Hereditary and congenital anomalies prevalent in Loralai district of Balochistan

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DEPARTMENT OF ZOOLOGY

FACULTY OF BIOLOGICAL SCIENCES

QUAID-I-AZAM UNIVERSITY ISLAMABAD

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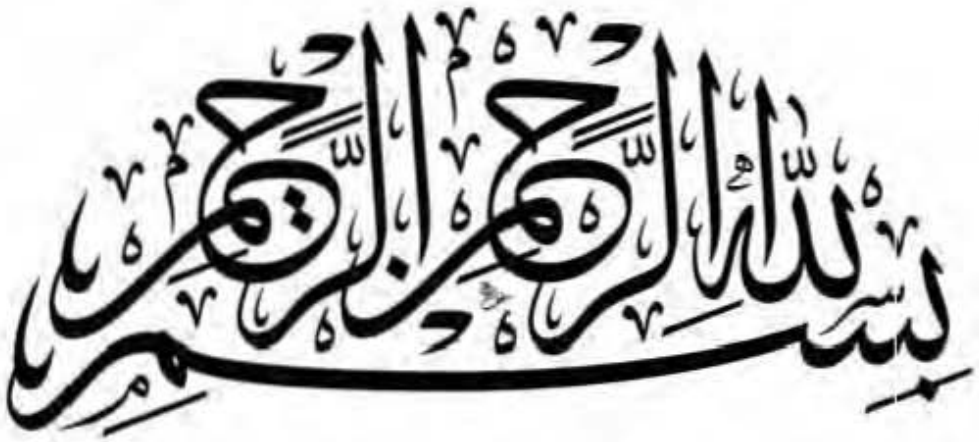

In the Name of Allah, the Entirely Merciful, the Especially Merciful
Al-Fatihah [1: 1], Nobel Quran

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A Dissertation submitted in the partial fulfillment of the requirements for the degree.

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Master of Philosophy

In Human Genetics

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Declaration

I hereby declare that the work accomplished in this thesis is the result of my own research work carried out in the Human Genetics lab, Department of Zoology, Quaid -I- Azam University Islamabad. The epidemiological data were collected from the Loralai district of Balochistan, Pakistan. This thesis has neither published previously nor does it contain any material from the published resources that can be considered as the violation of the international copyright law.

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Muhammad Qasim Khan

Dedication

This dissertation is dedicated to

My all Teachers

Especially to

Mam Firdous

For their uncountable financial support , encouragement and love to

My beloved parents

Thank you for your love, support and guidance have been the foundation of my academic success and I am forever grateful for everything you have done for me

To

My brother's

Masoom khan and Asmatullah

For being source of motivation

At last, but not least to my **wife** for her everlasting sacrifices

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In the name of **Allah,** the most merciful and beneficent. I bear witness that **Holy Prophet Hazrat Muhammad (PBUH)** is the last messenger of Allah Almighty. His (PBUH) life is perfect role model for a Muslim to be successful in this worldly life and hereafter. Without the blessing of Allah Almighty, I would not be able to complete my thesis.

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Abbreviations

CA	**Congenital anomalies**
CDC	**Center for disease control**
CHD	**Congenital heart disease**
CLDs	**Congenital limb deformities**
CP	**Cerebral palsy**
ICD	**International classification of disease**
ID	**Intellectual disability**
NMD	**Neuromuscular disorders**
NTD	**Neural tube defect**
OMIM	**Online mendelian inheritance in man**
TEVs	**Talipes equinovarus**
WHO	**World health organization**

Abstract

Birth defects or congenital anomalies are caused by structural or functional abnormalities during the course of intrauterine development. Numerous things, including chromosomal abnormalities, environmental teratogens, and gene defects, can lead to CA. A lack of certain micronutrients aetiologies for around 50% of CA are unknown. Children's disabilities and deaths are attributed mostly to CA in both developing and wealthy nations. This study's goal was to investigate the range of congenital and inherited abnormalities and their relationships to different demographic factors. In this study a total of n = 371 families were find out in different urban and rural areas of the loralai district. The data is collected from door-to-door survey, not from any hospital or other social welfare society of the district. The methodology was completely dependent on coordination between researchers and the study population which includes families and subjects. In the study the index subjects were diagnosed by their medical reports, photographs and family history of the disease in familial cases. The total collected date were classified into 9 categories in which neurological disorders were most prevalent n = 80 (22%) , followed by limb defects n = 78 (21%) , neuromuscular defects n = 67 (18%) , blood disorders n = 57(15%) , sensorineural defects n = 42(11%) , eye/visual impairment n =24 (6%) , musculoskeletal defects n = 8 (2%) , orofacial defects n= 8 (2%) and cardiovascular defects n = 5 (1%). We were observed n = 32 different types of minor anomalies in the population of loralai district in which cp were most prevalent n = 57 , followed by thalassemia n = 54 and than intellectual disorder n = 51.In the study we find out male were more affected n = 233 than female n = 138. Sporadic cases were more common n = 271 than familial n = 100. Isolated cases were more prevalent n =277 than the syndromic cases n = 94 , while neurological and neuromuscular defects syndromic were most common .Most of the subjects belonged from low economic status families. Parental consanguinity was 50% in the studied area and 50% non consanguinity was present.

The results of the current study will be beneficial for future investigation and give relevant information regarding the prevalence of CA in the studied region. Genetic counselling, prenatal diagnostics, and CA awareness campaigns can all lower illness chances. In underdeveloped nations with low levels of income, the high prevalence of CA imposes a major socioeconomic cost.

Chapter # 01

Introduction

1.1 Hereditary and congenital anomalies

Congenital abnormalities, as defined by the World Health Organization, are any morphological, functional, biochemical, or molecular issues that may manifest in the embryo and fetus from conception until delivery, regardless of whether they are identified at birth or later (World Health Organization (2016). More than 3 million babies and fetuses suffer significant birth defects each year (World Health Organization (2016). Congenital anomalies are a general term for physical abnormalities of the body's structure or function that are present at birth and have a prenatal origin. It has become clear that genetic disorders are a major source of disability, mortality, and human tragedy as infectious and nutritional diseases in industrialized nations are becoming easier to manage. Genetic illnesses can either be familial or sporadic depending on the pattern of inheritance. The word "familial" refers to genetic illnesses that run-in families, are more common in each family, and may be predicted to be inherited by future generations, whereas the phrase "inherited" refers to conditions that are passed down through generations. Hemanti et al. (2010), "sporadic" illnesses are those that do not run in families, manifest in an erratic pattern, and cannot be predicted by chance or inherited characteristics.

There are thousands of distinct genetic illnesses with known clinical manifestations. At least half of the 3 to 6 percent of babies with a recognized birth abnormality have a predominately genetic cause. Furthermore, chromosomally defective fetuses are involved in about half of all spontaneous abortions (miscarriages), which makes genetic disorders the most commonly known cause of pregnancy loss in developed countries.

In developed nations, genetic illness accounts for around 30% of all postnatal newborn mortality; 30% of pediatrics and 10% of adult hospital admissions are mostly

genetic in origin. Finally, medical researchers believe that at least 10% of all individuals have genetic abnormalities.

Not all birth anomalies are produced by the same things, and even those that seem to be the same in two persons may really have different underlying reasons, it is crucial to keep in mind. It is clear that many of these illnesses are the consequence of a mix of hereditary and environmental influences, even if the genetic and biochemical roots for the majority of recognized anomalies are still unknown. (DeSilva et al. (2016), structural abnormalities often manifest during the first trimester of embryonic development. While structural congenital anomalies encompass conditions where the body's structure is altered, such as cleft palates, limb abnormalities, and neural tube anomalies, functional congenital anomalies includes conditions where the operation of a specific organ or bodily component is disrupted (Taylor et al., 2020). Birth malformations might be discrete anomalies or a syndrome that contributes to infant mortality and morbidity. (Pascal et al. (2014).

"Birth defects", "congenital abnormalities" and "congenital malformations" are often used as synonyms. The World Health Organization (WHO , 2016) estimates that congenital malformations caused 270,000 fatalities worldwide in 2010 within the first twenty-eight days of birth, with neural tube defects (NTDs) being one of the most acute and prevalent of these disorders.

The population characteristics of numerous European nations have seen significant changes during the past 50 years. This has been seen in the UK's elevated levels of immigration from the old British Empire, especially from the Indian subcontinent.

As of the middle of 2009, there were over 9.7 million children in England (aged 0 to 15), 292,000 (or 3.0%) of whom were of Pakistani ancestry, according to figures from the Office for National Statistics. Like many newly established immigrant communities, British

Pakistanis are mostly concentrated in specific urban regions, such as Bradford in the northern English county of Yorkshire and Birmingham in the English Midlands. According to mid-2009 figures from the Office for National figures, Bradford has 114,500 children, 24,700 (21.6%) of whom are Pakistani.

Bradford has seen an increase in the quantity and proportion of Pakistani births throughout time. Between 2001 and 2003, deliveries to Pakistani women increased from 31.2 to 38.5% of all infants. Within their baradari, or traditional social groupings, UK-born Pakistanis favor both consanguineous marriages and endogamous unions.

Consanguineous marriage, which is commonly described as a relationship between two people who have one or more common ancestors, refers to unions between second cousins or near relatives in the context of medical genetics.

1.2 World prevalence and mortality of Congenital anomalies

Birth and death statistics are periodically gathered nationally, and records may be examined to determine rates by district and ethnicity. Children of Pakistani heritage frequently have high infant mortality rates; for example, in 2005, the IMR for Pakistani infants was 9.6 per 1,000, as opposed to 5.0 per 1,000 for all live births in England and Wales. Worldwide, congenital anomalies claim the lives of more than 29,5000 babies under the age of 28 per year (Verma et al., 2021). According to Claudia et al. (2017), 20% of all pediatric mortality are estimated to be caused by congenital anomalies.

1.2.1 Mortality

According to Ruben et al. (2019), 28% of newborn fatalities overall in Argentina are attributed to congenital anomalies. Congenital anomalies is responsible with 21% of infant mortality in Iran (Sourabh et al., 2017). According to Juliet et al. (2011), around 3.3 million children under the age of five die from birth abnormalities and 3.2 million remain permanently crippled. According to the global burden of disease study from 2013, Congenital anomalies is thought to be the main cause of mortality among children under the age of five. Global surveys reveal that due to diverse socioeconomic circumstances, the prevalence of congenital anomalies differs from one nation to the next (Rodica et al., 2016). Congenital heart problems and neural tube defects are the two most common types of congenital anomalies in India, where the frequency is 230 per 10000 newborns (Prajkta et al., 2016).

Baradari marriage contracts are based on social/professional groups, but they may also represent religious subgroupings and/or regional allegiances. Numerous other recent immigrant groups to the UK, such as those from the Middle East, Turkey, Iran, North Africa, and South India, as well as more enduring populations like the Irish Travelers, frequently have consanguineous marriages. However, due to their size and high rates of consanguinity, the Pakistani community has received a lot of recent public attention.

Congenital and inherited abnormalities (CA), a major contributor to infant mortality and morbidity, are common in Pakistan. Birth defects in form, function, or metabolism that occur throughout developmental stages are referred to as congenital and hereditary anomalies (CA) (World health organization , 2016).

One of the most prevalent hereditary diseases, thalassemia affects 1.5% of people worldwide. Thalassemia is an autosomal recessive condition that is brought on by mutations in the hemoglobin subunit beta gene on chromosome 11. Although it is increasingly

commonplace elsewhere, the condition is linked to people that originated in the Mediterranean, middle east, and Indian subcontinent. The kind of the mutation, whether it affects both alleles (thalassemia major, also known as -thalassemia), or only one allele (thalassemia minor), determine the severity of the condition. In Pakistan, 5-7% of the population suffers with -thalassemia. For these individuals, regular blood transfusions are necessary to decrease anemia. These patients are at a great risk of developing cardiac issues or liver cirrhosis because this is still the only therapy available, and they frequently pass away from iron overload at the age of 30 or younger.

For the years 2003 to 2007, there were 23.9 significant congenital abnormalities per 1,000 newborns. It was 80% live births. In the first week of life, 2.5% of live infants with congenital anomalies perished. From 20 weeks of gestation on, stillbirths or fetal deaths made up 2.0%. According to statistics from EUROCAT (European Surveillance of Congenital Anomalies), 17.6% of all instances included pregnancy terminations after prenatal diagnosis .

Birth defects are the prenatal beginning of illnesses that can be brought on by chromosomal problems, environmental teratogens, micronutrient shortages, and gene defects. Other factors that contribute to birth defects include rubella, diabetes mellitus, a lack of folic acid and iodine, use of tobacco, alcohol, and other drugs, exposure to certain chemicals in the environment, and radiation (WHO , 2016) .

Congenital anomalies (Cas) are one of the main causes of pregnancy and neonatal fatalities in low- to high-income countries. Each year, 7.9 million infants (6% of all births worldwide) are born with a serious genetic anomaly. In the US, between 3% and 5% of live births are thought to be affected by congenital anomalies in Europe, 2.1% of live births are reported.

1.3 Congenital disorder

A congenital disease is one that exists at birth and frequently even earlier. Additionally, it may encompass ailments that appear within the first month after delivery. Congenital illnesses can have a extensive of defects including chromosomal or genetic disorders, infections, birth trauma, or the environment the embryo was exposed to while in the womb**.**

1.4 Acquired disorder.

Contrarily, acquired illnesses appear after birth and might persist throughout a person's life.

1.5 Prevalence and mortality in Pakistan

The primary cause of morbidity and death has changed from infectious illnesses to congenital anomalies as a result of improvements in healthcare, cleanliness, and nutrition. Estimates place the frequency of congenital anomalies at 4% and 5% worldwide (Nelson K at al, 2019).Due to a number of circumstances, such as the high proportion of consanguineous unions, the size of sibling groups, the country's poor socioeconomic status, and maternal factors, the burden of hereditary disorders are particularly high in Pakistan.(World health organization , 2016).

1.5.1 In Pakistan

In Pakistan, the vast bulk of people live in post oral regions with poor healthcare facilities. Consequently, congenital anomalies add to the pressure on the healthcare system with limited resources. A recent estimation found that congenital anomalies contributed to 2.34% of all fatalities in Pakistan. An estimated 6% to 9% of prenatal deaths in Pakistan are

attributed to congenital anomalies. The causes of between 40 and 60 percent of congenital anomalies are unclear, with 20 percent linked to hereditary and other variables, 8 percent to a single gene mutation, 6 percent to chromosomal abnormality, and 5 percent to other causes. According to Bhatti et al. (2019), 2.3% of all deaths in Pakistan are attributed to congenital anomalies.

There are several obstacles in the way of Pakistan's healthcare system providing services to the population. The majority of people live in rural regions, where the health care infrastructure is existent but badly maintained, as well as deficient in contemporary technology and qualified personnel.

The newborn and neonatal mortality rates in Pakistan have significantly decreased over the previous 20 years, yet they nevertheless remain high. On the maternal mortality ratio index for 2015, Pakistan was placed 149th out of 179 nations, which is extremely concerning. In Pakistan, the distribution of financial and transportation resources for health care is not based on need.

An investigation found that 60% of Pakistanis are consanguineous, with 80% being first cousins. Punjab and Balochistan have the highest rates of first cousin marriages, respectively. Pakistan has the greatest rate of newborn deaths compared to the majority of the world's regions. That translates to 46 fatalities for every 1,000 live births. Additionally, 700 infants in Pakistan are born each year with genetic disorders.

The number of health care workers is also insufficient due to the rapid population expansion, and the current medical personnel lacks the most up-to-date practice facilities and is underpaid and undertrained. However, the majority of the health-care system's funding comes from private organizations, who charge more for modern facilities that the general

public cannot pay for. There are significant disparities in the population with low socioeconomic status's ability to receive healthcare services.

Congenital malformations are responsible for 6% to 9% of perinatal fatalities in Pakistan. 40 to 60 percent of these are congenital anomalies, of which 7.5% are attributable to single gene mutations, 6% to chromosomal abnormalities, 5% to maternal conditions like diabetes mellitus or infection, and 20% to a combination of heredity and other factors. According to estimates, cousin marriages have caused genetic abnormalities in 29 million people in Pakistan.

The current study examined the prevalence, kind, and type of inherited and congenital illnesses among the people of Balochistan's Loralai area. Congenital abnormalities are present in Pakistan, according to a number of research being undertaken there; however, these studies were mostly carried out in Punjab and other regions. There hasn't been much investigation into the frequency of genetic and congenital illnesses in Loralai City.

1.6 Types of Congenital anomalies

1.7 Neurological disorder

A significant contributor to mortality and morbidity worldwide, and especially in developing nations, are neurological illnesses.

Depending on the illness, different congenital neurological conditions have different prevalence rates. Congenital neurological conditions include cerebral palsy, spina bifida, and hydrocephalus are some of the more prevalent ones.

About 1 in 345 children in the United States have cerebral palsy, according to the Centers for Disease Control and Prevention (CDC). A neural tube abnormality called spina

bifida, which damages the spinal cord, affects one in every 1,500 babies born in the US. Approximately 1 in 1,000 infants in the United States are affected with hydrocephalus, an accumulation of fluid in the brain.

Other congenital neurological conditions with neurological underpinnings, including Down syndrome and autism spectrum disease, may have varied effects on different people. Congenital neurological disorders are far more common overall, and numerous.

1.7.1 Neonatal Neurological Disorders

Types of neonatal neurological disorders

Although a newborn may have serious neurological issues, these are the most typical:

1. **Congenital neurological defects**

This category of conditions includes brain and spinal cord abnormalities as its primary causes. This may include hydrocephalus (excess cerebral fluid) or neural tube abnormalities that impact the spinal cord and brain.

2. **Birth asphyxia:**

This condition occurs when an infant is afflicted because of insufficient oxygen before, during, or just after birth.

3. **Periventricular leukomalacia:**

This frequent neurological disorder, which is linked to damage to the periventricular white matter, a particularly specific region of the brain, affects preterm neonates.

4. **Seizures:**

These can happen for a number of reasons and range in severity.

5. **Encephalopathy:**

This term describes your baby's overall state of awareness as a result of a neurological disorder. Due to a drop in awareness, your baby can have trouble breathing and eating.

6. **Intracranial hemorrhage**:

The brain can bleed in a number of locations. The majority of intraventricular hemorrhages happen in preterm neonates.

