Prevalence-Pattern of Congenital Anomalies in the Population of Sukkur Region

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FACULTY OF BIOLOGICAL SCIENCES

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بسم الله الرحمن الرحيم

Declaration

I hereby declare that the work presented in this thesis is the result of my own research conducted in the Human Genetics Lab, Department of Zoology at Quaid-I-Azam University Islamabad. The epidemiological data were collected from the Sukkur region Sindh. Any part or content of this thesis if copied from any source has been properly mentioned with reference to the source of citation. This is original work and has not been submitted to any other educational institute.

Rehan Khan

February 2023

Dedication

This dissertation is dedicated to my beloved parents

Mr. and Mrs. Shoukat Ali Panhwar

For their endless support, encouragement and love. Their prayers always paved the way for my success

To my beloved Wife Shumaila

For her unconditional love, support and encouragement

To my siblings and friends

For their support and encouragement

And

To my teachers

For being source of inspiration and enlightenment

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

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Abbreviations

CA	Congenital anomalies
CLD	Congenital limb defects
CVS	Chorionic Villus Sampling
EUROCAT	European Surveillance of Congenital Anomalies
FASD	Fetal alcohol spectrum disorder
GBD	Global Burden of disease
ICD	International classification of disease
NTD	Neural Tube defect
OMIM	Online Mendelian Inheritance in Man
SNHL	Sensorineural hearing loss
VACTERL	Vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal, and limb abnormalities
WHO	World Health Organization

Abstract

Congenital anomalies (CA), also known as birth defects, occur as a result of functional or structural abnormalities. They may occur during intrauterine life causing ontogenetic development of fetus, at birth or later in life. CA are caused by a variety of factors, including genetic defects, chromosomal abnormalities, environmental teratogens, and a lack of micronutrients. Every year, an estimated 3 million fetuses are born with a birth defect. This descriptive epidemiological study was conducted in the population of Sukkur region of Sindh, Pakistan, with an objective to establish prevalence-pattern of CA considering the biological and socio-demographic variables of the studied population. In this epidemiological study, 311 families/index subjects were identified through a variety of sources, including special children's schools, rehabilitation centers, hospitals, and door-to-door survey conducted in certain rural areas. Structured questionnaires were created to collect phenotypic, familial, and demographic data, and pedigrees up to three generations were drawn. The data were entered and saved in Microsoft Excel for further analysis, and descriptive statistics were applied. The ascertained anomalies and index subjects were classified into five major categories. The representation of sensorineural/ear defects was highest, i.e., (63%). The second most prevalent CA was limb defects (14%), followed by visual/eye impairments (10%), and neurological disorders 6% (n=20). The ascertained index cases included 72% male and 28% female. The low contribution of female subjects could be attributed to the limited sampling strategy and conservative society. The highest number of cases were found in the age category of >10-20 years with a percentage of 45% (n=141). Familial cases were more common (67%) than sporadic cases (33%). Isolated cases were represented 96% (n=299) more than syndromic cases 4% (n=12). Many index cases belonged to low economic status. The second parity

was the most common, accounting for 30% of the total recruited index subjects. The percentage of parental consanguinity was 70%. The average paternal age was 35 years, and the average maternal age was 31 years. The current study provides valuable information about the prevalence pattern of CA in the study area, which will be useful for future research. CA awareness programs, genetic counselling, and prenatal diagnosis can all help to reduce disease risks. High prevalence of familial cases suggest that high level of consanguinity, ethnicity, and socio-cultural norms may have important etiological roots in the study area.

CHAPTER 1

INTRODUCTION

1.1 Hereditary and Congenital Anomalies

Congenital anomalies also known as birth defects are changes in the organ systems of a newborn that originate during pre-natal development and are identified before, during, or after birth. Congenital anomalies are defined by the World Health Organization (WHO) as morphological, biochemical, physiological, or molecular problems that may appear at birth or may be discovered later in the post-natal period and may develop in the foetus from conception until childbirth (Shawky *et al.,* 2011).

Congenitally abnormal infants cause parents to experience emotional and mental suffering in addition to raising concerns for medical specialists. Congenital anomalies include metabolic disorders, which lead to the deformation of the body's structure and function, as well as structural or functional anomalies. Examples of serious anomalies include cleft palates, limb defects, neural tube defects, and heart deformities (Connolly *et al.,* 2014). Long-term handicap brought on by congenital anomalies (CA), can have a profound impact on people, families, healthcare systems, and societies. Congenital anomalies continue to be stressful for the child-bearer and the entire family who have waited long enough to hold a normal kid. Further, caring for an atypical child, such as one with cleft lip or palate, can be highly traumatic for the family (Arijo *et al.,* 2022).

Congenital anomalies can either be familial or sporadic depending on the pattern of inheritance. The term "familial" describes genetic disorders that run in families, occur more frequently in each family, and can be passed down to future generations, whereas the term "sporadic" describes disorders that do not run in families, occur in an irregular pattern, and cannot be passed down to future

generations (Hemonta *et al.,* 2010). Genetic disorders can either be isolated or syndromic depending on which organs or body parts are affected. In isolated genetic disorders, only a single organ or parts of the body are affected while in syndromic various organs or the body's parts are affected (Sadler, 2019).

Congenital anomalies are prenatal illnesses with complicated fundamental etiologies, including single gene mutations (point mutations), multifactorial, chromosomal abnormalities (deletion, duplication, inversions, and translocations), environmental teratogenic agents, and micronutrient deficiencies. Other causes of include maternal rubella and Zika viruses, diabetes mellitus, iodine insufficiency, multivitamin deficiencies, folic acid deficiency, certain drugs addiction like alcohol and tobacco use, pollutants, and irradiation (El-Koumi *et al.,* 2013).

It has been estimated that approximately 495,000 fatalities globally are caused by congenital and inherited abnormalities. They are regarded as the primary contributor to prenatal mortality, morbidity, and disabilities in children around the world (Dastgiri *et al.,* 2011). In middle class and low-income nations, where mothers are more prone to macro- and micronutrient malnutrition and are exposed to perinatal infection at higher rates, significant congenital anomalies are thought to account for 94% of all cases. Chromosomal anomalies are also more prominent to occur with advanced maternal age. This also raises the high incidence of these conditions because of non-disjunction during meiosis, thus resulting in the form of monosomy or trisomy, such as Down syndrome, (21 trisomy) (Tomatir *et al.,* 2009).

1.2 Worldwide prevalence of congenital anomalies

Prevalence can be described as the total number of people per 1,000 people in a population. Congenital anomalies arise more frequently and in different types depending on the country and region. This depends on, how they were revealed, how long the population was surveyed, and the racial and socioeconomic makeup of the community under investigation (Aihw *et al.,* 2004).

Established on the International Statistical Classification of Diseases and Related Health Issues, 10th version, for 2007, 47% of cases ensured musculoskeletal anomalies, followed by 43% of cases that had anomalies of the eye, ear, face, and neck, 25% of cases that had nervous system anomalies, 23% of cases that had circulatory system anomalies, 17% of cases that had anomalies of the genital organs, 13% of cases had anomalies of the urinary system, 8% of cases have chromosomal malfunctions and 5% have cleft lip and palate (Soheir *et al.,* 2018).

A system of population-based registries called European Surveillance of Congenital Malformations (EUROCAT) carries out epidemiological scrutiny of congenital anomalies in Europe. In nearly 30 years 25 population-based EUROCAT registries identified 250,000 congenital abnormalities among 11.5 million newborns all over the Europe (Loane *et al.,* 2011).

Particularly in poor nations, congenital anomalies (CA) constitute a significant contributor to infant morbidity and mortality. In poorer nations, data on these abnormalities are still not well compiled. A handful of nations, the most of which are in Northern Europe, have reported higher than normal rates. Inclusion of a higher proportion of less serious congenital heart problems in some registers, as well as a greater prevalence of neural tube anomalies in Northern and Eastern Europe and

orofacial clefts in Scandinavian populations (with Finland being a very vital figure for cleft palate) may come into play. The majority of the remaining differences seem to be the result of different ascertainment methods. Less than 20/1000 overall congenital anomalies, or roughly 17/1000 non-genetic anomalies, are considered to indicate under-ascertainment (EUROCAT, 2011).

