

Parentall Qualification: ----------

Parental Economic status: (month/income): ----------

Genetic parameters

First cousins

Double first cousins

Second cousins (parents are cousins)

Distantly related (Biradri)

Reciprocal (watta satta) marriage

Non-related

Eye symptoms / medical history of subject:

Types of eye disorders

Esotropia (crossed/inward drifting eye/ deviated eye)

Exotropia (wandering /outward drifting/deviated eye)

Hypertropia (vertical deviation, eye drifts up)

Hypotropia (vertical deviation, eye drifts down)

Brown syndrome

Duane syndrome

Congenital ptosis

Congenital fibrosis extraocular muscles-CFEOM

Horizontal gaze palsy

Marcus Gunn Jaw Wink Syndrome-MGJWS

Coloboma

Microphthalmia

Other disorders----------

Do you have Esotropia?	Yes ⟹ both eye/left eye only/ right eye only

No/ Not sure

Do you have Exotropia? Yes → both eye/left eye only/ right eye only
No/ Not sure

Do you have hypotropia? Yes → both eye/left eye only/ right eye only
No/ Not sure

Do you have Hypertropia? Yes → both eye/left eye only/ right eye only
No/ Not sure

Do you have coloboma? Yes → both eye/left eye only/ right eye only
No/ Not sure

Do you have Amblyopia?

Yes, diagnosed at age/No/Not sure

Do you have congenital ptosis? Yes → both eye/left eye only/ right eye only
No/ Not sure

Do you have Duane Syndrome? Yes → both eye/left eye only/ right eye only
No/ Not sure

Do you have Horizontal Gaze Palsy? Yes → both eye/left eye only/ right eye only
No/ Not sure

Do you have superior Oblique Palsy? Yes → both eye/left eye only/ right eye only
No/ Not sure

Others------ Yes → both eye/left eye only/ right eye only
No/ Not sure

Are you the person in the family initially diagnosed with the eye disorder?

Yes/No

I am the person:

Mother/Father; Sister → FULL/HALF; Brother → FULL/HALF

MATERNAL
AUNT/UNCLE/COUSIN/GRANDMOTHER/GRANDFATHER

PATERNAL
AUNT/UNCLE/COUSIN/GRANDMOTHER/GRANDFATHER

Physician Information:

Did you ophthalmologist refer you to this study? Yes/ No/ not sure

Ophthalmologist Name: ----------

Hospital Affiliation: ----------

Phone: ----------

Email Address: ----------

ORIGINALITY REPORT

16%	9%	11%	4%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Jolene C. Rudell, Jérome Fleuriet, Michael J. Mustari, Linda K. McLoon. "Childhood Onset Strabismus: A Neurotrophic Factor Hypothesis", Journal of Binocular Vision and Ocular Motility, 2021 Publication	2%
2	Submitted to Higher Education Commission Pakistan Student Paper	1%
3	Tejaswi Bommireddy, Kate Taylor, Michael Patrick Clarke. "Assessing strabismus in children", Paediatrics and Child Health, 2020 Publication	1%
4	www.tandfonline.com Internet Source	1%
5	Submitted to British University In Dubai Student Paper	1%
6	www.ncbi.nlm.nih.gov Internet Source	1%