7. **Hypotonia:**

Your infant may have weak or floppy muscles. Numerous neuromuscular disorders may be to blame for this muscle weakness. Additionally, he can have trouble breathing and eating.

8. **Brain metabolic disorders:**

The brain is powered by a number of biochemical processes. Any interference with this process can alter brain function, some of which are reversible and others of which are not. Brain abnormalities are especially likely to affect premature newborns. Oftentimes, metabolic diseases like phenylketonuria, which can result in neurological issues, are discovered before birth.

1.7.2 A neurological condition can occur as a result of a number of birth-related problems. These consist of

- Physical damage to the skull that causes bleeding into the brain.
- A shortage of oxygen during or immediately after delivery.
- Specific diseases in the mother's vaginal system that are transmitted to the infant during the birth.

- These illnesses can be brought on in the period immediately following birth, but when the infant is still very small, by:
- Immune disorders or other medical issues

1.8 Eye/visual impairment

The World Health Organization (WHO) divides infant blindness into groups based on the anatomical region that is primarily affected. Infants may experience postnatal (during or after delivery) or prenatal visual loss. There were an estimated 596 million visually impaired persons in the globe in 2020; 43.3 million of them were blind, and 90% of them resided in developing nations. Congenital abnormalities, or anatomical malformations, usually manifest at birth. Congenital abnormalities of the eye and adnexa (CDEA) may be associated with significant physical, mental, and social impairments in addition to visual impairment and blindness. These developmental flaws can appear alone or as a part of a more serious systemic condition, and they can damage any part of the eye or cause ocular adnexa. Surface ectoderm, neural ectoderm, and mesoderm all work together to form the eye and its adnexa. Although there are several potential causes of CDEA, abnormalities in ocular embryogenesis, organogenesis, and differentiation during pregnancy are among the most significant. abnormalities affecting the eyes and vision that are present at birth or develop in the first few years of life are referred to as congenital eye and visual impairment abnormalities. A variety of visual impairments, such as the following, may emerge from these abnormalities that may affect one or both eyes:

1. **Cataracts:**

   A clouding of the lens of the eye may result in blindness or impaired vision.

2. **Glaucoma:**

   Which affects the optic nerve and can impair eyesight.

3. **Nystagmus:**

   Uncontrollable eye movements that might result in unsteady or unclear vision.

4. **Strabismus:**

   Is an eye alignment issue that can led to double vision or diminished depth perception.

5. **Coloboma:**

   A hole or gap in an eye structure, such as the iris.

6. **The underdevelopment of the optic nerve:**

   Known as optic nerve hypoplasia, can impair vision.

7. **Premature newborns may suffer from retinopathy of prematurity:**

   A disorder that can result in blindness or visual loss.

8. **Aniridia:**

   A uncommon genetic disease called aniridia results in the full or partial loss of the iris and can impair eyesight.

1.9 Congenital Heart Disorder

The most prevalent birth abnormality in the world, congenital heart disease (CHD), affects millions of infants each year. A structural abnormality of the heart and/or great vessels that exist at birth is commonly referred to as congenital heart disease (CHD). Although genetic abnormalities, teratogen exposure, or maternal diabetes may be blamed for around 20% of CHD incidence, there is still a great deal of mystery surrounding the risk factors for the other 80% of cases.

Congenital heart disease (CHD) refers to a structural flaw or issue with the heart that exists from birth, such as:

• A hole in the heart wall.

• Problems with the blood arteries (too many or too few, slow blood flow, going in the incorrect direction, etc.).

• Valve issues in the heart.

Some CHD cases are small and may not show any symptoms, while others can be deadly and require medical care.

1.9.1 The two main kinds of CHD are a cyanotic congenital heart disease and cytolytic congenital heart disease.

1. Cyanotic congenital heart disease, or low blood oxygen levels

Heart abnormalities associated with cyanotic congenital heart disease limit the quantity of oxygen given to the body as a whole. It's also known as a serious congenital cardiac defect. Infants with cyanotic congenital heart disease typically have low oxygen levels and require surgery. Examples comprise:

2. Left heart obstructive lesions:

This type of defect lowers systemic blood flow, or the flow of blood from the heart to the rest of the body. Examples include interrupted aortic arch (aorta is incomplete) and hypoplastic left heart syndrome (left half of the heart is too small).

3. Right heart obstructive lesions:

This kind of abnormality affects pulmonary blood flow, which is the flow of blood between the heart and the lungs. Examples include tricuspid atresia (incorrect valve development), pulmonary atresia, and tetralogy of Fallot (a set of four abnormalities.

4. Mixing lesions:

In this kind of abnormality, the body alternates between pulmonary and systemic blood flow. Transposition of the major arteries, which occurs when the direction of the two principal arteries exiting the heart, is one instance. Another is truncus arteriosus, in which there is just one major artery instead of two from the heart to the body for blood circulation.

- A cyanotic (appropriate blood oxygen level) a congenital cardiac condition cyanotic congenital heart illness is a condition that results in aberrant blood circulation throughout the body. For instance:
- Heart hole: One of the walls of the heart may have an abnormal opening. This condition may be known as an atrial septal defect, atrioventricular canal, patent ductus arteriosus, or ventricular septal defect depending on where the hole is located.
- An issue with the aorta: The major artery that transports blood from your heart to the rest of your body is the aorta. It (aortic coarctation) could be too thin. It is also possible for the aortic valve, which opens and shuts to control blood flow, to have a constricted opening or a more frequent defect termed a bicuspid aortic valve, which has only two flaps rather of the normal three.

5. Pulmonary artery issue:

The pulmonary artery transports blood from the right side of the heart to the lungs so that the blood may receive oxygen. Pulmonary artery stenosis refers to the condition when this artery is too narrow.

Early detection of heart abnormalities is possible, either before or soon after birth. However, in other cases, it takes until childhood, adolescence, or adulthood to diagnose CHD.

1.10 Musculoskeletal anomalies

Musculoskeletal disorders are the second most frequent birth malformations after anomalies of the central nervous system (KUMARI, OM and SINGH, VIVEK) Anomalies in the growth of the bones, joints, and muscles that happen during fetal development are referred to as congenital musculoskeletal anomalies. The arms, legs, spine, and pelvis are just a few of the bodily areas that might be affected by these defects.

Congenital musculoskeletal abnormalities are disorders that alter the growth or structure of the bones, joints, muscles, or other components of the musculoskeletal system. They are present at birth. These anomalies can be anything from slight deviations that hardly affect a person's life to more serious disorders that can seriously impair a person's capacity to live or even endanger their lives. Congenital musculoskeletal defects can include limb length disparities, clubfoot, scoliosis, hip dysplasia, and skeletal dysplasia. Environmental causes, genetic factors, or a mix of both may contribute to the development of certain disorders.

1.10.1 Achondroplasia

Over 97% of instances of achondroplasia are sporadic and are caused by one of two mutations (G1138A or G1138C) in the FGFR3 gene, which is located at chromosomal location 4p16.3. The achondroplasia gene is fully penetrant and inherited in an autosomal dominant manner. The specificity of these genes for achondroplasia has been demonstrated in American, European, Chinese, Japanese, Spanish, and Turkish populations.

It is infrequently possible for a birth defect to be thanatophoric dysplasia, a kind of dwarfism that is relatively common. All occurrences of this ailment are the consequence of

distinct mutations since infants with this syndrome nearly always pass die during the first day or two of life. Thanatophoric dysplasia I and thanatophoric dysplasia II are two different phenotypes.

The three mutations (R248C, Y373C, and S249C) in the FGFR3 gene that cause thanatophoric dysplasia occur most commonly. K650E, a single mutation in the FGFR3 gene, is the cause of thanatophoric dysplasia II.

The prevalence of these diseases is fascinating since they are both mostly caused by fresh or de novo mutations in the fibroblast growth factor receptor 3 gene (FGFR3). The mutation that causes achondroplasia has also been shown to originate almost exclusively from paternal germ cells.

Achondroplasia may serve as a sentinel birth defect that is monitored for signs of a rise in the frequency of mutations in human populations.

1.11 Sensorineural Disorder

An outdated phrase that is offensive especially when used to describe deaf persons who cannot speak is "deaf and dumb" or simply "dumb." Many Deaf persons are considered "mute" because they do not speak. The definition of "dumb" is "mute." Deaf and Dumb Definition .1.86 out of every 1,000 babies in the US have hearing loss, and hearing loss affects 4% of adults under the age of 45. The kind of hearing loss is often categorized as either steady or progressive, conductive, sensorineural, or mixed.

More than 50% of pediatric deaf children in the US have a hereditary basis for their condition. With X-linked, mitochondrial, autosomal dominant, or autosomal recessive modes of inheritance less than 5% of deaf children in the US have a deaf parent. According to its aetiology, it might have environmental or genetic (non-hereditary) sources again, the

beginning of sensorineural hearing loss is divided into congenital and acquired (or late-onset) categories. The pathophysiology of deafness can result from a single gene mutation or a combination of abnormalities in other genes. Hearing loss and deafness that run-in families might be conductive, sensorineural, a mix of the two, or no syndromic. Associated with external ear malformations or other organ anomalies, or no syndromic, meaning not connected to external ear malformations or other health issues. In the past a person who is deaf and uses sign language or who is both deaf and silent is referred to as a deaf-mute. These folks use sign language to communicate. When others can understand your message and respond to it in a comparable way, you have truly communicated with them. Physical muteness, or the inability to generate sounds, can be caused by problems with the throat or vocal cords, whereas deafness can result in the ability to produce noises but not speak because the individual is hearing-impaired. Other causes of muteness include heredity, medications like aminoglycosides and cisplatin, and although muteness is not a congenital ailment, one in every 1,000 school-age children has mutism, a psychological rather than a physical condition.

1.12Neuromuscular Disorder

About 1 in 1000 people worldwide are affected by a wide range of hereditary abnormalities known as neuromuscular disorders (NMD). They are characterized by skeletal muscular function impairments that are either primary or secondary to genetic abnormalities that cause progressive muscle degeneration and weakening. The majority of these mutations exhibit X-linked, autosomal recessive, or autosomal dominant inheritance. The disease can start in childhood and proceed rapidly, or it might start later in life and progress more slowly.

1.12.1 Muscular Dystrophy in Duchenne

In 1981 a girl with Duchenne muscular dystrophy (DMD) and an X-autosomal translocation with an Xp21 breakpoint was reported. Using this case and other similar cases reported in the literature to support the location of the Duchenne locus at Xp21 the Louis M. Kunkel group found the DMD gene in 1988.

1.12.2 Skeletal muscle dystrophies

In almost all of cases, the pelvic and scapular limb-girdles are affected by a series of diseases known as limb-girdle muscular dystrophies (LGMD). For LGMD, the inheritance patterns are either autosomal recessive (AR) or, less commonly, autosomal dominant (AD). Eight AD genes (*LGMD1A-1H*) and 19 AR genes (*LGMD2A-2T*) have been discovered by prior research. Patients may have a moderate illness that allows them to work into old age or a severe phenotype that is clinically quite similar to X-linked DMD. The sarcoglycanopathies *LGMD2C, LGMD2D, LGMD2E,* and *LGMD2F* are caused by mutations in the *SGCG, SGCA, SGCB*, and *SGCD* genes, which produce the proteins -*SG, -SG, -SG*, and -*SG.*

The dystrophin-glycoprotein complex is made up of these transmembrane glycoproteins as well as sarcospan, dystrophin, dystroglycans, syntrophins, and -dystrobrevin. This complex works in tandem with the muscle cell's cytoskeleton to keep the plasma membrane mechanically stable while the myofiber contracts .The gene for *AD LGMD1G* muscular dystrophy was discovered ten years before to our new discovery (Vieira et al., 2014).Two sizable, unrelated families, one from Brazil and the other from Uruguay, have mutations in the RNA-processing protein HNRPDL, a member of the heterogeneous ribonucleoprotein family that participates in mRNA synthesis and metabolism.

The identification of the *LGMD1G* gene demonstrated a novel association between a muscular disease and an RNA-related gene, demonstrating the importance of RNA binding/processing proteins in muscle development and disease. Significant phenotypic and

genotypic heterogeneity characterizes neuromuscular diseases, with similar clinical results caused by mutations in many genes and a range of symptoms connected to changes in a single gene.

1.13 Orofacial anomalies

One of the most prevalent birth abnormalities, orofacial clefts can occur alone or in combination with other congenital malformations. These orofacial clefts are mostly no syndromic. Each congenital structural flaw in the body is a result of an inherited mistake during morphogenesis and can have an impact on one or more systems. Between Days 25 and 28 of intrauterine life, organogenesis occurs. Malformations can result from any injury to the embryo at this time, whether it is environmental, dietary, or developmental. Organs impacted by associated abnormalities are categorized.

1.13.1 The three main categories of congenital abnormalities are as follows.

A) disruption

Is a rare aberration caused by the failure of the initial normal course of fetal development, such as a craniofacial cleft brought on by amniotic bands.

b) Deformations:

These happen as a result of mechanical stresses and result in abnormalities that are less severe than disruptions, such as club feet, cleft palates.

c) Malformations:

An organ that exhibits a morphologic anomaly as a result of an inherently aberrant developmental process, such as polydactyly, congenital heart defects, cleft lips, etc. Associated abnormalities with orofacial cleft prevalence might vary between populations.

Orofacial clefts (OC), which are usually split into isolated cleft palate (CP) and cleft lip with or without cleft palate (CL/P), are birth abnormalities that affect the face and oral tissues. Orofacial clefts is the most common congenital deformity while not often being considered a life-threatening condition.

Orofacial cleft has serious negative effects on the patient's health, finances, and psychological well-being as well as those of their families and society at large. The most often documented craniofacial aberration, orofacial clefts, affects around 1 in 700 people.

However, due to regional variances in birth rates and appropriate birth defect tracking systems worldwide, there is a considerable variability in the prevalence of orofacial clefts internationally. (Setó-Salvia and Stanier, 2014) Typical orofacial clefts (OFCs), particularly cleft lip and cleft palate, are among the most common congenital abnormalities and are probably produced by the interaction of a number of genetic and environmental risk factors.

1.14 Limb anomalies

Congenital limb deformities (CLDs) are frequent skeletal birth malformations that are immediately noticeable at birth. They have a variety of impacts on appearance and psychology, which can have a long-lasting negative impact on one's health and ability to integrate into society. The term "CLDs" refers to a group of illnesses that affect the upper and lower limbs and whose causes are still mostly unknown. CLDs are further broken down into "isolated" and "associated" categories depending on whether there are several congenital defects that cannot be categorized into a specific syndrome or whether there are just limb anomalies present.

Most congenital limb malformations that are present in children happen when a limb, or a portion of it, fails to develop normally during pregnancy. Due to the inability of numerous

components to correctly come together, reduction faults may cause crippling limb deformities. Polydactyly, which is characterized by whole or partial extra digits, and syndactyly, which is a fusion of two or more digits, are less devastating limb malformations. Congenital limb defects (CLD) appear to be most frequently caused by disruptive events. Disruptive occurrences during pregnancy, such as amniotic band or vascular disturbances, might result in the amputation or hypoperfusion of developing limbs. Thalidomide, which in the 1960s caused a wide range of congenital limb defects, including intercalary reductions and preaxial abnormalities, is the most well-known example of a teratogen responsible for congenital limb defects. The prevalence rates of congenital limb defects vary greatly between countries, ranging from 1-4 per 1000 live births, depending on criteria and classifications, notably the inclusion or exclusion of minor limb abnormalities. There is currently a dearth of research on the frequency of limb deformities in Asian countries. Only two prior research, both of which used information from a single university hospital, looked at the prevalence of all kinds of congenital limb defects in Thailand.

1.14.1 Polydactyly

The presence of additional digits is known as polydactyly. Because many doctors manage simple "nubbins" without sending them to orthopaedic experts, its prevalence is probably understated. As early as 14 weeks of pregnancy, ultrasonography can reveal polydactyly, with partial autoamputation occurring in the majority of isolated polydactylies. The thumb, which controls 40% of hand activity, has to be able to firmly pinch against the other digits. This movement is hindered by polydactyly when the duplicated digits are not aligned properly. According to Ezaki, the anatomy is more appropriately referred to as "split" than "duplicated." The classification of polydactyly can be done in a variety of dichotomous ways, such as preaxial (radial) against postaxial (ulnar), thumb versus triphalangeal, and

simple versus complicated. Preaxial and postaxial polydactyly are both considered to be present in mixed polydactyly. The heredity of polydactyly was recognized as early as 1896. As of 2010, 310 illnesses have been linked to polydactyly. Ninety-nine genes have been linked to the control of the anterior-posterior development of the limb bud. On day 26, the upper limb starts to develop within the womb. Individual digits develop as a result of apoptosis in the interdigital necrotic zones. It is assumed that the hypoplastic state of the tissue in polydactyly results from an improper connection between the mesoderm and ectoderm. Preaxial and postaxial alignment are determined by the zone of polarizing activity (ZPA) on the apical ectodermal ridge, which governs the creation of a limb bud. On the backside of the growing limb bud, the zone of polarizing activity (ZPA) is situated. Thus, polydactyly is one of the most common limb anomalies.

1.14.2 Club foot

One in every 1000 live newborns is affected by congenital talipes, the most common of which being clubfoot. If clubfoot is not addressed, it might hinder you from establishing a normal gait and endanger your life.

There are differences in birth prevalence among racial and ethnic groups: 6.8 out of 1000 live births in Polynesia, 1.12 out of 1000 in white people, 0.76 out of 1000 in Hispanic people, and 1.39 out of 1000 in Chinese people. Regardless of the population, Clubfoot dependably exhibits a 2/1 male-to-female ratio and bilateral involvement in almost half of all cases. The causes of the majority of clubfoot instances are unclear, while idiopathic clubfoot has a wide range of etiologies. Clubfoot has been associated with a number of maternal and environmental risk factors, while many of the reported findings are ambiguous or lack adequate research. There have been conflicting results regarding maternal age, maternal

education, marital status, and parity, as well as their links to idiopathic talipes equinovarus. Medicaid utilization and other risk factors like prenatal care have gotten less focus.

1.15 Blood disorders

Three to five percent of all inherited coagulation factor deficits are caused by rare hereditary bleeding illnesses, which are frequently passed down by an autosomal recessive mechanism. Among these deficiencies are those in fibrinogen, factor (F) II, FV, FV + FVIII, FVII, FX, FXI, and FXIII. The incidence of the seemingly homozygous variations in the general population varies from one instance per 500,000 for the most common deficit, FVII, to one case every 2-3 million for the rarest deficits, FII and FXIII. Most populations have reported rare bleeding disorders, more commonly in nations where consanguineous unions are common.