A newborn child is born with a genetic abnormality per 5 minutes (Parmar *et al.,* 2010). Although the prevalence of CA, is believed to range from 4 to 8 % globally, the percentage greatly differs between nations (Tomatir *et al.,* 2009). Such as it is 1% in Japan, 2% percent in South Africa, 2.5 percent in England, 3% in the USA, and 5% percent in Taiwan. The incidence of birth abnormalities in India as a whole ranges from 0.2 percent up to 3% (Bangladesh Bureau of Statistics, 2011).

Current population-based surveys in Gautemala (a Central American state) have revealed about 384 newborns were discovered to have a clinically apparent congenital anomalies out of 60142 births which is 63.8 per 10,000 births. The most frequent were cleft lips and palates 10.8 per 10,000, defects of the musculoskeletal system 10.8 per 10,000, and neurological defects 28.8 per 10,000. The incidence of miscarriage and child death were highest in children with abnormalities of the neurological disorders 14.6 and 9.0 per 10,000, respectively (Lester, 2020).

According to studies from various literature reviewed, the percentage of congenital anomalies varies by country, with 5% in Pakistan, 11% in Hong Kong, 3% in India, 30% in Tanzania, 14% in Egypt, and 2% in Ethiopia. As shown in the (Table 1) below (Silesh et al., 2021).

Table 1. Country-vice prevalence of congenital anomalies

Population	Prevalence/ 1000 births	Year
Tanzania	30%	2014
Egypt	14%	2013
Hong kong	11%	2014
Pakistan	5%	2015
India	3%	2016

(Silesh et al., 2021).

1.2.1 Mortality and morbidity rates of congenital anomalies

Each year, 30 lakhs fetuses and newborns are born with severe abnormalities (Birch *et al.,* 2004). Based on WHO Fig. s, congenital anomalies were responsible for 16 %to 42% of newborn deaths, with higher attributable rates documented in Malta 42%, and Ireland 41%. The biggest divergences were in Finland 0.8 per 1000 according to WHO, while the EUROCAT estimated figure was 28% greater at 1.19 in 1000, and Ireland 1.63 per 1000 according to WHO, where the EUROCAT estimated figure was 25% advanced at 2.05 per 1000. Amongst the eleven nations that were inspected, the average EUROCAT newborn death rate for congenital anomalies was 1.1/1000. Despite all, abortions of fetuses for congenital anomalies were nearly three times more common than newborn deaths and miscarriages as reported by EUROCAT from 2005 to 2009 (Boyle *et al.,* 2018).

Congenital abnormalities attributed to 5,10400 fatalities globally in 2010, representing 2% of total deaths including 5% of newborn and post-neonatal infant deaths, 3% of deaths 1-4 years, and placed 23rd amongst entirely causes of death, according to the 2010 Global Burden of Disease (GBD) study, twelve congenital anomalies regarded 14th among causes of mortality. Because congenital anomaly mortalities typically occur extremely early in life, hence the burden in terms of years of life lost is greater (Boyle *et al.,* 2018).

Annual WHO evaluations, suggest that 303,000 infants internationally pass away in just four weeks of birth as a result of CA and therefore this has a significant impact on not just the people involved but also on families, healthcare systems, and societies. Due to a shortage of adequate resources for their administration, the

outcomes for children with genetic anomalies in underdeveloped nations are worse than advanced nations (WHO, 2016).

1.3 Prevalence of congenital anomalies in Pakistan

Pakistan is a diverse country made up of the four provinces of Punjab, Sindh, Khyber-Pakhtunkhwa, and Baluchistan, as well as the sub province of Gilgit-Baltistan and the state of Azad Jammu and Kashmir. A dozen linguistic families, including those who speak Sindhi, Pashto, Balochi, Saraiki, Hindko, Urdu, Potohari, Kashmiri, Brahui, and Shinai, make up Pakistan's ethnic majority. Due to a number of beliefs, including the preservation of ancestors' land within the family, a strong family link, better compatibility, a lower divorce rate, and an easier marriage contract, practically everyone in a region favors consanguineous marriages (Jabeen and Malik, 2014).

Additionally, it has been well-known that due to their stringent religious beliefs, some religious groups such as Shias abstain from having outside-the-family marriages. An augmented risk of congenital anomalies with an autosomal recessive type is related to a great occurrence of consanguinity. When the biological relationship is closer for instance, a first cousin union, by inheriting a similar genotype from a common ancestor, the likelihood of anomalies occurrence also increases (Bennett *et al.,* 2002).

Pakistan, the sixth most colonized republic in the world, takes an extended history of cousin marriages being practiced. Genetic flaws are primarily caused by such intra-familial marriages. According to a scientific survey conducted in Pakistan, 29.2 million of the country's population are affected by congenital anomalies. The

most and least afflicted provinces, according to the distribution pattern, are Sindh and Punjab, respectively (Maddison, 2005).

Due to a number of situations, such as the high percentage of consanguineous unions, sibling sizes, low economic status, and maternal factors, the prevalence of congenital anomaly is particularly high in Pakistan. Thus, congenital anomalies are supposed to be responsible for 5-8% of infant mortalities (Bhatti *et al.,* 2019).

An estimated 41% to 59% of these instances have unclear causes, 19% have numerous causes, 6% have monogenic problems, 5% have aneuploidy, and 4% have conditions affecting the mother (Korejo *et al.,* 2007). But one of the greatest risk factors for the development of congenital abnormalities is consanguinity. The highest percentage of cousin marriages is 60-70% in Pakistan. The majority of studies that were conducted in Pakistan were hospital-based, and the frequency ranged from 2% to 6% with a prevalence of neural tube defects (Tayyeba *et al.,* 2021). Since the large bulk of people live in rural areas with no medical infrastructure (Kumar *et al.,* 2014).

The World Health Organization (WHO) estimates that hereditary anomalies are harming Pakistan's GDP by 11–13%. The unusually high rate of consanguineous marriages is the primary cause of this massive challenge for Pakistan.

Given the high level of illiteracy in the population, it is usual for Pakistanis to blame these anomalies on forces outside of human control. The elders of the family Nawabshah Sindh, believed witchcraft and black magic were to blame when sixteen of their children unexpectedly became totally disabled, with their limbs permanently twisted. Healthcare personnel became concerned about the cases, and it was later

determined that the disabilities were caused by a rare congenital neuromuscular defects. Consanguineous marriages are the actual cause.

Pakistani health researchers proclaimed that such genetic disorder has hardly ever been documented in any part of South Asia before because the ailment only affected members of a single family in Nawabshah and there have been no reports from other regions of Sindh or the entire nation. Each of the affected youngsters, the youngest of whom was just four years old, were under the age of 18, and all of them were bed-ridden due to neuromuscular defects. A chemical analysis of water samples taken from the victims' residential area to find out any further causes of the sickness, such as metallic harmfulness or infectious particles. Nonetheless, consumption from the same water reservoirs had not damaged anybody else in the adjoining areas, the testing find out the influence of environmental factors (Tribune, 2019).

The recent studies showed that the majority of the sociodemographic factors pertaining to the Sindhi population did not exhibit sex-specific differences in the distribution of congenital limb defects. When subpopulation-specific data were assessed, however, differences were very significant in a number of categories, illustrating differences in the sociodemographic variables of the Muslim and Hindu samples (Lal and Malik, 2015).

In the far-flung parts of Pakistan, caste and tribal systems are deeply ingrained. There are a lot of inter-family marriages because of the rigid caste system, which is notably prevalent among the Arain people who live in Punjab province. She claimed that this community frequently suffers from a number of hereditary problems. Tribal systems control family life in Pakistan's western Baluchistan province, southern Sindh area, and northwestern provinces (Deutsche, 2022).

Due to social, cultural, and other factors, first and second cousin marriages between families are common in the majority of Sindhi households. Because there is no enough trustworthy data, it's unclear how much interfamily marriages contribute specifically to the likelihood of congenital anomalies. The current study compared the prevalence of birth defects in marriages between members of the same family as those that do not (Tufail and Shiyam, 2016).

From 2013-2015, a cross-sectional survey in Sukkur, Sindh, recruited 50% of women of urban areas and 51% from rural areas. 46% of women spoke Sindhi as their first language, which is the majority. Approximately 88% of women identified as Muslim, 7% as Christian, and 2% as Hindu. 59% of women had gestational ages under 37 weeks, and 69% were married within their families. Congenital malformations occurred 12% of the time; of them, 49% had neurological defects, followed by 19% of cleft lip and palate, 11% by gastrointestinal, 11% by musculoskeletal, and 4% by ear, nose, and throat. The involvement of the neurological defects was the most frequent abnormality found in the investigation (Tufail and Shiyam, 2016).