Blood disorder (thalassemia) is inherited and is passed genetically from one generation to the next. The two main types of thalassemia are alpha and beta thalassemia. Each of these disorders can be minor to severe depending on how much hemoglobin your body generates.

Although thalassemia is a chronic disease, there are now better therapies available. These patients' quality of life has improved, and they live longer.

Pakistan has five provinces, the largest of which is Baluchistan, yet only 13 million of the nation's 208 million people reside there. One million people live in the northern region's capital, Quetta. The human development index of Baluchistan, which is an impoverished province, is the lowest in the nation1; in 2018, it was 0.477, compared to 0.678 in Islamabad. As a component of the Expanded Program on Immunization (EPI), the hepatitis B virus (HBV) vaccine was made widely available in 2004. A grant from the Global Alliance for

Vaccines and Immunization was used to pay for this in the years 2001–2002.2 Balochistan's EPI has struggled to stop the spread of infectious diseases that are of public concern, and poliomyelitis is still widespread. Thalassemia has been on the rise alarmingly in Balochistan over the past several years, with an 8.1 percent prevalence among Baloch people and a 5.6 percent prevalence in Pashtun-dominated areas.

In the Balochistan province, there are 2,000 children who are thought to have beta-thalassemia. Due to their constant need for blood transfusions for survival, these youngsters are at a significant risk of developing transfusion-transmitted illnesses (TTIs). The administration must be concerned about the loss because the province loses more than 500 lives annually.

1.16 Causes and Risk factors of Hereditary and congenital anomalies

The majority of congenital illnesses, particularly abnormalities, manifest irregularly in families as a single unique instance. The same occasional occurrence of genetic diseases is either due to inadequate family size or to a novel mutation that first occurred in the male or female germ cell, resulting in the conception of the afflicted kid. The majority of chromosomal abnormalities are sporadic, although there is a substantial link between rising maternal age and trisomy of chromosomes 13, 18, or 21. Mutations in maternal mitochondrial DNA cause a large number of inborn metabolic abnormalities. Genomic imprinting errors caused by parental dysfunction in the control of gene expression led to aberrant expression of the maternal and paternal alleles and impairment of embryonic development. Each parent contains one mutant copy (allele) of the specific gene in autosomal recessive illnesses, which are diseases inherited from both parents. No of how previous pregnancies turned out, every conception has the same risk of disease. Disorders brought on by the environment, such fetal alcohol syndrome, are probably avoidable.

According to estimates, around one-fourth of all congenital abnormalities might be hereditary in origin. Recent estimates, however, indicate that the percentage may be greater since cytogenetic and molecular procedures have improved significantly over the past 20 years, making it possible to discover previously undetectable chromosomal abnormalities, gene mutations, and genetic polymorphisms.

1.16.1 The two most prevalent genetic causes of congenital deformities are.

1. Single-gene problems and
2. Chromosomal abnormalities**.**

Genetics factors:

1.16 .2 Single Gene mutations

Single-gene issues are caused by structural alterations (mutations) to genes. They contribute to slightly more than 17% of congenital malformations. Single-gene anomalies may be passed on to children by one or both parents, and a chance (new) mutation may be to fault. New research is finding more and more isolated abnormalities caused by single-gene mutations, such as some forms of congenital heart malformations and cleft lip with or without cleft palate. However, compared to isolated malformations, several congenital deformities that are syndromic appear to be more commonly associated with single-gene problems.

1.16.3 Chromosomal abnormalities:

There are chromosomal anomalies in 10% of infants with congenital deformities, which can either impact the autosomes or the sex chromosomes. Chromosome structural abnormalities like deletions (like the deletion of the proximal region in the long arm of chromosome 22 associated with the DiGeorge and velocardiofacial syndromes) and duplications (like the duplication of the short a chromosome) as well as numerical

abnormalities like having an extra chromosome (like trisomy's like Down syndrome or trisomy 21, trisomy 13, and trisomy X) are examples of changes. Chromosomal abnormalities are almost often linked to patterns of various birth malformations.

1.16.4 Environmental factors

An estimated 4-10% of congenital abnormalities are caused by known environmental and maternal factors. Examples include maternal nutritional condition; chemical exposure; and perhaps use of illegal substances.

• Maternal illnesses, such as rubella

• physical elements, such as heat and ionizing radiation.

• Maternal chronic illnesses, such as diabetes

• exposure to prescription drugs that are known to have teratogenic effects (e.g., retinoic acid, valproic acid).

The reason is still unclear for around 66% of congenital abnormalities. Congenital abnormalities that are thought to have environmental origins or be multifactorial are included in this category.

1.16.5 Multifactorial:

It refers to the interaction of several unidentified gene variations with environmental variables to produce a particular abnormality.

In respect to various congenital malformations, a variety of putative gene-environment interactions have been investigated. For instance, various genes, such as TGFA, TGFB3, CYP1A1, NAT1, NAT2, and GSTT1, as well as their mutations and polymorphisms, have

been examined to assess their degree of relationship with an elevated risk for oral clefts in the kids of cigarette-smoking mothers. Prenatal exposure to the anticonvulsant medication phenytoin is another instance of how genes and the environment interact.

1.16 Demographic and socioeconomic variables

Congenital diseases may have a higher prevalence among families and nations with limited resources, where low income may be an indirect driver of these conditions. According to estimates, low- and middle-income nations account for 94% of cases of severe congenital abnormalities. This elevated risk, which is an indirect predictor, may be due to pregnant women's likely insufficient access to nutrient-rich meals, higher exposure to contaminants or factors like sickness and alcohol, or poorer access to healthcare and screening.

1.16.1 Maternal age

- Is another risk factor for inadequate intrauterine fetal development. With elder maternal age, the likelihood of chromosomal abnormalities, including Down syndrome, increases.

1.17 Screening and Prevention of Congenital anomalies

1.17.1 Prevention

Preventive public health initiatives seek to lower the prevalence of specific congenital diseases by removing risk factors or improving protective factors.

Make sure teenage girls and mothers eat a range of fruits and vegetables as part of a balanced diet and keep a healthy weight. Make sure teenage girls and mothers consume enough vitamins and minerals, particularly folic acid, in their diets.

Avoiding travel by pregnant women (and occasionally women of childbearing age) to areas suffering epidemics of illnesses known to be related with congenital abnormalities.

Ensuring that mothers stay away from harmful substances, particularly alcohol and tobacco, reducing or eliminating a pregnant woman's exposure to hazardous environmental pollutants (such heavy metals or pesticides).

treating gestational diabetes through counselling, diet, weight management, and, if necessary, insulin administration.

Ensuring that any drug or medical radiation (such as imaging rays) given to pregnant women is appropriate and supported by a comprehensive risk-benefit analysis.

Immunization, particularly for women and children against the rubella virus.

enhancing and bolstering training for medical professionals and others involved in the promotion of congenital disease prevention; and checking for infections, including syphilis, varicella, and rubella; and thinking about treatment.

1.17.2 Screening, Treatment and care

Preconception and peri-conceptional healthcare comprises standard reproductive health procedures as well as medical genetic testing and counselling.

1. **Preconception screening**:

   This can be useful in identifying those who are susceptible to either getting the ailment themselves or passing it on to their children. Screening, which involves gathering family histories and carrier screening, is extremely effective in countries where consanguineous marriage is common.

2. Peri – conceptional screening

Maternal characteristics may increase a woman's risk, therefore screening results should be used to identify the appropriate amount of care to be given. testing for early or advanced maternal age, testing for alcohol or tobacco usage, or looking for other issues may be part of this. Ultrasound may be used to screen for Down syndrome and substantial structural abnormalities during the first trimester, and it can also check for severe fetal anomalies during the second trimester. Maternal blood can be analyzed for placental markers or free fetal DNA, which can identify a range of chromosomal abnormalities, to predict the chance of developing chromosomal abnormalities or neural tube defects. Chromosome abnormalities and infections in high-risk pregnant women can be identified via diagnostic procedures including chorionic villus sampling and amniocentesis.

3 . Neonatal screening:

A crucial initial step in the detection procedure is screening babies. Congenital disease mortality and morbidity are reduced by permitting early referral and the start of medical or surgical treatment.

Early treatment of hearing loss and the opportunity to enhance language, speech, and communication skills are both made possible by early identification of hearing loss. Infants with congenital cataracts can benefit from early referral and surgical correction, which increases the likelihood that the kid will live to adulthood.

It is possible to screen newborns for a variety of metabolic, hematologic, and endocrine abnormalities, many of which may not show symptoms right away. Depending on incidence and cost, different illnesses are checked for in different countries. Even in low-income and middle-income nations, newborn screening is becoming more common.

1.17.3 Treatment and care

Some congenital disorders can be treated by medical or surgical techniques. Even while access to complicated care is improving in low- and middle-income nations, there may be regional and systemic differences in who can receive it.

Surgery and appropriate postoperative care can frequently lower the risk of mortality (as in the case of congenital heart issues) or morbidity (e.g., congenital talipes, cleft lip/palate) associated with structural congenital illnesses. Regarding the therapy's capacity to reduce mortality and morbidity, this aspect is typically disregarded. Results are improved by screening, referral, and care (at specialist facilities in the case of some disorders like heart abnormalities) at lower levels of the system.

Certain metabolic, endocrine, and hematological diseases can be treated medically to enhance quality of life. Congenital hypothyroidism is a prime example, since early discovery and treatment allow for full physical and mental development into healthy adulthood, but a missed diagnosis or the absence of a straightforward therapy increases the likelihood of severe intellectual handicap.

Some congenital abnormalities in children may need ongoing care, such as physical therapy, speech therapy, occupational therapy, and assistance from families and the community.

1.18 Study gape

As per the available literature on congenital anomalies there is no such study on congenital anomalies addressing the current epidemiological trends prevailed in the diverse and multi-ethnic population of the remote Loralai district.

1.19 Aims and objectives of the research.

Loralai is a remote area and we found no such data according to hereditary congenital anomalies so, it is consequential to investigate the prevalent of congenital anomalies in loralai district.

1.20 Objectives

- To find out the prevalence of hereditary congenital anomalies in Loralai district of Balochistan.
- To find out the ratio of consanguinity in the population of Loralai district.
- To know about the status of the affected families in Loralai District.
- To find out the ratio of comorbidities in the surveyed data.
- To learn about the clinical and demographic variables responsible for the congenital anomalies present in Loralai district.

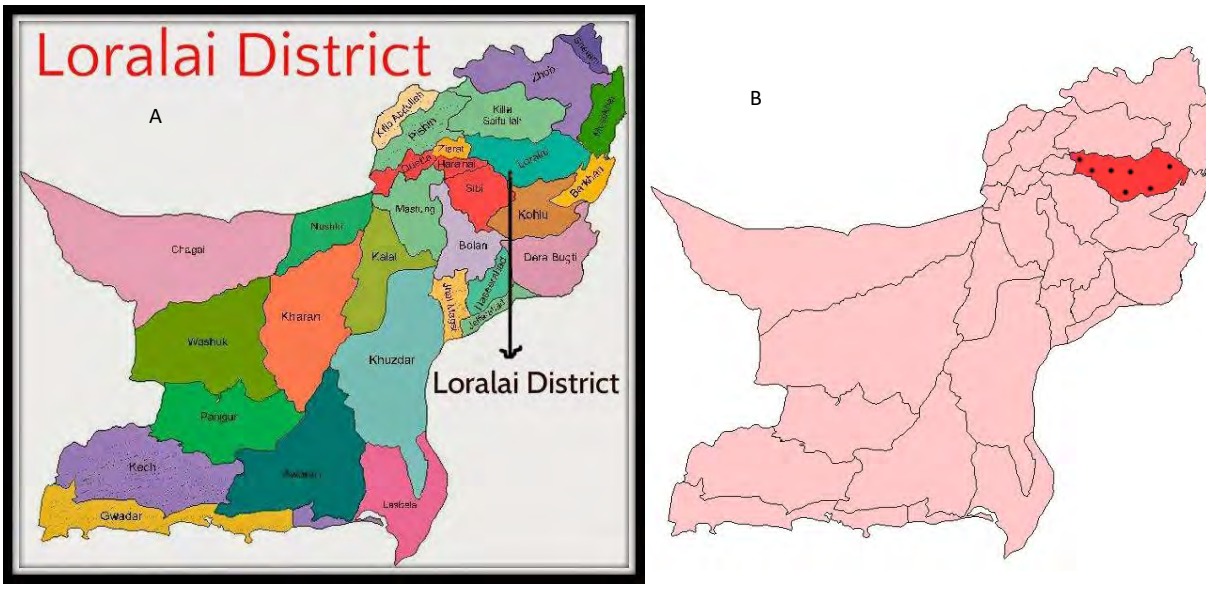
1.21 Prevalent of Hereditary and congenital anomalies in Loralai district

We are not found any literature according to congenital anomalies present in loralai district however we observed blood disorders (thalassemia) in many areas of loralai and other congenital and hereditary anomalies like dwarfism, cp etc

Chapter # 02

Methodology

2.1 Map of Loralai district



Google source**.**

In figure **A** Loralai district with other districts of Balochistan. In figure **B** the black dots in the red area show different areas of Loralai which observed during field work.

2.2 Geography of Loralai District

The Loralai district is located between 67° 41′ 18″ and 69° 44′ 22″ east longitudes and latitudes of 29° 54′ 50″ to 30° 41′ 28″ north. It is situated in northern Balochistan at a height of 1,450 meters above mean sea level. The district is bordered on the north by the Zhob and Kila Saifullah districts, on the south by the Kohlu Agency/district and the Sibi district, on the east by the Barkhan and Musakhel districts, and on the west by the Sibi and Ziarat districts.

The district got its name from the Loralai stream, which is located where the Anambar and Nari rivers meet. The town of Loralai, which acts as the district's administrative hub, is located to the north of the Loralai stream.

The district was originally known as Bori, after the Bori Valley, but when the Loralai town grew, the British transferred the district's administrative center there and changed the district's name to Loralai district.

2.2.1 Population:

According to 2017 census the population of loralai is 397,400**.**

Name	District Loralai	
Population		397,400
Area	7,199km	
Population density	48.8 persons /km	
Growth rate		2.50%
Male population		53.30%
Female population		46.50%
Urban population		16.31%
Literacy Rate		44%
Male literacy		61%
female literacy rate		22%
Major economic source	Agriculture and forestry	

Google source.

2.2.2 Education:

District Loralai is placed 97th out of 141 listed districts in Pakistan in terms of education score index, according to the Pakistan District Education Rankings. This statistic takes into account retention, gender equity, and learning within the district.

In the district, the literacy rate for those aged 10 and over in 2014–15 was 44%; however, it was just 22% for women.

With 89% of the schools in the district being elementary schools, post-primary access is a significant problem. Contrast this with high schools, which make up only 3% of the district's government institutions. The enrollment statistics for 2016–17, which show 12,192 students enrolled in classes 1–5, but only 586 in classes 9 and 10, also reflect this.

Another problem in the district is the gender pay gap. Only 28% of the district's schools are for girls. The district's main problem with girls' education access is reflected in the low female literacy rates.

2.3 Methodology

Methodology is the careful, theoretical examination of the practices employed in a particular field of study. It consists of the rules, procedures, and techniques used while doing research or study in a certain field.

2.3.1 Typically, methodology includes the following measures.

- Performa for data collection
- Ethical approval
- Assent from family
- Field visit
- Assembly of Pedigree
- Storage of data, analyzing and statistical analyses.
- Classification of hereditary congenital anomalies

2.3.2 Performa design

It was important to create a Performa that had all the questions that required to be asked in order to obtain the data for the patients with congenital defects before beginning the data collection. However, each lab have already template of Performa. We need to add a few extra rows for the extra data that was needed for the fieldwork. The Performa included the patient's name, local residence, union-council, origin, and all relevant information about the topic (having a congenital abnormality). Whether the subject resided in an urban or rural location and the subject's age. Additionally, the performance included details about the subject's cast (Quam or Berardi), mother language, kinfolk, and marital status. Whether the subject is married or single. It also included a few social characteristics, such as the subject's and his family's economic standing (whether poor, low, mid, low-mid, or affluent). There was information on whether or not the subject was photographed as well. Additionally, there was some information concerning sporadic (just one member of the family was afflicted) or familial (more than one member of the family was affected). The age of the mother and father when the subject was born was also included in that particular Performa. The questionnaire also included details on the parents' consanguinity. A variety of consanguineous connections, including father-brother-daughter (F.B.D.), father-sister-daughter (F.S.D.), mother-sister-brother-daughter (M.S.D.), second cousin, and no consanguinity at all, were also studied. Additionally, there was some information pertaining to the subject's ability to become pregnant or not. The parity order of the topics was another topic of contention. The performance also included information on the overall number of impacted people in the lineage and the subject generation. In short Performa have all the demographical, clinical variables necessary for a specific research.

2.3.3 Ethical approval

It refers to the process of obtaining permission from an institutional review board or ethics committee to conduct research involving human subjects.

Ethical approval makes sure that research carried out by universities adheres to ethical ideas and standards. An ethics committee or review board at the university, which assesses the research's ethical consequences, grants this approval. The committee evaluates the possible risks and advantages of the study, confirms that research participants have provided their informed permission, and guarantees that the research is carried out in a way that respects their confidentiality and privacy. The approval procedure is crucial to safeguard the rights and welfare of study participants as well as the responsible and ethical conduct of research. This study was approved by the ethical review board of Quaid -i- Azam university Islamabad and also by department of zoology.

2.3.4 Assent from family

Describe the objective of the data gathering start by outlining to the family members why you need to gather information on the impacted patient. In order to guarantee that they get the significance of the data gathering, be precise and succinct in your explanation. Inform the family members in full about the data collecting process, including the kinds of data that will be gathered, how they will be gathered, and the purposes for which they will be utilized. Obtaining their trust in the research was essential to the study's success. It was vital to assure them that all their moral principles would be upheld. The approval of oral consent was acquired. There were a variety of responses from the various families: some of them were completely open to taking the data, some of them were willing to offer the subject's personal

information but forbade taking their images, and others of them were unwilling to share any information at all. So, families show vary response during field work.