1.4 Types of congenital anomalies

There are following main divisions of congenital anomalies. Which include structural, functional, and metabolic congenital anomalies. Structural genetic anomalies are at the top of the list (Czeizel, 2005).

1.4.1 Structural congenital anomalies

Anomalies of structure are those that impact our numerous body organs. The body's regular physical state is severely altered as a result. Malformations and dysplasia are examples of structural anomalies that result from aberrant tissue development, while other morphological anomalies appear after abnormal organogenesis involving deformation and disruption. Cleft palates, talipes, limb deformities such as polydactyly, syndactyly, oligodactyly, and split hand-foot, heart problems, sensorineural/ear defects and visual/eye impairments are only a few examples of the congenital anomalies that are frequently observed (Laury *et al.,* 2007).

1.4.2 Functional congenital anomalies

Functional congenital anomalies is the second division. The normal functioning of the body is typically hampered by these anomalies, which change normal functions. Most of these illnesses are metabolic, meaning they involve either an excessive or insufficient production of various metabolic enzymes engaged in various metabolic processes. For instance, phenylketonuria is an autosomal recessive condition in which the body accumulates too much phenylalanine because the phenylalanine hydroxylase enzyme is absent. Functional abnormalities can potentially endanger life since an excess of this enzyme can damage the brain and hence leading towards the mental retardation. Some degenerative diseases are also brought on by a body's inability to operate properly, which is brought on by a genetic mistake. For example, muscular dystrophy, a condition caused by a shortage of a protein called dystrophin, eventually lessens muscles and damages the brain (Alkader, 2012).

1.4.3 Major and minor congenital anomalies

Depending on the degree of these anomalies in form and function and the requirement for medical care or treatment these disorders may also be categorized as major or minor anomalies (Bacino, 2018).

Major and minor congenital malformations are two different categories for congenital defects. Major may necessitate surgical treatment or perhaps result in the newborn's death. Minor congenital defects, on the other hand, have a negative impact on a newborn's health and quality of life (Sadler *et al.,* 2011).

The national CA prevention study's 2003 case classification standards found that 50% of the patients had major malformations, 19% had minor anomalies, and 30% had both. According to their provisional diagnosis, cases were divided into two categories: those with single anomalies 50%, those with multiple anomalies 48% and those with chromosomal abnormalities 13% (Soheir *et al.,* 2018).

On the basis of their severity, congenital anomalies can also be categorized into three classes.

1. Lethal: If the anomalies such as anencephaly or hypo plastic left heart syndrome, result in baby or stillbirth mortality or pregnancies that are aborted in more than 49% of the time following the prenatal diagnosis of fetal problems.

2. Severe: If the anomalies such as congenital pyloric stenosis or a cleft lip, result in disability or death without medical treatment.

3. Mild: If the conditions such as congenital hip dislocation or an undescended testis, necessitate medical treatment but the prognosis is good. Major congenital anomalies are malformations that are both fatal and severe (Czeizel, 2005).

The ICD-10 categorization of congenital anomalies shows that 49% of cases involved musculoskeletal defects, which were followed by 45% percent of cases involving both sensorineural/ear defects as well as visual/eye impairments. While other anomalies include such as neurological defects 27%, circulatory system 23%, genital organs 19%, urinary system 13%, chromosomal abnormalities 8%, cleft lip and cleft palate occur in 7% of cases respectively (Soheir *et al.,* 2018).

Furthermore, a large number of structural anomalies are linked to aneuploidy syndromes that can be identified by chromosomal sequencing and karyotype, the latter of which has been demonstrated to have a diagnostic yield of 5% in cases of structural defects that arise in uterus (Wapner *et al.,* 2012). However, the molecular basis of several anomalies, from isolated congenital cardiac defects to frequently observed patterns of malformations like VACTERL (vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal, and limb abnormalities), remains poorly understood. Recent advancements in human genetics and genomics have reshaped our knowledge of many major structural anomalies occurring in isolation or as part of a syndrome. The different manifestations of structural anomalies are still a mystery, even within a genetic disease with a clear definition, like Down's or Patau syndrome (Springett *et al.,* 2015).

1.4.4 Congenital anomalies of sensorineural defects

The ability to hear and repronounce sounds is a prerequisite for speaking. The first two years of life are the best time for speech acquisition, if a kid is not able to speak by the age of five or six, it will be difficult for them to later produce understandable speech. The hearing of a child who is suspected of having mental

retardation or a delay in speech-development should therefore be assessed, as well as their hearing in young children (Frank *et al.,* 2001).

One in 1000 children are known to have hearing loss, making it the most prevalent congenital sensorineural defects. 3% of those under the age of 45 have hearing loss impairment (Estivill *et al.,* 2003). Damage to auditory nerve network or the auditory structure results in sensorineural hearing loss (SNHL). SNHL can be inherited and can manifest either on its own, without the presence of any other diseases, or as a component of an inherited sensorineural defect. The severity or degree of the loss can also be used to classify sensorineural hearing loss. It can range in intensity from mild (26- 40 dB) to moderate (41- 55 dB), moderate to severe (56-70 dB), severe (71- 90 dB), and profound (90 dB) (Kochhar *et al.,* 2007).

A patient's sensorineural/ear defects can induce severe speech and language development, negatively impacting social, emotional, and academic outcomes. As a result, early screening, detection, and treatment are critical in minimising the negative consequences of hearing loss. As in United States, existing evaluation guidance include screening at conception and no later than the first month of age, with more extensive audiometric diagnostics and otologic assessment for infants with impaired hearing. Furthermore, after failing an annual hearing examination administered in many schools, children are frequently referred with further evaluation. Early diagnosis aimed at addressing the root cause of hearing loss is ideal for optimising developmental outcomes.

Sensorineural hearing loss (SNHL) is a type of hearing loss caused by problems with the central auditory structures or the vestibulocochlear nerve. Congenital SNHL can be genetic (isolated or syndromic) or the result of a sporadic

insult during foetal development. On imaging, the majority of patients with congenital SNHL have normal morphology of the inner ear and internal auditory canal structural features, with anomalies revealed in 24% to 41% of cases (Brien et al., 2021).

Congenital sensorineural/ear defects are the most common birth defect in developed societies, affecting nearly one in every 1000 live births. Hereditary hearing loss, which is caused by genetic mutations, accounts for more than 49% of all congenital sensorineural hearing loss cases. SNHL can be nonsyndromic or syndromic. Nonsyndromic sensorineural/ear defects are classified according to their mode of inheritance, which includes autosomal dominant, autosomal recessive, mitochondrial, and X-linked (Kadir et al., 2016).

1.4.5 Congenital anomalies of limbs

Congenital limb defects are immediately identifiable and seem to have lengthy effects on a person's physical, mental, and social well-being. The failure of appropriate limb development throughout embryonic stages is the cause of CLD. They can be categorized as upper or lower limb defects, preaxial or postaxial, isolated or syndromic, familial and sporadic depending on their involvement and type (Bhatti *et al.,* 2019). Congenital anomalies of the digits can also occur alone, in conjunction with other limb defects, or as a component of a hereditary disease. Adactyly and oligodactyly, syndactyly, symphalangism, polydactyly, macrodactyly, and amniotic bands syndrome, were also included in the list of limb defects (Marius, *et al.,* 2019). However the most common among is clubfoot, with a global incidence of at least 25 percent (Romano, 2011).

Polydactyly is a limb disorder in which additional fingers appear in the feet or hands and is among the most frequent limb deformities (Malik *et al.,* 2013). Polydactyly is divided into three types, pre-axial, meso-axial, and post-axial polydactyly. The incidence in newborns is reported to be 0.2-3.7 per 1000, and 1-10 per 1,000 in the overall population. Men are afflicted twice as often as females. Usually, polydactyly affects the right hand more than the left hand, the upper limbs more than the lower limbs, and the left foot more than the right foot (Malik, 2014).

Brachydactyly refers to finger shortness caused by aberrant development of metacarpals, phalanges, sometimes both. Brachydactyly can occur alone or in conjunction with other congenital anomalies. The incidence of brachydactyly varies by region, ranging from 0.4 to 5% (Temtamy *et al.,* 2008).

1.4.6 Congenital anomalies of visual/eye impairment

Visual/eye impairments including blindness, cataract and glaucoma, are all the disorders that largely affect numerous people because their prevalence is not only congenital but also rises with age. However, a number of significant causes of visual/eye impairments start early in life and could also be categorized as neurodevelopmental. Children with refractive errors, the most prevalent type of visual impairment, have particular challenges in low-income nations where many people lack access to eye-glasses and basic eye care services. Refractive errors can, however, be easily diagnosed and treated using low-cost procedures, which can be included in basic care screening services (Heldt and Wessels 2004).

In addition to these mentioned congenital anomalies, EUROCAT is a network of population-based congenital anomaly registries in Europe that encompasses some

non-EU nations and about 29% of the EU birth population. All significant congenital anomalies are recorded by EUROCAT, with the exception of a limited number of minor anomalies and conditions that are inadequately described or connected to prematurity at birth (Boyle *et al.,* 2018).

In nearly 30 years, 25 population-based EUROCAT registries identified 250,000 congenital abnormalities among 11.5 million births across Europe. That indicates rising rates of congenital cardiac disease, abnormalities linked to the GIT, and falling rates of limb defects (Loane *et al.,* 2011).

1.5 Causes and risk factors

Congenital anomalies have complicated and often unidentified causes. Despite the fact that genetic mutations are a common cause, other non-genetic or environmental causes can also result in congenital anomalies (Christianson *et al.,* 2004).

The majority of CA have multifactorial inheritance as their underlying etiology. Other causes include chromosomal abnormalities, intrauterine factors, maternal illnesses, congenital infections, gestational factors, drugs, dietary issues like folate deficiencies, and unidentified causes. Most affected children have no history of CA in their families (Hematyar *et al.,* 2005).

CA has a genetic 29-39% and an environmental 4-10% cause. Chromosomal abnormalities accounts for 5% of genetic etiology, single gene defects 24%, and complex 21-31%. However, the origin of approximately 49% of CA is unknown (Devi *et al.,* 2007).

Numerous studies have shown that consanguinity plays a role in the development of congenital anomalies. In many parts of the Middle East, Africa, and Indian subcontinent, parental consanguinity, especially first cousin marriages, has become a risk factor for a variety of congenital malformations as well as Mendelian conditions including inborn errors of metabolism. (Anbreen *et al.,* 2021).

Apart from, single gene disorders 5% to 6% the interaction of genetics and the environment 19-24%, and teratogen exposure 5-6%, have all been suggested as potential underlying causes of congenital anomalies. It is significant to remember that more than 49% of congenital anomalies have no recognized cause (WHO, 2018).

1.6 Causes of congenital anomalies

Almost 26% of all congenital defects are thought to be genetically based. A higher overall prevalence of congenital anomalies with genetic roots may be caused primarily by two factors: (i) women having children after the age of 35 and (ii) a high incidence of marrying cousins (Czeizel, 2005).

Chromosome abnormalities like Down syndrome and Mendelian single-gene problems like achondroplasia or Holt-Oram syndrome are the examples of genetic causes. Because they have a highly distinct inheritance pattern, such as dominant versus recessive, monogenic disorders, also known as Mendelian disorders, are simple to examine (Basson *et al.,* 2000).

The period when these anomalies are discovered and the genomic technology being employed must be taken into account when estimating the role of genetic disorders to structural malformations. The genetic pattern of congenital anomalies in live-born newborns may be different from that found in infants who do not survive the

pregnancy because several morphological anomalies result in spontaneous abortion or occur in pregnancies that are not continued (Heinke *et al.,* 2020). In contrast to the 36–50% on average explained in studies limited to stillbirths with structural anomalies using genome sequence, the population described by Holmes and Nelson included live- or miscarried infants. They estimated that 12% of cases with structural anomalies were observable by a particular gene responsible (Quinlan *et al.,* 2019).

1.6.1 Single gene disorders

Monogenic congenital anomalies are commonly known as Mendelian disorders. Which are those conditions that are caused by a mutation in a single gene deficiency. These types of anomalies are typically caused by mutations in one or two alleles of a single locus that could be found on the X chromosome, the autosomal chromosome, or mitochondrial genes from the mother. For instance, Marfan syndrome and Huntington syndrome are the examples of autosomal dominant single gene disorders, whereas cystic fibrosis and sickle cell anemia are examples of autosomal recessive single gene disorders. Contrarily, X-linked single gene abnormalities include color blindness, Duchene muscular dystrophy, familial rickets, hemophilia, and rickets. In each 1000 live births, there are 7, 2, and 0.5 cases of autosomal dominant, recessive, and X-linked single gene disorders, respectively. 2% for the combined frequency 10 in 1000 live births (Kor *et al.,* 2018).

Furthermore, there are numerous ways that chromosomal diversity might result in congenital abnormalities. Mendelian diseases, in which a disease-causing alteration at a single locus leads in a range of anomalies, may be the cause of some anomalies. Others might be connected to non-Mendelian genetic variables. These include single-nucleotide polymorphisms (SNPs) that increase vulnerability to a

specific condition, oligo genic disorders brought on by variations in a small number of genes, somatic pathogenic variants that occur in a specific tissue rather than all cells of the body (Lim *et al.,* 2015), and epigenetic modifications that affect the expression of specific genes (Hobbs *et al.,* 2014).

1.6.2 Polygenic disorders

The term "polygenic" can refer to a variety of things, including genetic consequences brought on by the interplay of several genes. It is possible to say that complex features with polygenic inheritance are determined by numerous genes at different loci, irrespective of the environment. Since no single gene is dominant or recessive to another, the effects of those genes are collective. Polygenic disorders in people are far more common than monogenic ones and have a significant socio-economic impact. Because a wide range of hereditary and environmental variables often act in conjunction to create human diseases (Brodwall *et al.,* 2018).

Since it includes the combined effect of several individually working or interacting polymorphic genes thus contributing to polygenic disorders. The individual effect of each gene may be insignificant or even undetectable. The presence of clinically diverse disease types and the efficacy of managements can be influenced by the presence of specific gene combinations. Congenital heart defects, neural tube defects, cleft palate, and congenital hip dysplasia are all the examples of congenital deformities that have problematical, multiple and interacting causes. Hence, "polygenic" can have a range of aftermaths, including genetic outcomes brought on by the relationship of several genes. A trait whose appearances are influenced by two or more genes, along with environmental influences, is said to have a multifactorial inheritance. Cohort studies and animal research published over the

past few decades have recommended that the etiological phenotypic differences of congenital defects is caused by the interaction of genes and environmental factors (Zhu *et al.,* 2009).

1.6.3 Multifactorial disorders

A multifactorial genesis is the result of gene-environment interaction. This etiological group contains the mainstream of common congenital abnormalities, comprising of neural-tube defects, orofacial clefts, cardiovascular malformations, congenital pyloric stenosis, congenital hip dislocations, undescended testicles, hypospadias, etc. Approximately 60 percent of all congenital anomalies are supposed to be of problematical origin, assuming congenital abnormalities of unknown origin are also included in this category (Zhu *et al.,* 2009).

1.6.4 Chromosomal abnormalities

In terms of congenital defects' non-disjunctive separation of chromosomes during meiotic cell division, can lead towards the number of syndromes. Moreover, some structural anomalies may be a sign of an underlying Mendelian disorder. Cardiac anomalies like the hypo plastic left heart syndrome and aortic arch problems, are less frequently linked to a hereditary abnormality than others like truncus arteriosus and interrupted aortic arch (Li *et al.,* 2017). Other prevalent anomalies caused by chromosomal abnormalities include Down's syndrome (Trisomy 21), Edward syndrome (trisomy 18), and Patau syndrome (trisomy 13).

The type of genetic abnormality sometimes referred to as Edwards syndrome, is a common chromosomal abnormality that results from having an extra copy of chromosome number 18. After trisomy 21, this disorder is the most prevalent

autosomal trisomy syndrome. The prevalence of living parturitions is thought to be between 1 in 6,000 and 1 in 8,000, but the inclusive prevalence is assumed to be between 1 in 1500 and 1 in 1600 for the reason that of the high rate of miscarriage and pregnancy termination after prenatal diagnosis. Trisomy 18 is becoming more common as maternal age propagates. About 1% of families that have a baby with complete trisomy 18 will experience reappearance. Fetal growth deficiency, unusual craniofacial traits, a peculiar hand posture with overriding fingers, nail hypoplasia, a short hallux, a short sternum, and severe abnormalities are among the key clinical signs that serve as diagnostic cues in the perinatal period particularly involving the heart (Anna *et al.,* 2012).