2.3.5 Field visit and data collection

1. Study population

The Loralai district is located between 67° 41′ 18″ and 69° 44′ 22″ east longitudes and latitudes of 29° 54′ 50″ to 30° 41′ 28″ north. It is situated in northern Balochistan at a height of 1,450 meters above mean sea level. The district is bordered on the north by the Zhob and Kila Saifullah districts, on the south by the Kohlu Agency/district and the Sibi district, on the east by the Barkhan and Musakhel districts, and on the west by the Sibi and Ziarat districts**.** The total population is 397,400 census of 2017 in which population density is 48.8km2. Total male population is 53.30% and female population is 46.50% .Total literacy rate is 44% in which male literacy is 61% while female is 22% only. The major economic source is agriculture and forestry and in some areas cattle's are the main earning source. The major language is Pashto because majority of the population is comprised on pathan tribe. Congenital malformations were the subject of a sort of population-based study, and patients were approached through door-to-door surveys.

2.Study design and duration

The survey was carried out at a number of union councils. The research took place from September 2022 to December 2022, lasting 4 months. We collected 371 cases from different union council of the Loralai district of Balochistan which consist of hereditary and congenital anomalies. We covered urban areas of the city as well as remote rural areas**.** Both

type of parental union is present in the population about 50% is consanguinity and 50% is out of family marriages

2.3.6 Assembly of Pedigree

We draw a pedigree on the back side of Performa .A family tree that shows the pattern of inheritance of a certain trait or illness within a family is created as part of the assembling of a pedigree. In order to achieve this, data on family members' connections, medical histories, and genetic status are gathered. The data is then arranged into a family tree diagram, with symbols denoting each family member and links between them illuminating their connections. A pedigree uses circles for females, squares for males, and diamonds for member whose gender is unclear. A symbol that is shaded denotes the presence of the trait or condition under study, whereas a symbol that is unshaded denotes the absence of the trait or disease. Pedigree is important for the understanding of the inheritance pattern in the family under study.

2.3.7 Storage of data, analyzing and statistical analysis

2.3.8 Data storage

After the pedigree data has been gathered, it must be kept in a database or spreadsheet. This makes it simple to access and modify the data during analysis. In order to prevent data loss or corruption, it is crucial to make sure that it is kept securely. So, we entered all the data on excel sheet for easy access for further use.

2.3. 9 Analyzing the Data

Pedigree analysis entails looking at how members of a family are related to one another and finding patterns of inheritance for a certain trait or disease. A pedigree chart or data analysis tools can be used to visually represent this. Finding people who carry a certain characteristic, evaluating the likelihood of inheritance, and identifying any possible concerns for future generations are all possible parts of the investigation. This makes easy to observe the possible inheritance pattern in the family.

2.3.10 Statistical Analysis

The pedigree data may be further examined using statistical analysis. This entails putting theories regarding the inheritance patterns for a certain feature to the test using mathematical models. To check if the observed inheritance pattern differs significantly from what would be predicted by chance, one can apply a chi-square test, for instance. Any substantial correlations between genetic variables and a certain characteristic or disease can be found through statistical analysis.

2.3.11 Classification of Hereditary congenital anomalies

Depending on where they are, how severe they are, and what the underlying reasons are, congenital malformations can be divided into many groups.

2.3.12 Congenital abnormalities can be categorized

- Anatomically according to where they are found in the body, such as craniofacial anomalies (affecting the head and face), limb malformations, cardiovascular anomalies, and urogenital anomalies.
- Functional classification: Anomalies that affect how the body works, such as respiratory, neurological, and gastrointestinal, might be categorized as congenital.
- Classification of congenital abnormalities according to severity: Congenital anomalies were categorized according to their severity, from minor defects that have little to no effect on health to large anomalies that can be life-threatening or result in considerable handicap. So, we were classified all the collected data in the analytical and statistical way and created different tables and charts on excel sheet.

Chapter # 03

Results

Demographic Distribution of index subjects

3.1 Paternal and maternal age intervals

The age covers a very huge amount of data therefore we convert into intervals. We placed in 6 different intervals, start from 26≥ up to ≤75. Large number of paternal and maternal ages are present in 26 ≥35 interval followed by interval 36≥45 and 16 ≥25, in this interval number of maternal ages is greater than paternal. Very less number is present in other intervals like 45≥55, 56 ≥65 and in 66 ≥75.

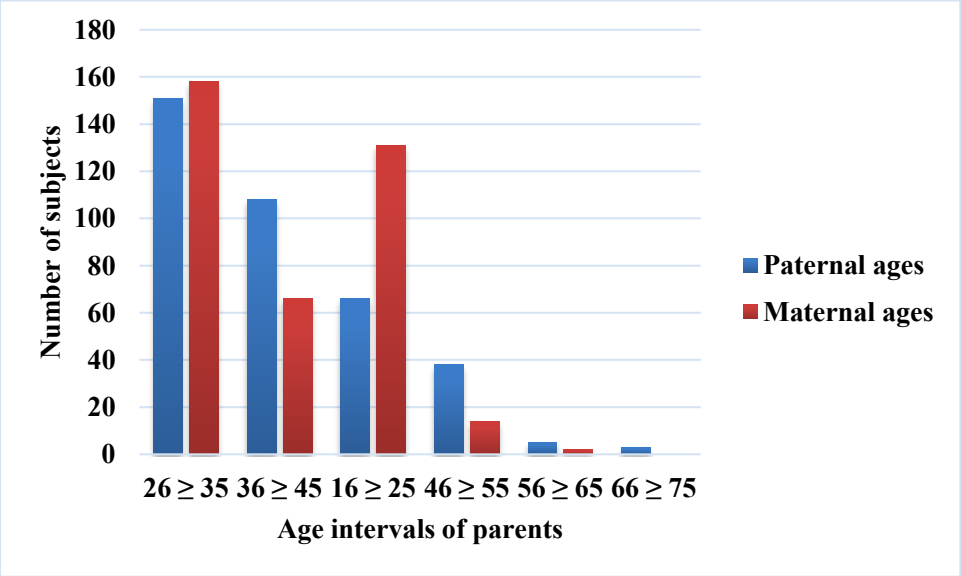


Figure 3.1 Paternal and maternal age intervals

3.2 Distribution of gender with respect to marital status of the subjects

The marital status of the subjects are illustrate in the below figure which shows that greater number of the subjects are single in which males are n = 229 while female are n= 135.The married status of the subjects are very low in number, only n= 4 males are married and n = 3 females are married.

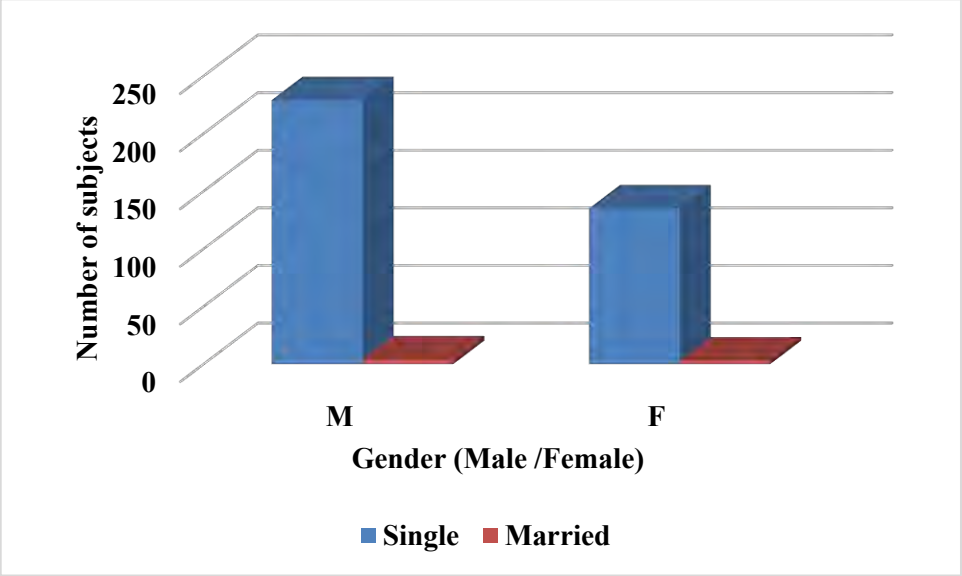


Figure 3.2 Distribution of gender with respect to marital status of the subjects

3.3 Distribution of subjects with respect to extended/ nuclear nature.

The distribution of subjects was based on gender. The number of male subjects are high in both extended and nuclear variable. While the numbers of female subjects are low in both. The male subjects are n = 139 in extended families while in nuclear males are n = 94. The females are as shown in figure low in number n =72 in extended and in nuclear families n = 66 in numbers. So more number of males subjects are belong to extended families.

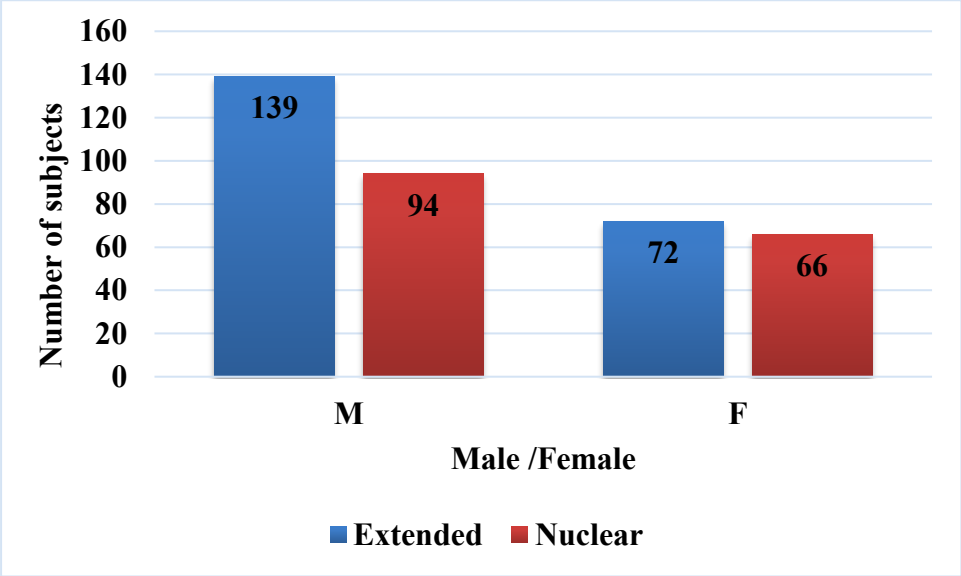


Figure 3.3 Distribution of subjects with respect to extended/ nuclear nature

3.4 Distribution of gender with respect to major caste of the subjects

The subjects are categorized into 5 different castes in which Kakar caste is the highest number followed by Nasir then Khilji, Baloch and then Luni. We placed castes which are very low in number in “other” category because they are very low in number. The district Loralai is consist of 99% of Pashtun tribes therefore mostly people are belong to Pashto tribes.

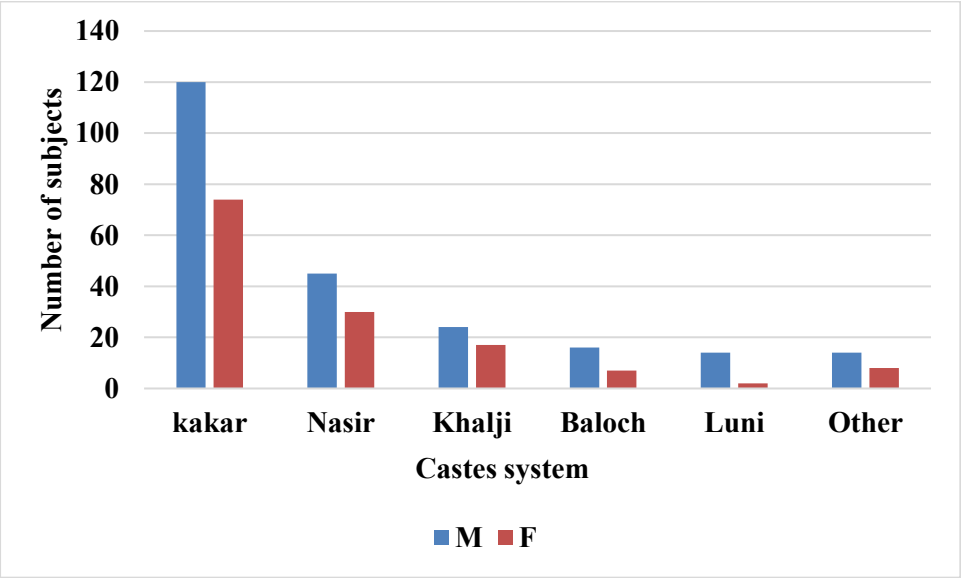


Figure 3.4 Distribution of gender with respect to major caste of the subjects

3.5 Distribution of mother tongue with respect to gender of the subjects

The distribution of the mother tongue is categorized into 4 different languages in which Pashto is the highest in number n = 208 in males and n = 125 in females. Other languages like Saraiki, Balochi and Farsi are very less in number. Some other languages are very few in numbers therefore we placed in "other". These languages are very common in district loralai and due to Pashton tribe community Pashto language is very high.

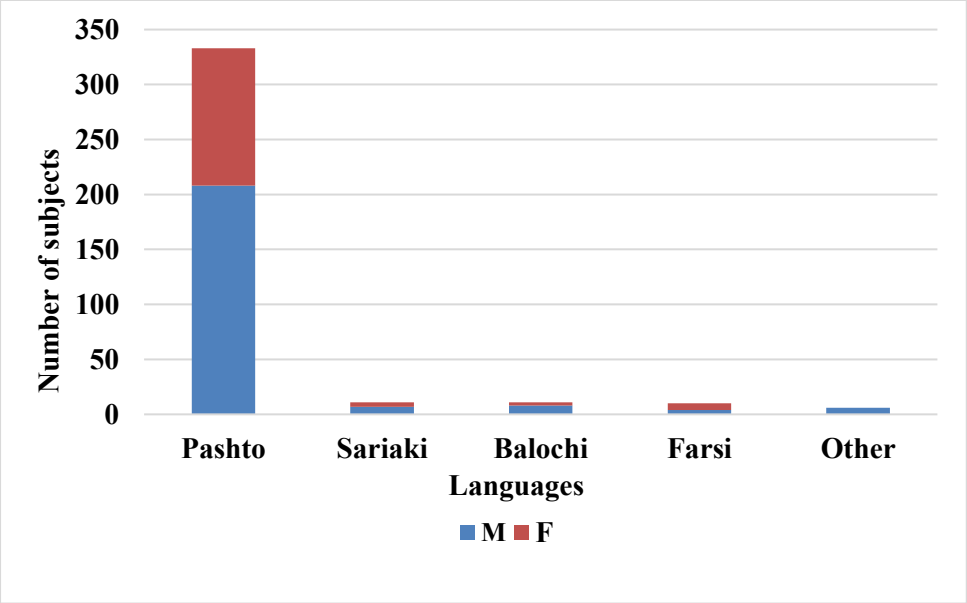


Figure 3.5 Distribution of mother tongue with respect to gender of the subjects

3.6 Distribution of gender of the subjects with respect to guardian occupation.

The occupation of the guardian is placed in 7 different classes in which more of the families are belong from labor class, followed by government job, shopkeeper, driver, teacher, farmer and business. While very few families are belonging from other occupation, so we placed in “other” class.

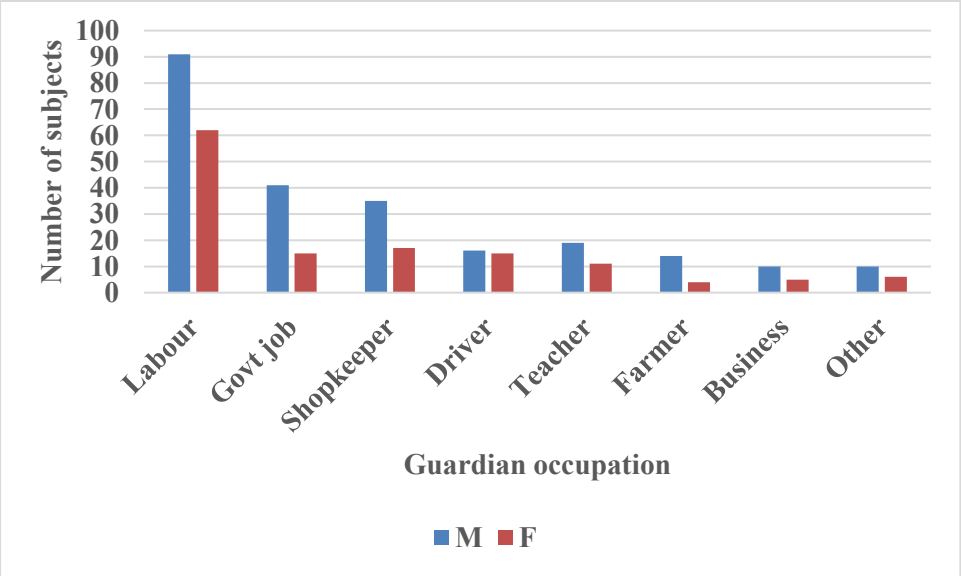


Figure 3.6 Distribution of gender of the subjects with respect to guardian occupation.

3.7 Distribution of all the demographic variables with their frequency and percentage

In table 3.1 all the demographic variables are given in detail with their frequency and percentage, in which gender of the subject is on the top, which is categorized into male and female, male was n= 233 in number while female was n =138. All other variables were also included like subject origin, age, marital status, family type, economic status, education, caste, language, the maternal and paternal education and the guardian occupation. All these demographic variables were collected from the subject guardian in door to door survey during field work.

Table: 3.1 Distribution of all the demographic variables with their frequency and percentage.

Variables		Frequency (n)	Percentage (%)
Gender (n=371)	Male	233	63
	Female	138	37
Origin (n=371)	Urban	260	70
	Rural	111	30
Patient Age range(years) (n=371)	Up to 5	66	18
	>5 to 10	96	26
	>10 to 15	90	24
	16 to 20	57	15
	21 to 25	25	7
	>25	37	10
Patient Education Level (n=320)	Illiterate	236	74
	Literate	84	26
	• Primary	36	42
	• Middle	21	25
	• Matric	16	19
	• F.A	5	6
	• B.A	6	7
Martial status (n) = 92	Single	85	92
	Married	7	8
Family Type	Extended	211	57
	Nuclear	160	43
Caste system			
	Kakar	194	52
	Nasir	75	20
	Khilji	41	11
	Baloch	23	6
	Luni	16	4
	Others	22	6
Economic status	Poor	144	39
	Low	227	61

Language			
	Pashto	333	90
	Saraiki	11	3
	Balochi	11	3
	Farsi	10	3
	Other	6	1
Religions	Islam	370	100
	Christianity	1	0
Paternal age(years) at birth	>16 to 25	66	18
	26 to 35	151	41
	35 to 45	108	29
	46 to 55	38	10
	56 to 65	8	2
Maternal age (Years) at birth	>15 to 25	131	35
	26 to 35	158	43
	36 to 45	66	18
	46 to 55	16	4
Paternal Education	Illiterate	195	53
	literate	176	47
	• Primary	24	14
	• Middle	20	11
	• Matric	27	15
	• F. A/F.Sc	48	27
	• B.A	32	18
	• M.A	25	14
Maternal Education	Illiterate	348	94
	Literate	23	6
	• Middle	3	13
	• Matric	10	43
	• F.A	10	43
Guardian occupation	Labor	153	41
	Govt job	56	15
	Shopkeeper	52	14
	Driver	31	8
	Teacher	30	8
	Farmer	18	4
	Business	15	4
	Other	16	4

3.8 Demographic Variables with respect to gender and their percentage.

We were distributed all demographic variables with their gender and familial/sporadic nature in the next 2 tables 3.1 and 3.2 respectively. In origin 70% subjects were belong from urban while 30% subjects were belonging from rural areas, higher percent in urban areas may be due to large population size or may be easily approachable. In table 3.2 the patient education level shows significant value due to the very high number n = 236 of illiterate and very less number were literate n =84, patient education is count on age ≥5. All other variables with respect to gender showing nonsignificant values in the given table. We also distributed demographic variables with respect to the familial/sporadic nature in the next table 3.3 in which all were shown nonsignificant values**.**

Table 3.2 Demographic Variables with respect to gender and their percentage.

Variables	Gender (No.)		Gender (%.)		Total (No.)	Total (%)
	Male	Female	Male	Female		
Origin (n= 371)						
Rural	68	43	61	39	111	30
Urban	165	95	63	37	260	70
	χ^2 = 0.1612, df = 1					
	P value = 0.6880					
	Nonsignificant					
Age range (years) n= 371						
Up to 5	43	23	65	35	66	18
>5 to 10	51	45	53	47	96	26
>10 to 15	56	34	62	38	90	24
16 to 20	40	17	70	30	57	15
21 to 25	16	9	64	36	25	7
>25	26	11	70	30	37	10
	χ^2 = 6.213, df = 5					
	P value 0.2861					
	Nonsignificant					
Patient Education level (age > 5 years, n=320)						
Illiterate	133	103	56	44	236	74
Literate	66	18	79	21	84	26
	χ^2 =13.00, df =1					
	P value =0.0003					
	Significant ***					
•Primary	24	12	67	33	36	42
•Middle	20	1	95	5	21	25
•Matric	12	4	75	25	16	19
•F. A	5	0	100	0	5	6
•B. A	5	1	83	17	6	7
Economic Status						
Poor	87	57	60	40	144	39
Low	146	81	64	36	227	61
	χ^2 = 0.573, df =1					
	P value 0.4487					
	Nonsignificant					
Marital status age > 18, n=92						
Single	60	25	71	29	85	92

Married	4	3	57	43	7	8
	χ^2 = 0.552, df = 1					
	P value 0.4574					
	Nonsignificant					
Family type						
Nuclear	94	66	59	41	160	43
Extended	139	72	66	34	211	57
	χ^2 = 1.978, df = 1					
	P valu = 0.159					
	Nonsignificant					
Caste System						
Kakar	120	74	62	38	194	52
Nasir	45	30	60	40	75	20
Khilji	24	17	59	41	41	11
Baloch	16	7	70	30	23	6
Luni	14	2	88	12	16	4
Others	14	8	64	36	22	6
	χ^2 = 5.281, df = 5					
	P value = 0.3826					
	Nonsignificant					
Language						
Pashto	208	125	62	38	333	90
Saraiki	7	4	64	36	11	3
Balochi	8	3	73	27	11	3
Farsi	4	6	40	60	10	3
Other	6	0	100	0	6	2
	χ^2 = 6.263, df = 4					
	P value = 0.1803					
	Nonsignificant					
Religion						
Islam	232	138	63	37	370	100
Christianity	1	0	0	100	0	0
	χ^2 = 0.5939, df = 1					
	P value =0.4409					
	Nonsignificant					
Paternal age(years) at birth						
>16 to 25	44	22	67	33	66	18
26 to 35	87	64	58	42	151	41
35 to 45	72	36	67	33	108	29
46 to 55	25	13	66	34	38	10
56 to 65	5	3	62	38	8	2
	χ^2 =2.996, df =4					
	P value = 0.558					
	Nonsignificant					
Maternal age interval at birth						
>15 to 25	86	45	66	34	131	35
26 to 35	89	69	56	41	158	43
36 to 45	48	18	73	27	66	18
46 to 55	10	6	63	37	16	4
	χ^2 = 6.072, df = 3					

	P value = 0.108					
	Nonsignificant					
Paternal Education						
Illiterate	114	81	58	42	195	53
Literate	119	57	68	32	176	47
	χ^2 =3.317, df = 1					
	P value = 0.068					
	Nonsignificant					
Primary	18	6	75	25	24	14
Middle	13	7	65	35	20	11
Matric	38	10	79	21	48	15
F. A/F. Sc	15	12	56	44	27	27
B.A	18	14	56	44	32	18
M.A	17	8	68	32	25	14
Maternal education						
Illiterate	220	128	63	37	348	94
Literate	13	10	57	43	23	6
	χ^2 = 0.4142, df = 1					
	P value = 0.519					
	Nonsignificant					
Middle	1	2	33	67	3	13
Matric	5	5	50	50	10	43
F. A/F. Sc	4	0	100	0	4	17
B. A	3	3	50	50	6	26
Guardian Occupation						
Labor	91	62	59	41	153	41
Govt job	41	15	73	27	56	15
Shopkeeper	35	17	67	33	52	14
Driver	16	15	51	49	31	8
Teacher	19	11	63	37	30	8
Farmer	14	4	78	22	18	5
Business	10	5	67	33	15	4
Other	10	6	63	37	16	4
	χ^2 =7.226, df = 7					
	P value = 0.405					
	Nonsignificant					

Table 3.3 Distribution of demographic variables with respect to familial /sporadic nature.

Demographic Variables	Familial attributes N0.		Percentage %		Total N0.	Percentage %
	Familial	Sporadic	Familial	Sporadic		
Origin (n= 371)						
Rural	29	82	26	74	111	30
Urban	71	189	27	73	260	70
	χ^2 =0.055, df = 1					
	P value = 0.814					
	Nonsignificant					
Age range (years) n= 371						
Up to 5	12	54	18	82	66	18
>5 to 10	26	70	27	73	96	26
>10 to 15	32	58	36	64	90	24
16 to 20	15	42	26	74	57	15
21 to 25	11	14	44	56	25	7
>25	9	28	24	76	37	10
	χ^2 = 9.170, df = 5					
	P value = 0.102					
	Nonsignificant					
Education level (age ≥ 5 years, n=320)						
Illiterate	62	174	8	74	236	74
Literate	25	59	30	70	84	26
	χ^2 = 0.3813, df = 1					
	P value = 0.536					
	Nonsignificant					
•Primary	11	25	31	69	36	42
•Middle	7	14	33	67	21	25
•Matric	4	12	25	75	16	19
•F. A	2	3	40	60	5	6
•B. A	2	4	33	67	6	7
Economic Status						
Poor	41	103	28	72	144	39
Low	59	168	26	74	227	61
	χ^2 = 0.275, df = 1					
	P value = 0.599					
	Nonsignificant					
Marital status age ≥ 18, n=92						
Single	23	62	27	73	85	92
Married	2	5	29	71	7	8
	χ^2 = 0.007, df = 1					
	P value = 0.931					
	Nonsignificant					
Family type						

Nuclear	50	110	31	69	160	43
Extended	50	161	24	76	211	57
	χ^2 = 2.637, df = 1					
	P value = 0.104					
	Nonsignificant					
Caste System						
Kakar	56	138	29	71	194	52
Nasir	17	58	23	77	75	20
Khilji	11	30	27	73	41	11
Baloch	5	18	22	78	23	6
Luni	6	10	38	62	16	4
Others	5	17	23	77	22	6
	χ^2 = 2.482,df = 5					
	P value = 0.779					
	Nonsignificant					
Language						
Pashto	91	242	27	73	333	90
Saraiki	1	10	9	91	11	3
Balochi	5	6	45	55	11	3
Farsi	1	9	10	90	10	3
Other	2	4	33	67	6	2
	χ^2 = 5.302, df = 4					
	P value = 0.257					
	Nonsignificant					
Religion						
Islam	99	271	27	73	370	100
Christianity	1	0	100	0	1	0
	χ^2 = 2.717, df = 1					
	P value = 0.099					
	Nonsignificant					
Paternal age(years) at birth						
>16 to 25	15	51	23	77	66	18
26 to 35	49	102	32	68	151	41
35 to 45	22	86	20	80	108	29
46 to 55	10	28	26	74	38	10
56 to 65	4	4	50	50	8	2
	χ^2 =7.459, df = 4					
	P value = 0.113					
	Nonsignificant					
Maternal age interval at birth						
>15 to 25	41	90	31	69	131	35
26 to 35	39	119	25	75	158	43
36 to 45	16	50	24	76	66	18
46 to 55	4	12	25	75	16	4
	χ^2 = 1.947, df = 3					
	P value = 0.583					
	Nonsignificant					
Paternal Education						

Illiterate	48	147	25	75	195	53
Literate	59	117	34	66	176	47
	χ^2 = 3.576, df =1 P value = 0.058 Nonsignificant					
Primary	8	16	33	67	24	14
Middle	6	14	30	70	20	11
Matric	11	37	23	77	48	15
F. A/F. Sc	9	18	33	67	27	27
B.A	12	20	38	62	32	18
M.A	13	12	52	48	25	14
Maternal education						
Illiterate	96	252	28	72	348	94
Literate	4	19	17	83	23	6
	χ^2 = 1.139, df = 1 P value = 0.285 Nonsignificant					
Middle	1	2	33	67	3	13
Matric	2	8	20	80	10	43
F. A/F. Sc	0	4	0	100	4	17
B. A	1	5	17	83	6	26
Guardian Occupation						
Labor	37	116	24	76	153	41
Govt job	18	38	32	68	56	15
Shopkeeper	13	39	25	75	52	14
Driver	14	17	45	55	31	8
Teacher	7	23	23	77	30	8
Farmer	2	16	11	89	18	5
Business	3	12	20	80	15	4
Other	6	10	38	62	16	4
	χ^2 = 10.45, df = 7 P value = 0.164 Nonsignificant					

3.9 Distribution of congenital anomalies into major and minor categories.

The major classification comprised into 9 groups as mentioned in table number 3.4 . In which the neurological disorders were the most common(n= 80) ,followed by limb defects (n= 78) ,neuromuscular defects (n= 67) ,blood disorders (n= 59), sensorineural defects (n= 42), eye/visual impairment(n= 24), musculoskeletal defects (n = 8) , orofacial defects = 8 and then cardiovascular defects (n=5) These major categories are taken against the gender of the subjects and the familial and sporadic nature of the subjects.

The Chi square test is significant for familial /sporadic because of a very varied number of data while nonsignificant for gender due to approximately equal amount of data.

The minor classification are according to their percentage, OMIM number and ICD -10 (Table 3.5) in which cerebral palsy is the most common (n= 57), than thalassemia (n=54), deaf and mute (n= 36) ,club foot n= 35 .

Table 3.4. Distribution of congenital anomalies with respect to gender (male /female) and familial /sporadic nature.

Congenital anomalies	No. of Subjects (n = 371)	Proportion	Gender (n=371)		Sporadic /Familial (n = 371)	
			Male	Female	Familial	Sporadic
Neurological Disorders	80	0.215	51	29	16	64
Limb defects	78	0.210	49	29	16	62
Neuromuscular defects	67	0.180	40	27	13	54
Blood Disorders	59	0.159	42	17	30	29
Sensorineural Defects	42	0.113	25	17	11	31
Eye/visual impairment	24	0.064	13	11	9	15
Musculoskeletal defects	8	0.021	7	1	3	5
Orofacial defects	8	0.021	5	3		8
Cardiovascular defect	5	0.013	1	4	2	3
Total	371		233	138	100	271
			$\chi^2 = 9.052$, df = 8		**$\chi^2 = 27.86$, df = 8**	

	P value = 0.338 Nonsignificant	**P value = 0.0005 Significant *****

Table 3.5. Minor Anomaly Classification.

Anomaly (major/minor)	**N0. of cases**	**Percentage %**	**OMIM**	**ICD-10**
Neurological Disorder	**80**	**22**		
Intellectual disability	51	**64**	300419 300298 300253	F 70 F 71 F 72
Macrocephaly	1	**1**	615637	Q75.3
Down syndrome	8	10	190685	G90.0
Epilepsy	12	15	607208	G 40
Spina bifida	6	8	182940	
Microcephaly	2	3	251200	
Sensorineural defect	**42**	**11**		
Deaf and mute	36	86	304400	Q 18
Microtia	4	10	600674	
Mute only	2	5		
Eye /Visual impairment	**24**	**6**		
Blindness	13	54	613216	
Farsightedness	3	13		
Strabismus	4	17		
Heterochrome	3	13		
Ptosis	1	4		
Blood Disorder	**59**	**16**		
Thalassemia	54	92	613985	
Sickle cell	4	7	603903	
Hemophilia A	1	2	306700	
Musculoskeletal Defects	**8**	**2**		

Dwarfism	5	63	100800	
Skeletal dysplasia	2	25	618870	
Genu valgum	1	13		
Neuromuscular Defects	**67**	**18**		
CP	57	85	605388	G 80.9
Muscular dystrophy	10	15	310200	G 71.0
Limb Defects	**78**	**21**		
Club foot	35	45	119800	Q 66.8
Polydactyly	27	35	174200	Q69.0
Anisomelia	7	9		M21.7
Syndactyly	3	4	609815	Q70.9
Oligodactyly	2	3		
Other	4	5		
Cardiovascular defects	**5**	**1**		
Atrial septal defect	5	100	108800	
Orofacial Defects	**8**	**2**		
Cleft palate	8	100	119530	

3.10 Distribution of anomalies with respect to isolated/syndromic nature.

The major anomalies are taken against the isolated/syndromic nature and their percentages are given in the table number 3. 6.The total number of isolated cases is 277 which comprised on 76% 0f the total, while the syndromic cases are 94 in number and their percentage is only 16% of the total. So, the isolated cases are greater in number in our data. The highest percentage of the syndromic cases are the neuromuscular(n=63%), followed by the neurological which is n= 54%, others are very less in number in syndromic nature. The chi square test is significant for this variable due to the varying number of data, and the isolated/syndromic nature is great influence on the subjects.

Table 3.6. Distribution of anomalies with respect to isolated/syndromic nature.

Anomaly	Number of subjects	Proportion	Isolated/ Syndromic Attributes		Percentage %	
			Isolated	Syndromic		
Neurological Disorder	80	0.215	37	43	46	54
Limb defects	78	0.210	75	3	96	4
Neuromuscular defects	67	0.180	25	42	37	63
Blood Disorders	59	0.159	59	0	.100	0
Sensorineural Defects	42	0.113	41	1	98	2
Eye/visual impairment	24	0.064	23	1	96	4
Musculoskeletal defects	8	0.021	6	2	75	25
Orofacial defects	8	0.021	7	1	88	12
Cardiovascular defect	5	0.013	4	1	80	20
Total	**371**		**277**	**94**	**76**	**16**
			χ^2 = 143.7, df = 9 **P value = P<0.0001** **Significant *****			

3.11 Distribution of congenital anomalies with respect to parity order of the subjects.

The parity order is taken against the anomalies. The parity order is the important variable of the data. Parity order was analyzed to establish any link between the parity order and the types of anomalies which we observed .The total number of the subjects are n= 371 in which n= 31 number are present in the fifth order and greater than ≥5 , followed by n=26 and than n=24 all are present in ≥5 order. The chi square is not significant for the parity order.

Table 3.7. Distribution of congenital anomalies with respect to parity order of the subjects.

Major anomaly	Total No.	Parity order					Percentage %				
		1	**2**	**3**	**4**	**≥5**	1	2	3	4	≥5
Neurological Disorders	80	22	14	11	9	24	28	18	14	11	30
Limb defects	78	20	7	12	13	26	26	9	15	17	33
Neuromuscular defects	67	18	4	7	7	31	27	6	10	10	47
Blood Disorders	59	20	8	8	8	15	34	14	14	14	25
Sensorineural Defects	42	8	7	3	7	17	19	17	7	17	40
Eye/visual impairment	24	6	2	6	5	5	25	8	25	21	21
Musculoskeletal defects	8	1	4	0	0	3	13	50	0	0	38
Orofacial defects	8	3	0	3	0	2	38	0	38	0	25
Cardiovascular defect	5	1	0	1	0	3	20	0	20	0	60
		χ^2 =41.46, df = 32 **P value = 0.1222** **Nonsignificant**									

3.12 Distribution of familial /Sporadic cases with respect to Parity order.

The parity order is also taken against the familial /sporadic nature of the subjects in which out of total 371 cases n=100 is familial and n=271 are sporadic. The highest percentage of the familial cases are present in the 2nd parity order which is n= 41% and the highest percentage of the sporadic cases exist in the 3rd parity order. The parity order with familial /sporadic nature is statistically significant.

Table 3.8 Distribution of familial /Sporadic cases with respect to Parity order

Parity order	Familial /Sporadic		Total No.	Percentage %	
	Familial	Sporadic		Familial	Sporadic
1	31	68	99	31	69
2	19	27	46	41	59
3	9	42	51	18	82
4	16	33	49	33	67
≥5	25	101	126	20	80
	100	271	371	27	73
	χ^2 = 11.18, df = 3				
	P value = 0.0108				
	Significant *				

3.13 Distribution of sibship with respect to familial nature of the subjects.

The sibship is taken against the familial nature and the major anomaly types. The total number of the familial cases are the n=100, so the sibships are categorized into the 1st , 2nd and 3rd and the highest number of sibship is exist in the 1st which is n=77 which are affected ,followed by n=19 in the 2nd and n=4 in the 3rd sibship. The highest number of familial cases are present in the blood disorder n=30 which is present in the 1st sibship. The chi square is

statistically is taken without the orofacial defects due to null values in the data and it is not significant.