Moreover, in 1960, Dr. Patau and his colleagues identified trisomy 13 as the root cause of a specific clinical condition that included, Cerebral deformities, apparent anophthalmia, cleft palate, hare lip, simian creases, trigger thumbs, polydactyly, and capillary hemangiomata" were the original descriptions of the clinical condition. Trisomy 13 is more likely to occur in older mothers because nondisjunction occurs more frequently in older mothers. However, 20 percent of Patau syndrome cases may be brought on by an imbalanced translocation, and mosaicism only rarely occurs. Numerous significant research have described the dismal prognosis of Patau syndrome patients (Grant *et al.,* 2019).

Another type of trisomy caused by an extra copy of chromosome 21 is the most frequent cause of Down syndrome newborns. When chromosome 21 fails to separate during gametogenesis of either spermatogenesis or oogenesis, hence result in the trisomy of autosomal pair 21, karyotype 47-XX + 21 for females and 47- XY + 21 for males. DS is also caused by the chromosomal translocations. It is estimated that only 1-3% of all chromosomal translocations are Robertsonian translocations. When

the long arm of chromosome number 21 is joined to another chromosome generally chromosome 14, this is called Robertsonian translocations. While mosaicism talks about the errors that happens during cell-division after fertilization. Because of this, persons with mosaic disease DS have two cell lines that contribute to their muscles and organs—one with the even number of chromosomes and the other with an extra 21 (Ambreen *et al.,* 2015).

More severe effects are produced by sex chromosome addition or deletion. Turner syndrome is caused by missing X chromosomes in a female embryo (XO), while Klinefelter's syndrome is caused by an extra X chromosome added to the typical combination of one X and one Y chromosomes in a male baby (XXY) (Blackburn, 2017).

1.7 Risk factors

According to estimates, risk factors account for 6% to 11% of all congenital anomalies (Nelson and Holmes, 1989). Nutritional inadequacies, maternal illnesses, viral diseases, and teratogenic medicines are examples of environmental factors. The extent of the harm caused by an exposure depends on a number of variables, including the exposure itself, the stage of pregnancy, and the person's genetic predisposition (Toufaily *et al.,* 2018).

Risk factors which cover teratogenic medicines, alcohol, smoking, environmental contaminants, maternal disorders such as diabetes mellitus, infectious diseases like rubella, and diseases with high fever. About 14% of all congenital anomalies may have risk factors etiology (Czeizel, 2005).

Advanced parental age and specific sociocultural norms in a particular society can make congenital abnormalities worse. Congenital malformations are more common as a result of genetic issues, and social practices like consanguinity (marriage between blood relations) all contribute to this (Christianson *et al.,* 2006). While teratogens are substances, that cause congenital defects, typically present from maternal exposure are among the non-genetic risk factor variables. In addition, risk factors like maternal use of recreational drugs, smoking, and multivitamin and mineral deficiencies, infectious diseases of viruses, other maternal conditions like insulin-dependent diabetes mellitus, and maternal medications like thalidomide and anticonvulsants are all linked to congenital anomalies (Sarmah *et al.,* 2016).

Congenital malformations are also greatly influenced by other contaminants, such as pesticides, food supplements, plastic components, solvents, metals, and other air pollutants. (Marry and Lopez, 2013). Nevertheless, only a tiny percentage of congenital malformations (between 4% and 9%) are known to be brought on entirely by environmental causes (Christianson *et al.,* 2006). The majority of environmental birth defects are complicated and frequently involve genetic-environmental interactions (Sarmah *et al.,* 2016).

The most frequent risk factor of congenital anomalies is prenatal ethanol exposure. Fetal alcohol spectrum disorder is an umbrella term used to describe the whole range of abnormalities brought on by mother's alcohol consumption during gestation. Incidences of FASD range from 1-3% in children born in America, while FAS affects two to seven out of every 1000 live births (May and Gossage, 2001). The variety of abnormalities is seen in maternal drinking frequency, embryonic stages of alcohol exposure, and inherited vulnerability, that all likely to have a major role in determining clinical result (Muralidharan *et al.,* 2013; Eberhart and Parnell, 2016).

In animal experiments, fetal alcohol exposure causes cardiac abnormalities that are similar to those found in human patients. Maternal alcohol use was also thought to be linked to neural tube defects (NTDs) (Grewal *et al.,* 2009). Animal studies simulating alcohol consumption found evidences of severe NTDs in rats exposed to ethanol (Sulik *et al.,* 2006). Micropthalmia, coloboma, optic nerve hypoplasia, cataracts, photoreceptor vision loss, poor eyesight, and aberrant responses recorded by retinal cells are among the most common abnormalities (Stromland and Pinazo, 2002).

Apart from, causes of fetal tobacco exposure comprise maternal cigarette smoking, passive smoking, chewing tobacco, and nicotine patch use. Since tobacco smoke is a combination of almost 4,000 harmful and cancer-causing compounds, exposure to smoking can have a variety of effects on embryonic development. Reduced birth weight, respiratory disorders, sudden infant death syndrome, cognitive deficits, and disorders of attention deficit are among the identified anomalies in infants and children. The nicotine, is a strong stimulant found in tobacco, is thought to be the most likely culprit behind the intellectual disability shown in smokers' offspring (Rogers, 2008).

Higher maternal cigarette use during gestation period was associated with an increased risk of septal heart abnormalities, particularly atrial and ventricular septal defects of the heart (Alverson *et al.,* 2011; Lee and Lupo, 2013; Zhang *et al.,* 2016).

Recent studies on the connection between NTDs and maternal smoking, particularly passive smoking, indicated that exposure to tobacco smoke was related with an increased risk of having children with NTDs (Suarez *et al.,* 2011).

Other birth defects linked to maternal smoking include those that affect the musculoskeletal system particularly affecting limb-length, the face, and the eyes (Hackshaw *et al.,* 2011).

1.7.1 Consanguineous marriages and congenital anomalies

A consanguineous marriage is a marriage between close blood relatives. It is stated as the connection via marriage among first and second cousins in medical genetics (Hamamay, 2012). In the Gulf Region and among Islamic communities, consanguineous marriage is most popular. The incidence for this familial marriage varies by country and is influenced by factors such as educational status, religion, local culture, and socioeconomic position (Bittles, 2001). Consanguineous marriages are at high risk for congenital and genetic anomalies because it increases the chance of homozygosity in their children by bringing the recessive variant in both the couple to a single zygote and providing a chance to express (Bernadette, 2002). Consanguineous union may result in the transmission of two recessive faulty processes to progeny, one inherited from the maternal and the other from paternal, side which may result in the manifestation of congenital malformations (Niaz, 2019).

1.7.2 Advanced maternal age

Advanced maternal age during gestation period increases the risk of congenital anomalies (CA) in a foetus (Katherine, 2016). Numerous morbidity and mortality are associated with the advanced maternal pregnancy, including chromosomal abnormalities such as trisomy caused by unfaithful delivery of chromosomes with progressing ovum age, abortion, fetal growth restriction, and stillbirth (Gill, 2012). The majority of chromosomal abnormalities occur as a result of non-disjunction

during meiosis 1. Since maternal meiosis 1 begins when the foetus is in the ovary after the first meiotic division, it is arrested until ovulation occurs many years later. Because egg cells can be mutated during this prolonged period of meiotic detention, it contributes to aneuploidy (Hassold, 2007).

1.7.3 Folic acid deficiency

Neural tube disorders, such as spina bifida, which cause motor dysfunction and occasionally intellectual damage in surviving newborns, are more common earlier in pregnancy. Deficiency of folic acid during pregnancy results in CA like anencephaly and spina bifida (Benjamin, 2017). Folic acid is important in the first trimester of fetal development, due to its role in organ formation, like neural tube development. Childbearing women need 0.4 to 0.8 mg of folic acid for the healthy development of the fetus. In the absence of a diet high in folate, mutations of the methylene-tetra-hydrofolate reductase gene are linked to elevated levels of maternal plasma homocysteine and the development of neural tube abnormalities in the children (Harris, 2017).

1.8 Prevention and diagnosis of congenital anomalies

Congenital anomalies is one of the most common newborn health issues, and it applies to every abnormalities evident at delivery, whether inherited or not. Infants with CA require expensive medical assistance, and full recovery is typically unattainable (Tayebi *et al.,* 2010).