Table 3.9 Distribution of sibship with respect to familial nature of the subjects.

Anomaly	Total No.	Familial cases (n= 100)	Sibship with disease		
			1	2	3
Neurological disorder	80	16	12	3	1
Limb defects	78	16	11	4	1
Neuromuscular defects	67	13	9	3	1
Blood disorder	59	30	22	8	0
Sensorineural defects	42	11	11	0	0
Eye/visual impairment	24	9	7	1	1
Musculoskeletal defects	8	3	3	0	0
Orofacial defects	8	0	0	0	0
Cardiovascular defects	5	2	2	0	0
Total	371	100	77	19	4
			χ^2 = 9.910, df = 14		
			P value = 0.768		
			Nonsignificant		
			We exclude orofacial defects due to zero values in all rows.		

3.14 Distribution of affected subjects with respect to familial nature.

The affected subjects are distributed against the major anomalies and the familial nature of the subjects and the affected cases are kept into different generations like 2nd , 3rd ,4th and 5th so, the highest number of affected subjects are exist in the 2nd generation ,followed by 3rd and then 4th and 5th . In the 2nd generation the highest number are present n =50, followed by n=31 in the 3rd generation . In the table below the total familial cases are n=100 so we taken total affected subjects according to familial cases which are also only n=100.

Table 3.10 Distribution of affected subjects with respect to familial nature

Anomaly	Total	No. of familial cases.	Affected subjects with generations			
			2	3	4	≥ 5
Neurological disorder	80	16	7	8	1	0
Limb defects	78	16	11	4	1	0
Neuromuscular defects	67	13	6	4	1	2
Blood disorder	59	30	16	8	3	3
Sensorineural defect	42	11	4	2	3	2
Eye/visual impairment	24	9	4	3	1	1
Musculoskeletal defects	8	3	1	2	0	0
Orofacial defects	8	0	0	0	0	0
Cardiovascular defects	5	2	1	0	1	0
Total	371	100	50	31	11	8
			$\chi 2 = 18.75$, df = 21			
			P value = 0.600			
			Nonsignificant			
			We exclude orofacial defects due to zero values in all rows			

3.15 Distribution of total male /female with respect to major anomaly.

In the given table we are taken all the affected subjects in the collected data which are n=556 in number. So, we distributed against the gender of the subjects and the major anomalies, and then taken their percentages in a row. Out of total 556 subjects the male is greater in number which are 333 and the female are 223 in number. So, males are more affected in the given data.66% males are affected from the blood disorder while 34 % female are affected from the same disorder. After the blood disorder the second largest number are exist in the neurological disorder which is n =106 and their percentages are 61% and 34% for male and female respectively. The distribution of affected subjects is not statistically significant.

Table 3.11 Distribution of total male /female with respect to major anomaly.

Anomaly	Total No. of affected. (n= 556)		Percentage %		Total No.	Percentage %
	Male	Female	Male	Female		
Neurological disorder	65	41	61	39	106	19
Limb defects	56	44	56	44	100	18
Neuromuscular defects	54	38	59	41	92	17
Blood disorder	76	40	66	34	116	21
Sensorineural defect	43	27	61	39	70	13
Eye/visual impairment	20	22	48	52	42	8
Musculoskeletal defects	9	4	69	31	13	2
Orofacial defects	5	3	63	37	8	1
Cardiovascular defects	5	4	56	44	9	2
Total	333	223	60	40	556	100
	χ^2= 5.571, df =8 P value = 0.695 Nonsignificant					

3.16 Distribution of generation with disease with respect to familial cases.

The distribution of anomalies with respect to generation in the familial cases of the subjects are discussed in the below table in which the generations are categorized into the 1st , 2nd , and 3rd .In which the highest number are exist in the first category which is n=83 in number ,followed by n=14 in 2nd and only n=3 in the 3rd generation . The highest number in the 1st generation out of n=83 is present in the blood disorder which is n=24 in number, followed by n=14 in neurological disorder also exist in the 1st generation.

Table 3.12 Distribution of generation with disease with respect to familial cases.

Anomaly	Total No.	Familial cases	Generation with anomaly		
			1	2	3
Neurological Disorders	80	16	14	1	1
Limb defects	78	16	11	4	1
Neuromuscular defects	67	13	10	2	1
Blood Disorders	59	30	24	6	0
Sensorineural Defects	42	11	11	0	0
Eye/visual impairment	24	9	8	1	0
Musculoskeletal defects	8	3	3	0	0
Orofacial defects	8	0	0	0	0
Cardiovascular defect	5	2	2	0	0
Total	371	100	83	14	3
			$\chi 2$ = 9.99, df = 14		
			P value = 0.762		
			Nonsignificant		
			We exclude orofacial defects due to zero values in all rows.		

3. 17 Classification of minor anomalies with respect to gender, familial/sporadic and isolated /syndromic nature.

Distribution of limb defects with respect to gender, familial/sporadic, isolated/syndromic.

Classification of limb defects are based on their subcategories which includes club foot, polydactyly, anisomelia, syndactyly and oligodactyly. These sub classifications are further distributed against the gender, familial/sporadic and isolated/syndromic nature.

The limb defects are comprised on n=78 of the total number of anomalies. In which club foot is the highest in number n= 35 which includes n=20 male and n= 15 female and n=34 is isolated and only 1 is in syndromic form.

In the subcategories of limb defects male are more affected n=49 while female is n=29 but more sporadic cases are present n=59 similarly isolated cases are greater in number n= 75 and syndromic are n=3 only. The distribution of limb defects with respect to gender, familial /sporadic and isolated/syndromic is statistically not significant.

Table 3.13 Distribution of limb defects with respect to gender, familial/sporadic, isolated/syndromic

Anomaly	No.	Gender		Familial /Sporadic		Isolated /Syndromic	
		Male	Female	Familial	Sporadic	Isolated	Syndromic
Club foot	35	20	15	9	26	34	1
Polydactyly	27	18	9	7	20	25	2
Anisomelia	7	3	4	0	7	7	0
Syndactyly	4	3	1	3	1	4	0
Oligodactyly	2	2	0	0	2	2	0
Other	3	3	0	0	3	3	0
Total	78	49	29	19	59	75	3
		χ^2=5.062, df = 5 P value =0.408 Nonsignificant		**χ^2=9.503, df = 5 P value = 0.090 Nonsignificant**		**χ^2 =1.658, df =5 P value = 0.894 Nonsignificant**	

3.18 Distribution of neurological disorders with respect to gender, familial/sporadic, Isolated/syndromic.

The distribution of neurological disorder which includes are sub categories, intellectual disability n=51, epilepsy n=12, Down syndrome n=8, spina bifida n= 6 ,microcephaly n=2 and macrocephaly n=1 are based on gender , familial/sporadic and isolated/syndromic nature.

Males are more affected in which n=29 in intellectual disability out of n=51, followed by epilepsy in which number of affected males are n=10. The sporadic cases are more in number than familial n=64 and in the isolated number of intellectual disability n = 26 while n=25 in the syndromic cases. The chi square s is nonsignificant.

Table 3.14 Distribution of neurological disorders with respect to gender, familial/sporadic, Isolated/syndromic

Anomaly	No.	Gender		Familial /sporadic		Isolated/ syndromic	
		Male	Female	Familial	Sporadic	Isolated	Syndromic
Intellectual disability	51	29	22	13	38	26	25
Epilepsy	12	10	2	2	10	5	7
Down syndrome	8	4	4	0	8	1	7
Spina bifida	6	6	0	0	6	3	3
Microcephaly	2	1	1	1	1	1	1
Macrocephaly	1	1	0	0	1	1	0
Total	80	51	29	16	64	37	43
		χ^2 7.837, df = 5 P value=0.165 Nonsignificant		**χ^2 =5.91, df = 5 P value= 0.314 Nonsignificant**		**χ^2 =5.434, df = 5 P value =0.365 Nonsignificant**	

3.19 Distribution of neuromuscular disorders with respect to gender, familial /sporadic, isolated /syndromic.

The neuromuscular disorders are further sub classified into 2 minor groups cp and muscular dystrophy. Cp is the most common n= 57 in which males are more affected n= 33 while female is n= 24 and more are sporadic cases but syndromic are greater in number n= 41. The muscular dystrophy is n=10 and isolated cases are more common while familial are

greater in number in muscular dystrophy n=7 and sporadic is n=3. The chi square test is statistically not significant, which is given in table 3.15.

Table 3.15 Distribution of neuromuscular disorders with respect to gender, familial /sporadic, isolated /syndromic

Anomaly	No.	Gender		Familial /sporadic		Isolated / syndromic	
		Male	Female	Familial	Sporadic	Isolated	Syndromic
CP	57	33	24	6	51	16	41
Muscular dystrophy	10	7	3	7	3	9	1
Total	67	40	27	13	54	25	42
		χ^2 =0.518, df =1 P value= 0.471 Nonsignificant		χ^2 =0.518, df =1 P value =0.471 Nonsignificant		χ^2 = 13.95, df = 1 P value = 0.0002 Significant ***	

3.20 Distribution of blood disorders with respect to gender, familial /sporadic, isolated/syndromic.

The distribution of blood disorders which includes thalassemia n=54, sickle cell anemia n= 4 and hemophilia n= 1 with respect to gender, familial/sporadic and isolated/syndromic. The thalassemia is highest in number, and more cases are familial, all are isolated. Males are more affected in blood disorders. The chai square is nonsignificant for blood disorder distribution.

Table 3.16 Distribution of blood disorders with respect to gender, familial /sporadic, isolated/syndromic.

Anomaly	No.	Gender		Familial / Sporadic		Isolated / syndromic	
		Male	Female	Familial	Sporadic	Isolated	Syndromic
Thalassemia	54	38	16	30	24	54	0
Sickle cell anemia	4	4	0	0	4	4	0
Hemophilia A	1	1	0	0	1	1	0
Total	59	43	16	30	29	59	0
		χ^2 =2.033,df = 2 P value =0.361 Nonsignificant		χ^2 =5.651 ,df = 3 P value =0.129 Nonsignificant			

3.21 Distribution of sensorineural defects with respect to gender, familial /sporadic, isolated/syndromic.

The sensorineural defects are sub divided into 3 minor groups which includes deaf and mute n = 36, microtia n = 4 and mute only n= 2. The highest number is deaf and mute and n=11 is familial and n = 35 is isolated and n= 1 is syndromic. Males are more affected in sensorineural defects.

Table 3.17 Distribution of sensorineural defects with respect to gender, familial /sporadic, isolated/syndromic

Anomaly	No.	Gender		Familial/sporadic		Isolated/Syndromic	
		Male	Female	Familial	Sporadic	Isolated	Syndromic
Deaf and mute	36	19	17	11	25	35	1
Microtia	4	4	0	0	4	4	0
Mute only	2	2	0	0	2	2	0
Total	42	25	17	11	31	41	1
		χ^2 =4.760,df = 2 P value =0.1926 Nonsignificant		**χ^2 =2.484, df = 2 P value 0.2888 Nonsignificant**		**χ^2 =0.170,df= 2 P value = 0.918 Nonsignificant**	

3.21 Distribution of eye/visual impairment with respect to gender, familial/sporadic, isolated /syndromic.

The eye /visual impairment are comprised on subgroups which includes blindness n = 13, farsightedness n = 3, strabismus, heterochrome and ptosis. Blindness is the highest category of the sensorineural defects. Males are more affected in this category, while familial /sporadic are n = 9 and n = 15 respectively. Syndromic cases are very less in number. The chi test is statistically not significant.

Table 3.18 Distribution of eye/visual impairment with respect to gender, familial/sporadic, isolated /syndromic.

Anomaly	No.	Gender		Familial / sporadic		Isolated /syndromic	
		Male	Female	Familial	Sporadic	Isolated	Syndromic
Blindness	13	8	5	5	8	12	1
Farsightedness	3	2	1	3	0	3	0
Strabismus	4	0	4	1	3	4	0
Heterochrome	3	3	0	0	3	3	0
Ptosis	1	0	1	0	1	1	0
Total	24	13	11	9	15	23	1
		χ^2 =8.921, df = 4 P value = 0.063 Nonsignificant		**χ^2 =7.672, df = 4 P value 0.104 Nonsignificant**		**χ^2 =0.882, df = 4 P value= 0.927 Nonsignificant**	

3.23 Distribution of congenital anomalies with respect to parental marriage types.

Parental consanguinity is the important variable for any congenital disorder. In the given table the parental marriage type against the anomalies is described. In our data consanguinity is 50% and other 50% marriages are non consanguineous. In the table it is described that 88% of musculoskeletal defects are cousins followed by neuromuscular and eye/visual impairment which are 58%. The chi square test is statistically not significant.

Table 3.19 Distribution of congenital anomalies with respect to parental marriage types.

Anomaly	Parental Relationship type		Percentage %		Total N0. Of anomaly
	CU	NCU	CU	NCU	
Neurological	40	40	50	50	80
Neuromuscular	39	28	58	42	67
limb defect	34	44	44	56	78
Blood	26	33	44	56	59
Sensorineural	22	20	52	48	42
Eye/visual impairment	14	10	58	42	24
Musculoskeletal	7	1	88	12	8
Orofacial	3	5	38	62	8
Cardiovascular defect	1	4	20	80	5
Total	**186**	**185**	**50.1**	**49.86**	**371**
	χ^2 = 11.48, df = 8 P value = 0.176 Nonsignificant				

3.24 Distribution of parental marriage types with respect to gender and familial /sporadic nature.

The parental marriage type is given against the gender in which 63% are male while 37% are female. The males are n=115 which shows consanguinity while n = 118 shows non consanguinity. Females n= 71 are showing consanguinity while n = 67 shows non consanguinity. It is not statistically significant. For familial/sporadic the test is significant because 73% are sporadic while 23% are familial.

Table 3.20 Distribution of parental marriage types with respect to gender and familial /sporadic nature.

Variable	Parental marriage type		Percentage %		Total No.	Total %
Gender	**Consanguineous**	**Non consanguineous**	**CU**	**NCU**		
Male	115	118	49	51	233	63
Female	71	67	51	49	138	37
	χ^2 = 0.1519, df = 1 P value = 0.6968 Nonsignificant					
Familial /sporadic						
Sporadic	126	145	46	54	271	73
Familial	60	40	60	40	100	27
	χ^2 = 5.329, df = 1 P value = 0.021 Significant *					

Risk Factors

3.25 Distribution of socio-economic status of the subjects with respect to anomalies.

The socio – economic status of the subjects is categorized into two forms poor and low. The percentage of low is high in our data, and it is very clear in the below table. All the subjects belong to a low economic status family. The distribution of Chi Square is not significant.

Table 3.21 Distribution of socio-economic status of the subjects with respect to anomalies.

Major Anomaly	Total No.	Socio -Economic Status		Percentage %	
		Poor	Low	Poor	Low
Neurological Disorders	80	38	42	48	52
Limb defects	78	28	50	36	64
Neuromuscular defects	67	28	39	42	58
Blood Disorders	59	24	35	41	59
Sensorineural Defects	42	16	26	38	62
Eye/visual impairment	24	7	17	29	71
Orofacial defects	8	0	8	0	100
Musculoskeletal defects	8	2	6	25	75
Cardiovascular defect	5	1	4	20	80
		χ^2 = 10.57, df = 8 **P value = 0.227** **Nonsignificant**			

3.26 Distribution of congenital anomalies with respect to delivery spot (hospital/home).

The delivery spot is distributed against the anomalies which shows that the greater number of subjects are born in homes n = 317 and in hospital n = 54, it is shown in the given below table. Although 25% of the neuromuscular and musculoskeletal subjects are born in hospital followed by sensorineural which is n = 17 and neurological and limb defects which are n = 14 in numbers. The chi square is significant because of vary data percentages of hospital n = 15%, while home n = 85%.

Table 3.22 Distribution of congenital anomalies with respect to delivery spot (hospital/home).

Anomaly	Total No.	Proportion	Delivery spot		Percentage %	
			Hospital	Home	Hospital	Home
Neurological disorder	80	0.215	11	69	14	86
limb defect	78	0.210	11	67	14	86
Neuromuscular defects	67	0.180	17	50	25	75
Blood disorder	59	0.159	6	53	10	90
Sensorineural defects	42	0.113	4	38	17	83
Eye/visual impairment	24	0.064	0	24	0	100
Musculoskeletal defects	8	0.021	2	6	25	75
Orofacial Defects	8	0.021	1	7	13	87
Cardiovascular defects	5	0.021	2	3	40	60
Total	371		54	317	15	85
			χ^2 = 15.55, df =8 **P value = 0.049** **Significant ***			

3.27 Distribution of anomaly with respect to maternal age.

Maternal age is also one of the important risk factors for the cause of the disease. We take the maternal age ≥ 35 in which total n = 101. These n = 101 are the ages which are greater or equal than 35 years. In neurological n = 27 subjects are present which have greater age. The distribution of the maternal age with respect to anomalies is not statistically significant.

Table 3.23 Distribution of anomaly with respect to maternal age.

Major anomaly	Total No.	Maternal age at birth ≥ 35 (n=101)	Percentage %
Neurological Disorders	80	27	34
Limb defects	78	20	27
Neuromuscular defects	67	18	27
Blood Disorders	59	12	20
Sensorineural defects	42	15	36
Eye/visual impairment	24	4	17
Musculoskeletal defects	8	1	13
Orofacial defects	8	1	13
Cardiovascular defect	5	3	60
Total	**371** $\chi^2 = 5.876$, df = 8 P value = 0.661 Nonsignificant	**101**	

3.28 Distribution of congenital anomalies with respect to Isolated/syndromic nature.

The isolated/syndromic variable is also important due to its risk factor character .The table lists the key abnormalities measured against the isolated/syndromic nature and their percentages' overall number of isolated instances is 277, making up 76% of the total, whereas the total number of syndromic cases is 94, making up just 16% of the total. Therefore, isolated cases are more prevalent in our data. Neuromuscular disorders account for the majority of syndromic cases (n=63%), followed by neurological disorders (n=54%), other disorders are rare in syndromic nature. Due to the wide range of data and the isolated/syndromic character, the chi square test has significance for this variable.