An attempt is made to help a person understand their risk for an inherited condition and the choices for reducing that risk without unnecessarily raising stress as

part of genetic counselling. The accuracy of a person's perception of their risk of contracting the disease and their understanding of the genetics of the disease must be improved with no negative emotional effects for genetic counselling to be judged effective (Braithwaite *et al.,* 2004).

Congenital abnormalities are more common at birth in developing nations than they are in wealthy ones. However, due to a lack of suitable services for the treatment of sick infants as well as a higher rate of exposure to infections and hunger, the health effects of birth abnormalities are more severe. Several poor countries are using effective strategies for preventing congenital abnormalities. Public education about pre-conception and prenatal dangers is the foundation of primary preventive efforts. Teratogen information programs and prenatal testing for fetal malformations are two examples of prevention based on reproductive possibilities. Programs for early detection and treatment of congenital abnormalities at birth are also helping with secondary prevention (Victor, 2002).

Not even all birth defects can be prevented, but the incidence and severity of congenital anomalies can be minimized with the right preventive measures. The first step in preventing birth abnormalities is health education and awareness. In order to enhance maternal and child health across all 50 states in the US, organizations like the March of Dimes, public and private health care systems, and others offer mothers educational tools and multiyear strategic planning (Sarmah *et al.,* 2016).

Taking care of one's health includes adopting a healthy lifestyle, staying away from dangers, improving one's food, and making sure one is getting enough vitamins and minerals, especially folic acid. While maintaining a healthy lifestyle which includes abstaining from drugs, alcohol, smoking and maintaining a balanced diet are

some of the more difficult behaviors to follow, all of these behaviors have been shown to have an impact on the course of pregnancies. There is substantial evidence that prenatal folic acid supplementation reduces the risk of congenital anomalies (Sarmah *et al.,* 2016).

Above all, there are two types of approaches for the prevention of congenital anomalies.

1. Screening test 2. Diagnostic test

A screening test predicts the likelihood of birth defects in an apparently normal fetus while a diagnostic test totally confirms or completely disproves the presence of deformities or anomalies in a fetus thought to be at high risk. The value of screening tests is important in low-risk populations (Todros *et al.,* 2001).

1.8.1 Prenatal screening tests

The typical number of imaging examinations each pregnancy has grown since the development of fetal ultrasonography in the 1960s. Visualizing embryonic and early fetal anatomy has been significantly enhanced by significant advancements in signal analysis and magnification imaging. The incidence and effectiveness of ultrasound throughout pregnancy are subject to significant practice variation. In some instances, the examination of fetal life has benefited from diagnostic advancements like magnetic resonance imaging and echocardiogram.

A few anomalies can be found as early as the late first trimester, while the majority of birth defects have no established risk factors. Initial eighteen to twenty weeks are ideal for a typical full mother and the fetus scan. Additionally, some soft anatomic indicators can reveal cytogenetic chromosomal abnormalities risk.

Observing congenital anomalies in fetuses has been greatly increased because of advances in sonography, and several deformities possess extensive data on their natural histories and probable consequences. Newborn screening are now made at the early stage of pregnancy feasible due to the capacity to either comfort a high-risk mother with healthy fetal pictures as well as provide thorough counselling and provide choices in situations with highly suspected deadly or significant abnormalities.

Genetic screening has moved to the earliest feasible stage of pregnancy due to the ability to convince a high-risk woman with normal fetal abnormalities and to provide thorough counselling with the choice to abort in situations of highly suspected deadly or significant abnormalities.

Endoscopic ultrasound and quantification of mother sera human chorionic gonadotropin levels have served as the hallmarks throughout the evaluation and treatment of pre - natal issues that can be brought on by an aberrant developing embryo for the past two decades (Bree *et al.,* 1989).

A false alarming assessment of non-viability may have serious aftermaths for either an early pregnancy with questionable survival or a gestation with uncertain placement. A healthy fetal development can be destroyed or badly damaged by hasty clinical or invasive surgery (Doubilet *et al.,* 2013).

There seems to be debate concerning the reliability of ultrasonic examination-based diagnosis. In tertiary care hospitals, it was 34% sensitive, but in rural hospitals, it was 12% sensitive, highlighting the need of skilled staff. When looking for neural tube defects, it is occasionally used during combination with a screening procedure

called the maternal plasma alpha feto-protein test. Contrary to an ultrasound alone, it demonstrates greater sensitivity (Todros *et al.,* 2001).

1.8.2 Analysis of Maternal blood plasma

Pregnant mother can have a blood test called the maternal serum screening test. They benefit from knowing the likelihood that their unborn baby will have certain birth defect including Down's syndrome, Edward syndrome, and neural tube defects. A test could be conducted between fourteen and twenty weeks or about ten weeks. A more recent test, the non-invasive pregnancy test, would reveal mostly all pregnancies if they are impacted by Down syndrome, Patau syndrome, and so on (Norwitz *et al.,* 2013).

The mother's circulation throughout gestation includes a mixture of DNA from her cells and the cells from the placenta. The tissue in the uterus known as the placenta connects the mother's blood supply with the developing fetus. All across the gestation, many cells are released into the mother's blood. Typically, the DNA of the placenta and the fetus are similar. It is possible to identify some genetic anomalies early without endangering the fetus by analyzing combined DNA from the placenta (Wang *et al.,* 2014).

1.8.3 Amniocentesis

The most generally employed procedure for discovering chromosomal abnormalities is amniocentesis, which involves the collection of amniotic fluid via a mother's abdomen membranes. Such treatment is often conducted between the

fifteenth and twentieth week of conception, and early measures can result in reduced performance, more failed cell culture, higher risk, and fetal problems (Rapp, 2004).

Amniocentesis can be performed for both diagnosing and treatment. The most common diagnostic reasons include embryonic genetic studies, fetal lung maturation assessment, and examination of fetal illness, anemia, detecting the kind of platelets or blood, and neural tube anomalies (Lehmann, 2016).

1.8.4 Chorionic villi sampling

Chorionic villi sampling is a paternity test which examines chorionic villi, which are small finger-like growths seen in the placenta. The placenta is the organ in the uterus that feeds the growing infant. The test searches for genetic defects in the newborn. Chromosomes are biological components that hold your genes. Genes are pieces of DNA that have been handed down from your mother and father. In most cases, persons have 46 chromosomes (Mascio *et al.*, 2020).

The hazards of chorionic villus collection are comparable to the risks of amniocentesis that included fetal death, hemorrhage, infections, tissue disruption, and inconclusive findings. The fetal rate of loss has reduced as ultrasound guidance skill and technique have improved; nonetheless, chorionic villus sampling has a challenging learning curve. A comprehensive analysis of the consequences of chorionic villus sampling found that utilizing an abdominal technique, total fetal loss was 1% within fourteen days, 1.5% within thirty days, and 3% for loss at any point throughout the pregnancy. The overall percentage of fetal death within fourteen days in the amniocentesis group was 0.5%. Beyond everything, therapeutic results of initiatives to treat genetic illnesses have been inconsistent. More research is needed before the medicines may be considered successful (Mujezinovic *et al.*, 2007).

1.9 Aims and objectives

The aims and objectives of the current study are given below

- To observe the prevalence pattern of different genetic disorders in Sukkur region.
- To explore the distribution of subjects with genetic anomalies with respect to various socio-demographic characteristics.
- To explore the association between consanguineous marriages with hereditary anomalies.
- To observe various biological and genetic attributes of hereditary anomalies.

CHAPTER: 2

METHODS AND METHODOLOGY

2.1. Study Population

Sukkur is Sindh's third biggest city, behind Hyderabad and Karachi. As per Pakistan's 2017 Census, the inhabitants of Sukkur are 551,357 people. Over 69% of the people speak Sindhi well, whereas 21% speak Urdu fluently. Approximately 95% of the city is Muslim, with the remaining 3%% made up of ethnic minorities, primarily Hindus.

Since ages, people have lived in the area surrounding Sukkur. The remains of Lakhan-jo-daro, situated close to an industrial park on the edge of the city of Sukkur, date from the mature Gandharan period of the Indus Valley Civilization, between 2600 BCE and 1900 BCE, encompass more than 300 acres of land and are regarded as the second-largest city of the Indus Valley Civilization, located only 75 kilometers away from the Moen-Jo-Daro Larkana.