Table 3.24 Distribution of congenital anomalies with respect to Isolated/syndromic nature

Anomaly	Number of subjects	Proportion	Isolated/ Syndromic Attributes		Percentage %	
			Isolated	Syndromic		
Neurological Disorders	80	0.215	37	43	46	54
Limb defects	78	0.210	75	3	96	4
Neuromuscular defects	67	0.180	25	42	37	63
Blood Disorders	59	0.159	59	0	100	0
Sensorineural Defects	42	0.113	41	1	98	2
Eye/visual impairment	24	0.064	23	1	25	75
Musculoskeletal defects	8	0.021	6	2	75	25
Orofacial defects	8	0.021	7	1	88	12
Cardiovascular defect	5	0.013	4	1	80	20
Total	**371**		**277**	**94**	**76**	**16**
			χ^2 = 143.7, df = 9 P value = P<0.0001 Significant* **			

3.29 Distribution of the major anomalies with respect to their total numbers

We are classified all the anomalies in different categories which include 22% of neurological disorder, 21% of limb defects, 18% of neuromuscular defects, 16% of blood disorders, 11% of sensorineural and 6% of eye/visual impairment . While some anomalies are very few in numbers, so we placed in “other” categories.

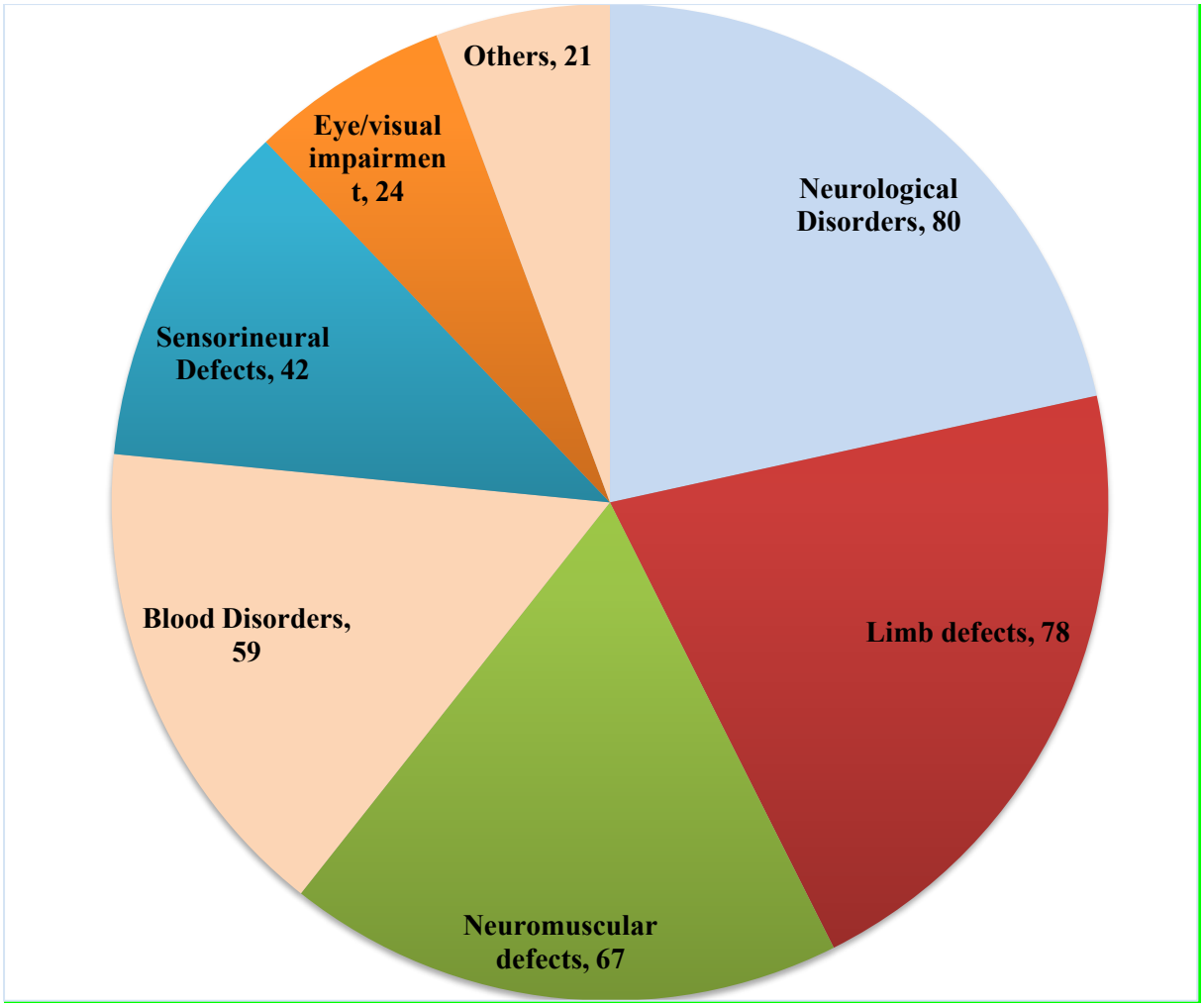


Fig. 3.7 Distribution of major anomalies.

3.30 Distribution of the anomalies with respect to socio-economic status of the subjects

The socio-economic status of the subjects is classified into 2 categories which includes poor and low. In the given below figure it is shows that large number of the subjects are belong to low economic status. In neurological disorders more than 50% subjects are present which belong from low economic status. Similarly in the limb defects 64% are belong from low status. Very small number of subjects are present in poor category.

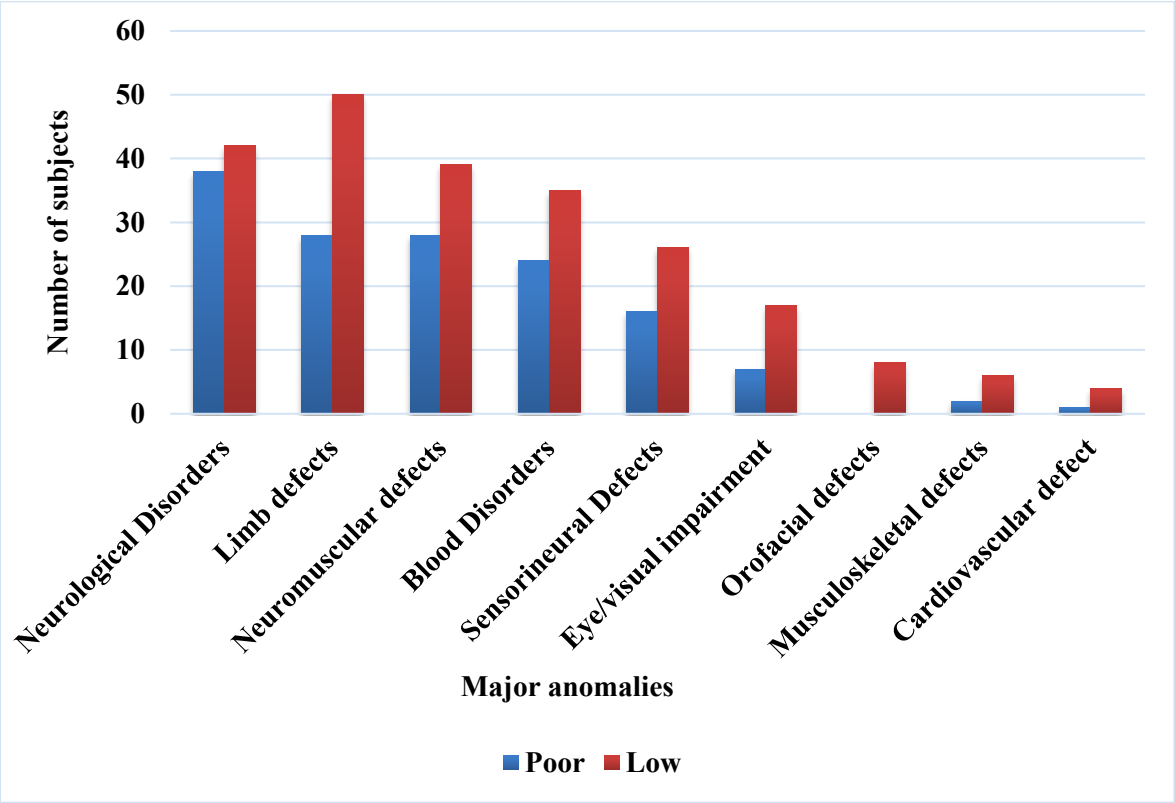


Figure 3.8 Distribution of the anomalies with respect to socio-economic status of the subjects

3.31 Distribution of the major anomalies with respect to gender of the subjects

This figure illustrates the distribution of the major anomalies with respect to gender of the subjects. It is described that most of the anomalies are present in male, or the number of males subjects are greater. In higher categories males are more than 50% as it is shown in the below figure. Some anomalies are very less in number like musculoskeletal defects, orofacial defects and cardiovascular defects but still males are present n these categories.

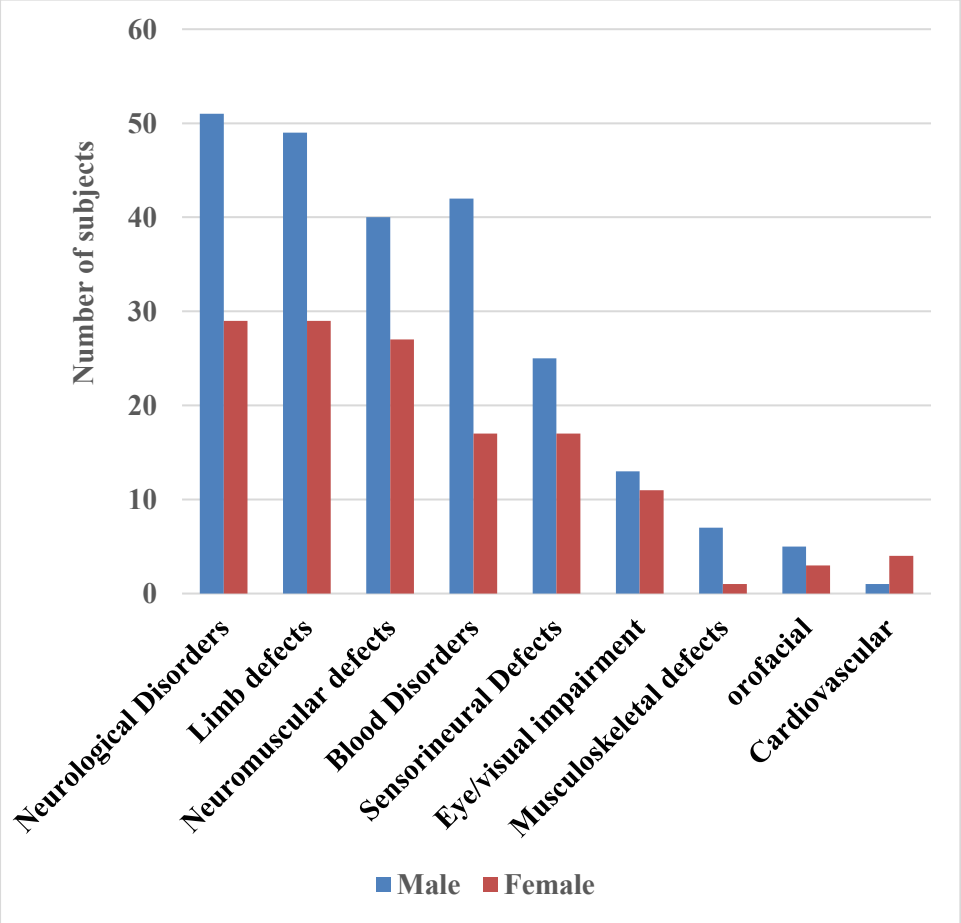


Figure 3.9 Distribution of the major anomalies with respect to gender of the subjects

3.32 Distribution of major anomalies with respect to familial /sporadic nature

The major anomalies are distributed with respect to the familial/sporadic nature of the subjects in which more subjects are present in the sporadic type of anomalies. In the blood disorders more than 50% are familial cases while others like neurological, limb, neuromuscular, sensorineural and eye/visual impairment these are also present up to 20% in familial cases. In orofacial defects all are sporadic cases. In the cardiovascular defects both familial and sporadic cases are present.

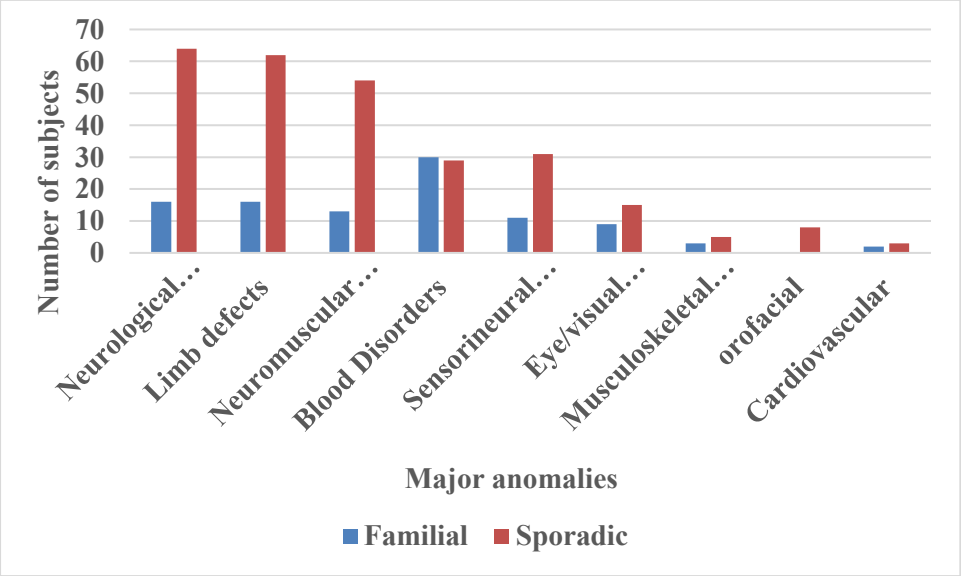


Figure 3.10 Distribution of major anomalies with respect to familial /sporadic nature

3.33 Distribution of the parental consanguinity with respect to major anomalies

In the distribution of parental consanguinity it shows in the figure that both consanguinity and non consanguinity is 50% in the neurological disorders but in neuromuscular, , sensorineural defects and in eye/visual impairment consanguinity is greater than nonconsanguinity. In the musculoskeletal defects consanguinity is 88%,. While in the cardiovascular defects more cases are non consanguineous 80%.

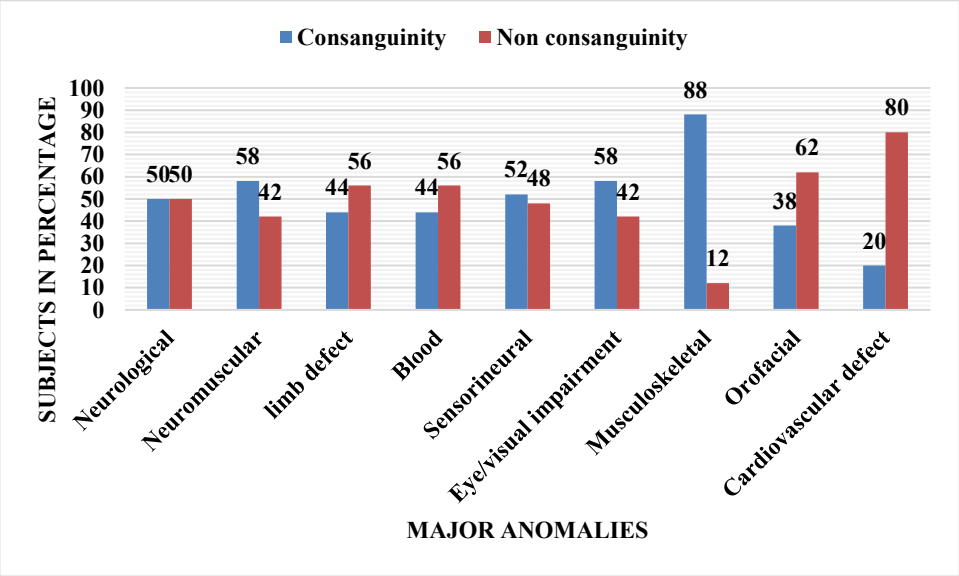


Figure 3.11 Distribution of the parental consanguinity with respect to major anomalies

3.34 Distribution of the major anomalies with respect to isolated/syndromic nature

In the below figure it is described that the isolated nature of distribution is greater than syndromic. But in some anomalies like neurological disorders, neuromuscular defects and in limb defects syndromic cases are also present in more than 40% cases. The isolated cases are highest in the limb defects, sensorineural defects and in blood disorders.

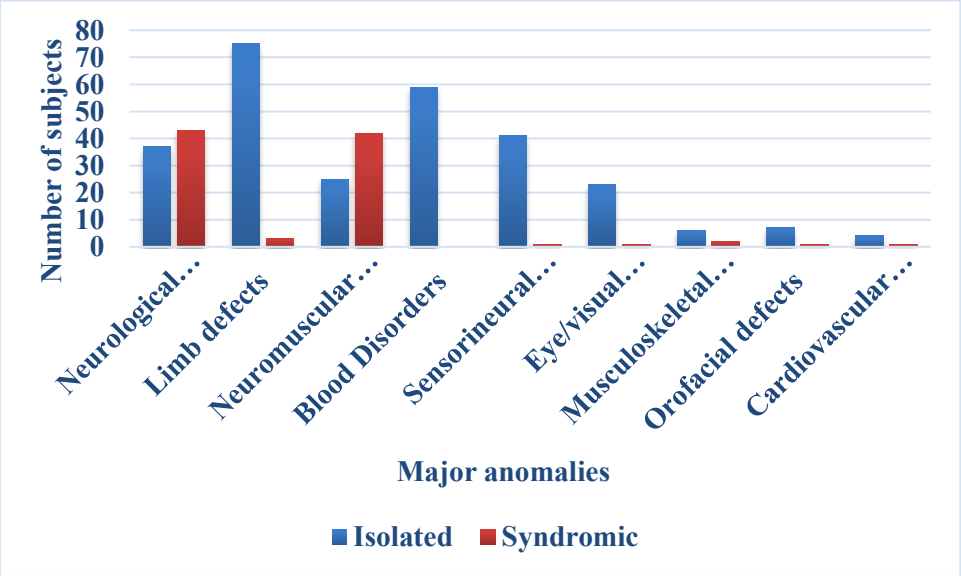


Figure 3.12 Distribution of the major anomalies with respect to isolated/syndromic nature

Chapter # 04

Discussion

The current study has been done in the Loralai district of Balochistan. The research area is in the northeast of Pakistan; it is one of Pakistan famous place for its almond and apple production. The climate of loralai is dry but it varies with the elevation at the high altitude it is cold and dry whereas in the low altitude especially in the south area the temperature is uniform throughout the year. The winters are very cold and windy, whereas summers are mild. Loralai is also rich in marble and its marble tiles are gaining popularity throughout the country. Loralai is an administrative division of Balochistan province, Pakistan. It was bifurcated from Zhob division in 2021. The division consists of barkhan , Loralai , Musakhail and Duki districts.

Loralia is also famous by its large mountains, difficult topography, and harsh weather conditions. In our study loralai district is observed in high prevalence of hereditary and congenital anomalies due to its very remote location and teratogenic exposure, lack of family planning, poor socioeconomic situations, maternal diseases, and late and early marriages all contribute to the high occurrence of congenital and inherited anomalies. The families and society at large suffer economically, socially, and mentally as a result of the health care system's inability to handle and assist the subject/families afflicted by certain congenital and inherited disease. Due to the inadequate infrastructure of healthcare facilities and personnel, accurate recording of births and congenital malformations is lacking in the mentioned region. During data collection we collected data from different union council of loralia district which includes Bawar , Pathan kot , Lahore , Makhter , Nasar abad and Hashmi mullah .

The results showed that most of the anomalies were neurological disorders (22%) followed by limb defects (21%) , neuromuscular defects (18%) , blood disorders (16%) , sensorineural defects (11%) , eye/visual impairment (6%) , musculoskeletal defects (2%) , orofacial defects (2%) and cardiovascular defects (1%). Our finding were comparable to those of (Bhatti et., al 2017) who found that neurological disorders the second most prevalent

anomaly (31%) after (limb defects 46%), musculoskeletal defects (9%) and neuromuscular defects (4%) . The study follow out by (Zahra et., at al) also reported that neurological disorders were the most common anomalies (34%) followed by limb defects (21%) and musculoskeletal defects (23%) . We were observed n = 32 different types of minor anomalies in the population of loralai district in which cp were most prevalent n = 57 , followed by thalassemia n = 54 and than intellectual disorder n = 51

In the current finding neurological disorders are the most common in number n = 80 (22%) in which 64 cases were sporadic and 16 cease were familial, 43 cases are syndromic, and 37 cases are isolated, males are more affected n = 51 and 29 females are affected. We further classified neurological disorders into sub categories which includes intellectual disability is the most prevalent (64%) , followed by epilepsy (15%) , down syndrome (10%), spina bifida (8%) and microcephaly and macrocephaly both are 2% and 1% respectively in present study. The current study is congruent with that of Taye et al. (2019), who reported the highest proportion of participants with neurological diseases. The results of the current study concur with those published by (Zahra et al., 2016) and (Amin et al., 2018), respectively most people with neurological conditions. The majority of the people with intellectual disabilities that are seen also have clinical symptoms such talipes, epilepsy, dwarfism, limb deformities, and seizure disorders. The found clinical feature associations, such as muscular hypotonia, epilepsy, and microcephaly, are consistent with the current association abnormalities reported in (Redin et al., 2014) research. Based on medical records, phenotype, internet databases, resident doctors, and information from the family, the majority of people with neurological diseases were found.

According to research, there are 12 to 24 cases of severe mental impairment for every 1000 persons in Pakistan and India (Sharma et al., 2015). An ongoing study of the literature found that different regions and ethnic groups have different distributions of inherited and

congenital abnormalities. aspects that are social, economic, racial, ethnic, and ecological. Anomalies and discrepancies may be impacted by the consanguinity rate. The type of sample utilized, and the diagnosis made might be additional explanations for discrepancies.

According to (Penchaszadeh et al., 2002), women who are capable of carrying a pregnancy should consume 400 micrograms of folic acid and use of iodine salt daily. This may explain the high prevalence of intellectual disability in the current study area. Extreme climatic circumstances, a deficient healthcare system, ignorance of congenital defects, the terrain of the region, and socioeconomic factors.

Limb defects were observed the second most prevalent anomaly in current study n = 78 (21%). Limb defects are further classified into sub groups like club foot n = 35 (45%) , followed by polydactyly n = 27 (35%) , anisomelia n =7(9%) , syndactyly n = 3(4%) and oligodactyly n= 2(3%) . Few limb defects are very less in number so we placed in other categories n = 4 (5%) . In limb defects 62 cases are sporadic and 16 are familial, isolated cases are more prevalent n 75 and only 3 cases are syndromic, males are more affected n = 49 and 29 females are affected. The current study is comparable with (Ullah et., at al) , their finding showed that polydactyly is the most common limb defects (71%), it is also shown by (Shawky et., at al 2010) but in our study polydactyly is the second most common limb defect n = 27. We are also observed their isolated/syndromic nature, in polydactyly 24 cases are isolated and 1 is syndromic, 20 cases are sporadic and only 7 cases are familial in current study. Club foot /talipes was the most prevalent n = 35, in which sporadic cases were high in number n =26 and 9 were familial, 34 cases were isolated and only 1 was syndromic. This finding contradicts the (Paton et., at al 2010) who reported maximum number of syndromic cases. Twin studies revealed, according to (Wang et al., 2019), that environmental variables such maternal smoking and medication usage play a substantial influence in a etiology of

talipes/ clubfoot. The study's high frequency of limb deformities due to extragenic, stochastic, and environmental variables all play a part in a etiology of limb anomalies.

The third most prevalent congenital and hereditary anomaly was neuromuscular defects n = 67 (18%) in the present study. The neuromuscular defects further classified into 2 minor groups which consist of cp and muscular dystrophy. The results of this study agree with those of (Bhatti et al., 2019), whose findings similarly show a significant percentage of neuromuscular abnormalities. The cp is the most common and prevalent type of neuromuscular defects n = 57 (85%) followed by muscular dystrophy which is n =10 (15%) in present study. The syndromic cases are more common in neuromuscular defects n = 42 while isolated are less in number n = 25. The familial/sporadic nature of the neuromuscular defects are also observed in the study in which number of familial cases of cp were 6 while in muscular dystrophy it were 7 . The sporadic cases were most prevalent in cp n = 51 while in muscular dystrophy it was only 3 in number. According to Jan et al. (2006), cp is a non progressive motor condition that can cause a variety of issues in its victims, including intellectual incapacity, seizures, squint eyes, and difficulties walking. the majority of cp sufferers with the assistance of the resident physician and other medical experts, the current investigation was categorized.

In the present study blood disorders were the fourth most prevalent anomalies n = 59 in which all are isolated cases. In the blood disorders male are more affected n = 42 than female n = 17. Blood disorders are further divided into sub groups which comprised on thalassemia which is the most common and prevalent type of blood disorder in all the areas of loralai division especially in (Duki district, tehsil luni). Out of total blood disorder n = 59, thalassemia is n =54 , followed by sickle cell anemia n = 4 and hemophilia n =1. Out of total thalassemia cases n = 54 , n = 30 are familial and n = 24 are sporadic , it is shown in the

above results that thalassemia is the highest prevalent familial disease in the population of loralai district. The subject of blood disorders was identified by patient medical reports.

The fifth most common anomaly present in the population of loraali district were sensorineural defects n = 42. The defect were further classified into 3 categories which comprised on deaf and mute n = 36 and it iss the most common type of sensorineural defects, followed by microtia n= 4 and only mute were n = 2 . The familial and sporadic cases were present n = 17 and n = 25 respectively in the deaf and mute category, other were all sporadic. The population-based investigation of congenital hearing loss is uncommon in the literature, despite the fact that it is regarded as a major cause of illness burden. The incidence of hearing impairment in children under the age of 15 was 1.4% worldwide. In 2008, 10% of females and 12% of boys over the age of 15 reported having this condition (Stevens et al., 2013). The present study are slightly less than the study carried out by (Glueria et., at al 2017) , whose finding were (13%).

The sixth prevalent anomaly in the current study is eye/visual impairment in which n = 24 (6%). The eye/visual impairment is further categorized into minor groups which includes blindness which is the most common group of eye/visual impairment in the present study n = 13, followed by farsightedness n = 3 , strabismus n =4, heterochrome n = 3 and ptosis n =1 . Blindness is also present in the familial form in the population of loralai people. Out of total 8 cases 5 were familial with association of other anomalies like limb defect.

The seventh prevalent anomaly in the present study was musculoskeletal defects which is present in less number n =8 . This defect is not further classified due to their less number. Out of 8 cases 6 were isolated and 2 were syndromic .

After the musculoskeletal defects we also observed some cases of orofacial defects in the people of loralai n = 8 . The orofacial defects include cleft palate and cleft lip. The cleft lip is the more common in population than palate.

The last but not the least congenital anomaly in the present study was the cardiovascular defects which were observed less in number n = 5 . We also observed some other cases of cardiovascular defects in the population, but these families were out of city therefore not mentioned in the results. We also observed other congenital anomalies in the population of loralai like albinism, skin disorders but due to not easily approaching we were not collected their data.

The total 371 families were also analyzed based on the familial / sporadic nature. There are 100 familial cases and 271 are sporadic cases. In the neurological disorders most, cases were sporadic n = 64 and 16 are familial, in this n =38 were sporadic in the intellectual disability and n = 13 were familial. In the microcephaly 1 case was familial and 2 cases in the epilepsy were also familial, all others are sporadic the sporadic cases are the most prevalent in the current study. The results of that study (Ullah et al., 2015), which likewise showed the largest number of sporadic cases (n=120) and familial instances (n=33), are consistent with those of the current investigation. There have been a significant number of familial (n=20) and sporadic cases of neurological diseases recorded (n=88). The results are in line with those of research by Zahra et al. (2016), which found that sporadic instances were more prevalent.

The present study's greatest incidence of sporadic instances is caused by a lack of vital minerals like iodine and folic acid, which are necessary for preventing pregnancy problems and promoting brain development. The third element is the region's sociocultural norms, which prevent people from disclosing personal information like consanguinity or ancestry.

In the blood disorder familial cases were more prevalent as mentioned in the above paragraph due to high cousin marriages in the population. Out of total 59 cases 30 cases are familial and 29 are sporadic. In the other anomalies like limb defects, orofacial defects, musculoskeletal defects and neuromuscular defects sporadic cases are most prevalent in the current study.

The present study was also analyzed based on the isolated/ syndromic nature of the subjects. Most of the families were observed in the isolated nature. But in the neurological disorders, and neuromuscular defects syndromic cases were most prevalent n= 43 and n = 42 respectively out of total 80 and 57 cases respectively. The isolated cases in both of neurological and neuromuscular defects were less in number n = 37 and n = 25 are isolated. In all other anomalies the isolated cases were most common like in the blood disorder all 59 cases were isolated, in sensorineural defects 41 cases were isolated only 1 was syndromic. In other defects like musculoskeletal, cardiovascular and orofacial isolated cases were most common. The male parent of the family is most likely to be aware of the behavior and other physical flaws in the index subjects' bodies, which may account for the majority of isolated cases in the current study.

The current study also comparable with the research by (Najam Abdi et al 2011) who reported the most isolated cases (n=37) and the fewest syndromic cases (n=4).

In the present study the ratio of the male is higher than the female, the total male number were 233 (63%) while female n = 138 (37%). So, the male gender was the most affected.

The socio-cultural norm of Pakistani culture, particularly in rural regions where appropriate consent is required to contact female subjects and where females are restrained in

their rightful jurisdiction, was the cause of the low proportion of female subjects in the current study. In the public places where the majority of the male subjects were found, it was challenging to find female subjects. The current study is consistent with epidemiological studies where a large percentage of male individuals were enrolled. In research on congenital and inherited defects in the Pakistani area of Sialkot, where the prevalence of male respondents was (75%) and the prevalence of female individuals was (25%). The ratio of male to female participants was greater and consistent with the investigation (Bhatti et al., 2019). The findings of (Zahra et al., 2016) who reported a higher percentage of afflicted males (54%) than females (46%) are also supported by our findings. In a different study, Ochoga et al. (2018) found that there were significantly more male patients (60%) than female subjects (40%) who had congenital abnormalities.

Our findings concur with those of Baruah et al. (2019), who investigated the issue in Assam, India, and discovered that the proportion of affected men (58%) was much higher than that of female patients (48%). In the research (Hemonta et al., 2010), which was carried out in Assam, India, 66% of the male subjects were afflicted greater by 35% than females. This result followed the current study, the ratio of men to females was greater.

The current study also analyzed based on the age groups of the subject, the congenital and hereditary anomalies were most common in the age group of ≥10 to 15 . The results of the current study are in resemblance to those of a prior study by Taye et al. (2019), which found that the majority of the participants with congenital defects were under the age of 17 years. 2019 (Bhatti et al.).

The total 371 cases were also analyzed based on the socio-economic status of the families , most of the subjects were belong to the low category n = 227 (61%) and n =144

(39%) belong to poor families so , in the current study most families were belong from the low socio – economic status.

In the current study the subjects with the congenital anomalies were also analyzed based on the parity order. The parity order was categorized into 5 orders in which most of the anomalies present in the ≥5 followed by the 1st order, 2nd 3rd and 4th.

The subjects were also analyzed based on the generation with disease in the familial cases only. Most of the cases were present in the first generation 83% followed by 2nd generation 14% and in 3rd generation 3% cases were present.

The sibship with disease of the subjects were also analyzed only in the familial cases in which greater number of sibship were present in the first order n = 77, followed by 2nd n = 1 and in the third only n = 4 were present.

In the present study all the subjects were analyzed based on the delivery spot and the family type. Most of the subjects were born in homes n = 317 and n = 54 born in hospitals, it may be due to not proper awareness and hospitals were not present in all the rural areas of the loralai district. Most of the subjects were also belong from the extended families n = 211 and n =160 subjects were belong from the nuclear families, it is due to people of loralai are living in a joint families because these people are most influenced by their socio culture environment.

The consanguinity of the parents also observed in detail of the total cases in which 50% marriages were shown consanguinity and 50% shown non consanguinity in the present study, it was observed during our field work that consanguinity was present in the population of loralai . In the present study 186 cases were shown consanguinity while 185 cases were non consanguinity. In all anomalies only in the neuromuscular defects the consanguinity was

high 58% while non consanguinity were 42 percent out of total 67 cases, in all other anomalies non consanguinity is higher.

Conclusions

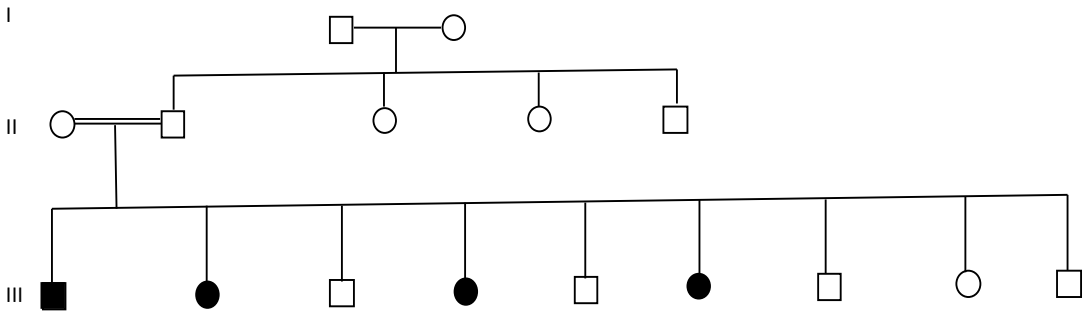
The present study observed high prevalence of neurological disorder n= 80, followed by limb defects = 78 in total 371 cases of congenital anomalies. Male were more affected than female. Sporadic cases were more prevalent in the current study. In the blood disorder familial cases were more prevalent. Consanguinity was 50% in the observed families of the district loralai. Most of the subjects belong from low socio – economic status families. The study is conducted in both rural and urban areas of the loralai district.

Some representative pictures of the subjects

A = Heterochrome (Eye/visual impairment) ,**B** = Cleft palate and lip (Orofacial defect) ,**C** = Down syndrome (Neurological disorder) ,**D** = Macrocephaly (Neurological disorder) , **E**= Polydactyly (Limb defect) , **F** = Oligodactyly (Limb defect) ,**G** = Dwarfism (Musculoskeletal defects) , **H** = Club foot (Limb defect) and **I** = Heterochrome (Eye/visual impairment.

Some representative pedigree of the subjects (Families) A and B.

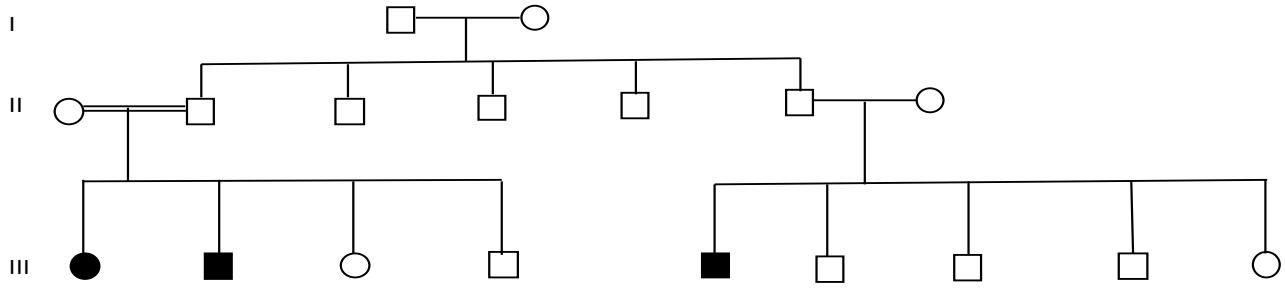
A



Pedigree A is showing normal and affected indiviuals , It is 3 generation pedigree. This is the pedigree of dwarfism, 3 sisters are affected by dwarfism while1 brother is affected by club foot.The pedigree is also show consanguinity in second generation .

Pedigree B

B



Pedigree B is showing normal and affected indiviuals , It is 3 generation pedigree. This is the pedigree of intellectual disability, two sibship are affected from same disorder. Skip of generation is present , so it inheritance pattern is recessive.

Chapter # 5

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