Sukkur is also classified as a Division. Sukkur Division is one of the seven divisions of Pakistan's Sindh Province. This division of governance was eliminated in 2000, but was reinstated on July 11, 2011. Sukkur is the regional capital of the Sukkur Division, which contains 3 districts:

Historically, in 1843, the East India Company invaded Sindh. Officially, they set up three districts in Sindh: Hyderabad, Karachi, and Shikarpur. The regional headquarter was moved from Shikarpur to Sukkur in 1883, and the district rank was changed from Shikarpur to Sukkur again in 1901.

Sukkur is the regional headquarters of the Sukkur Division, which includes the three districts listed below.

1. Khairpur 2. Ghotki 3. Sukkur

Sukkur District is a district in Pakistan's Sindh Province. It is split into five official towns (also known as talukas), Sukkur City, New Sukkur, Rohri, Saleh pat, and Pano-aqil. Sukkur City and New Sukkur are urban centers, whereas Pano aqil is known for being one of the country's major military cantonments. Rohri is Sukkur District's smallest tehsil in terms of territory and inhabitants, yet it is home to a major railway station. Shikarpur in 1977 and Ghotki, in 1993, were separated from the boundaries of Sukkur (Table 1).

Table 1. Taluka-vice Population Summary of District Sukkur

Taluka	Population (2017)	Area (km^2)	Union councils
1. Sukkur	231589	150	11
2. New sukkur	319768	150	9
3. Rohri	371104	1319	12
4. Salehpat	129619	2339	3
5. Pano-aqil	435823	1233	12
Total	**1487903**	**5165**	**54**

Source. Adapted from google census report 2017.

Sukkur area has 1487903 residents as of the 2017 census report, 776332 of whom were male and 711882 of them were female. Urban residents made up 720,806 making 47% while rural residents made up 767,566 with 52%. Males have a literacy rate of 66%, while females have 43% (Table 2).

Table 2. Population breakup of Sukkur district into Urban and Rural

Administrative Unit	Population 2017	Male	Female	Trans	All sexes
Sukkur	1,487,903	776,332	711,882	158	1,487,903
Rural	767,566	399,143	368,358	65	767,566
Urban	720,806	377,189	343,524	93	720,806

Source. Adapted from census report 2017.

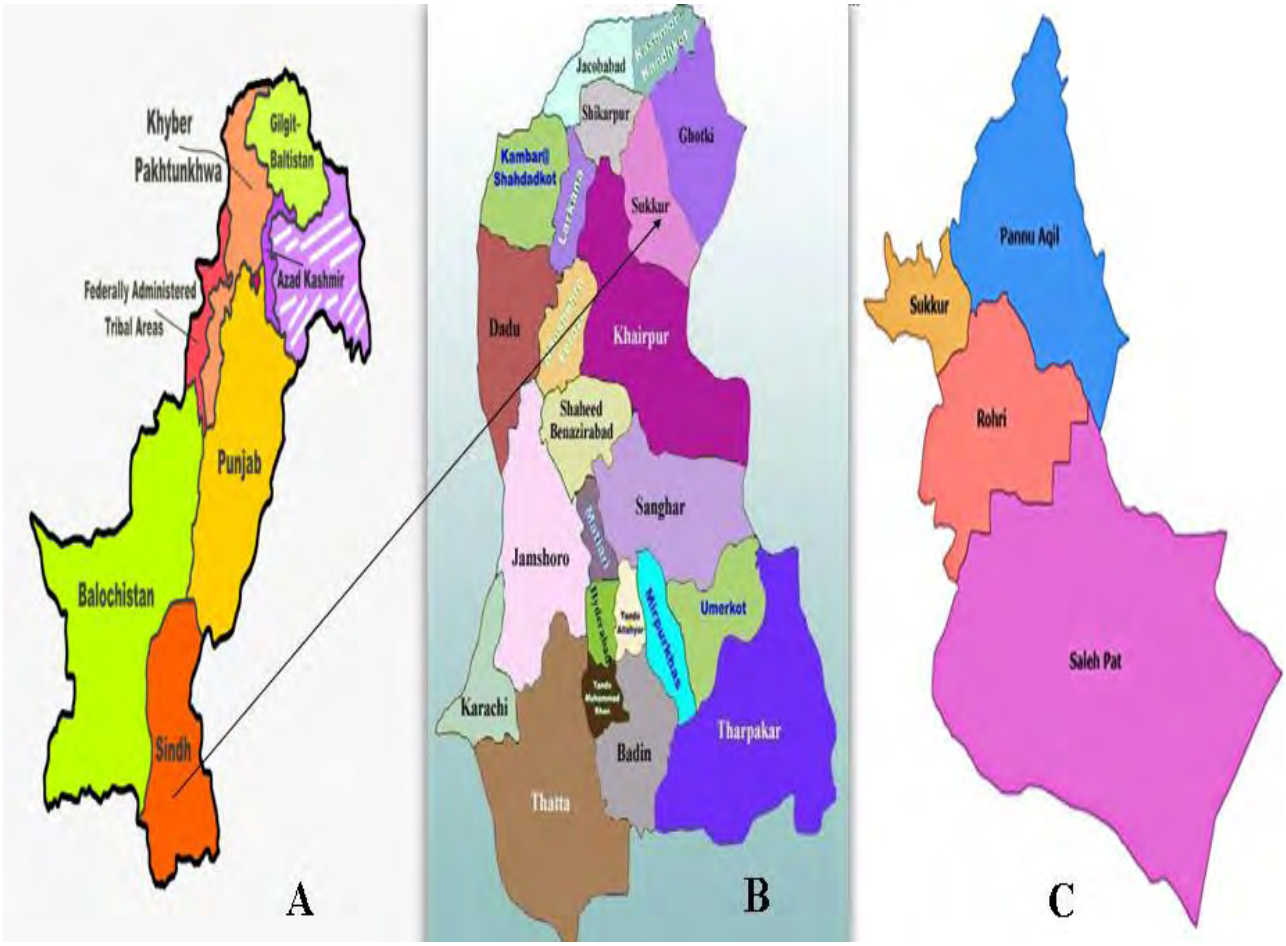

Fig. 1.1 (A). Map of Pakistan, (B). Sindh (C). District Sukkur (relevant study area)

(Source:Google-map)

2.2. Sukkur as study area

Sukkur is Sindh's third biggest city. It is inhabited by people of diverse ethnicity from different parts of Pakistan. Having 84% of the populace, Sindhi is the most populous ethnicity in this region. The majority of people live in remote rural parts of several talukas or tehsils, especially New-Sukkur, Sukkur city, Rohri, Saleh-pat, and Pano-aqil. Therefore, this region was preferred for genetic studies due to following reasons.

Firstly, it is a native hometown where a great number of approachable individuals are living over there to help in ascertainment of affected families. Being a teacher, by profession, of many students in Sukkur, has also made it helpful in the ascertainment of affected families from villages, hospitals, rehabilitation centers and special schools.

Secondly, not enough literature is available for reporting the congenital anomalies from sukkur region. Which acted as a motivational force to locate genetic cases in this area.

Thirdly, there is a high prevalence of consanguinity in order to develop strong intra-family bond. In most of the cases, people have a false assumptions regarding consanguinity. They think that marriage with blood related persons is an obligation in Islam. Hence it is the main reason behind the high prevalence of congenital anomalies in Sukkur region due to consanguinity.

Fourthly, the lack of awareness among the local populations of Sukkur has also aggravated the prevalence pattern of genetic anomalies. People who live here are

not much aware about the consequences of congenital disorders their prevention, care, and treatment. Most of the people lack awareness regarding the idea of consanguinity and many of them treat these serious disorders as general diseases. Consequently, it was very important to impart knowledge and awareness among these people and to make them realize the severity and consequences of these disorders.

Being a researcher, it is fundamental to make people aware about these serious and lethal disorders. Life-threatening birth abnormalities affect about 3-6 percent of all births. While some of these are attributable to poor maternal health caused by poverty, the availability of pesticides, and the use of specific pharmaceuticals that might cause chromosomal problems, the main cause is due to the diet that occurs when parents are related by blood.

Finally, the majority of rural women in Sukkur work in the field crops, where they are constantly exposed to chemicals such as fertilizers. These pollutants have played havoc on maternal health, leading to an increase in hereditary and congenital anomalies in the area. Patients with congenital anomalies were taken into current study, but those produced by an injury or trauma were not.

Furthermore, big sib-ships and cultural norms were factors in the emergence of some congenital diseases. The majority of individuals don't really believe in the link between cousin marriages and congenital anomalies.

2.3. Sampling and ascertainment of families

Sampling and ascertainment of families, was approached through various resources. Which includes the help of family members, ancestors of locality, students, Physicians, friends, and some noble persons of rural areas. A door-to-door survey was

conducted in specific rural regions, and impacted households were selected at random. Apart from, most of the families of index cases were approached by visiting the Special Schools, rehabilitation centers and Civil Hospitals. Number of meetings were held with the parents of affected child, head of the departments in hospitals, as well as with the Principals of the Special schools and rehabilitation centers in order to collect data with their consent.

The majority of the information gathered from these sources concerned deaf-mutes, limb abnormalities, eye diseases, neuromuscular defects, skeletal defects, and brain illnesses such as mental disabilities. The current study did not look at metabolic problems that demanded clinical tests to diagnose, such as coronary heart disease, diabetes, and hereditary susceptibility to certain ailments.

2.4. Ethical approval

Studying human subjects for the purpose of genetic research has always been a matter of deep concern in our society on ethical and moral grounds. The approval of the Ethical Review committee was attained from the Institutional review board (IRB), Quaid-I-Azam University Islamabad. Moreover, proper consent was also taken from the families included in my field work. All the particulars of reported families on proforma were taken with their consent.

2.5. Study duration

The research work was conducted from March 2022 to August 2022. Several visits were conducted in the different study areas rendering the convenience of the affected individuals. Before starting the field work, goals and objectives of the study

were determined clearly. A lot of effort was made to take all the relevant data necessary for complete analysis of the reported cases.

2.6. Proforma designing and filling

A standard questionnaire was designed for data collection, and it consisted of three parts. The first part contained demographic information containing both categorical and continuous demographic variables like age, gender, origin residence, cultural background, socioeconomic status, occupation, religion, language, education, family type etc.

The part two of the questionnaire included data on the family. It included details such as marriage status, marital type (consanguineous or non-consanguineous), number of afflicted family members, number of normal and affected siblings, mother and father age, and so on.

The third and final section of the pro forma includes clinical and phenotypic information, as well as anthropometric measures such as height (standing or sitting), weight, circumference of the head, neck, and chest, and information on the affected body parts. This form is used for a variety of anomalies. Apart from this, each case was physically investigated, and pictures and medical records were obtained if they were available.

2.7 Pedigree construction

A pedigree was constructed using data provided by the family's head or guardian. A pedigree is a genetic representation of a family tree that displays the inheritance pattern of a trait and identifies which family members express the trait and

which relatives are carriers, as well as the marriage type, i.e., consanguineous or non-consanguineous.

Males, females, siblings, twins, marriage kinds, affected and deceased people were all represented by standard symbols in pedigrees. Males and females were represented by squares and circles, respectively. Rhombus denotes an uncertain gender. Non-consanguineous unions are indicated by a single line between forms, whereas consanguineous unions are shown by a double line. A slash is drawn across the shapes to represent a deceased person. The manner of abnormality inheritance was extensively explored; generation was denoted by roman numerals, whereas individuals were identified by Arabic numerals.

2.8 Data storage and analyses

All the data was recorded into an MS Excel sheet for further analysis after an exhaustive and prolonged field work, data gathering, and proforma filling. Different spread sheets were prepared on Excel sheet so that different categories of data can be sorted easily. Photographs of the affected subjects were taken along with their names and family IDS on the basis of availability and were saved in digital format. All the data was summarized, and data was represented using different tables and graphs.

2.9 Public representation and heredity anomalies

In district Sukkur, individuals have a variety of opinions about congenital and genetic illnesses. Many women thought that abnormalities in their infants were caused by a lunar eclipse during pregnancy or by black magic and the jinnat influence. There were several widespread misunderstandings about these illnesses.

The majority of instances included consanguineous marriages in successive generations. Some folks were quite interested in sharing information about a certain genetic abnormality. Despite my assurances and the primary goal of my research investigations, the vast majority of respondents were hesitant to provide family knowledge about genetic abnormalities. As a result, gathering data from afflicted families remained a challenge. The majority of individuals living in rural regions have little economic resources and hence request financial aid, but they are subsequently informed that this is only a research poll. According to my observation, there has been no prior survey within the region.

2.10 Database search and literature Survey

The anomalies were classified with the help of resident doctors and medical specialists. After searching different databases and research articles and comparing the pictures, photographs, medical reports, and clinical presentation of the index subjects, anomalies were classified into broad categories like division. Broad categories were subdivided into sub-categories according to the criteria of Online Mendelian Inheritance in Man (OMIM). The anomalies were divided into syndromic and non-syndromic, based on the involvement of multiple organ systems and divided into familial and sporadic. These anomalies were also classified according to socio-demographic Variables, including living area rural or urban of the subject, age range, caste/ethnicity, occupation type, literacy level, economic status, marital status, and family type.

CHAPTER.3

RESULTS

A total of 311 independent index cases with certain types of genetic anomalies were observed in the Sukkur region.

3.1 Demographic distribution of index subjects

3.1.1 Distribution of subjects with respect to gender and familial/sporadic nature

The distribution of subjects was based on gender. The ratio of male subjects was found to be very high as compared to the female subjects in both the rural and urban cases. The percentage of male subjects was 72% (n=224), whereas the percentage of female subjects was 27.9% (n=87). Most of the cases were familial in nature representing 66.8% (n=208) while sporadic cases counted 33.1% (n=103) (Fig. 2).

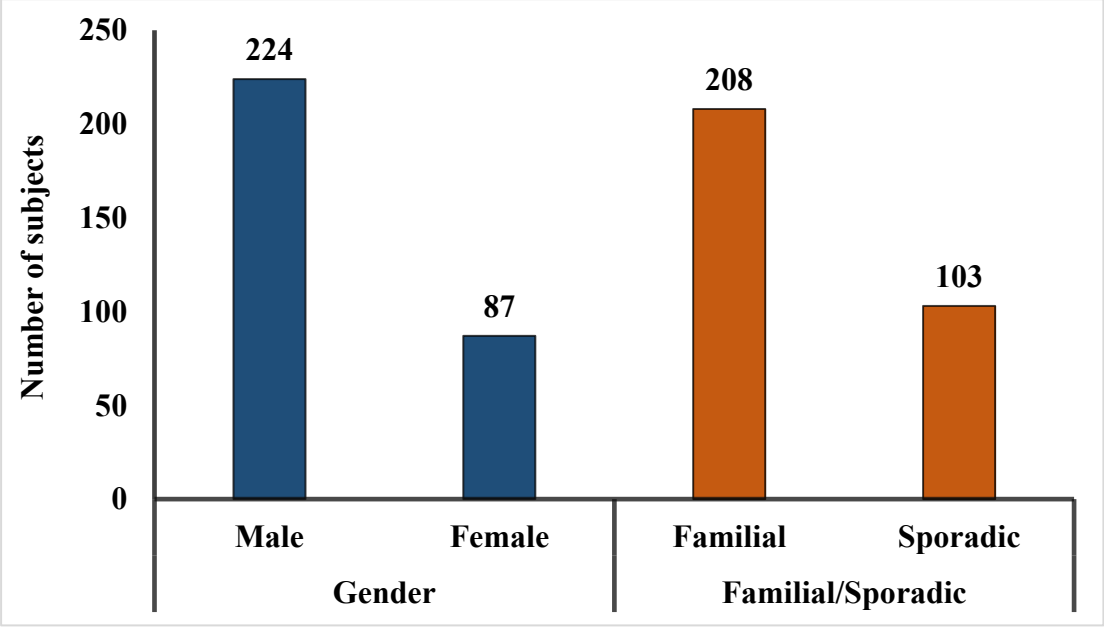

Fig. 2. Distribution of subjects with respect to gender and familial/sporadic nature

3.1.2 Distribution of subjects with respect to rural and urban origin

Most of the cases belonged to the rural parts of the region counting 61.4% (n=191) while urban cases only accounted 38.5% (n=120). On the other hand, familial cases were dominant in the rural areas as compared to the sporadic cases and contributed 70.1% (n=134), while sporadic cases were 29.8% (n=57). Similarly, familial cases were also dominant in the urban areas and contributed 61.6% (n=74) whereas sporadic cases were recorded 38.3% (n=46) (Fig. 3).

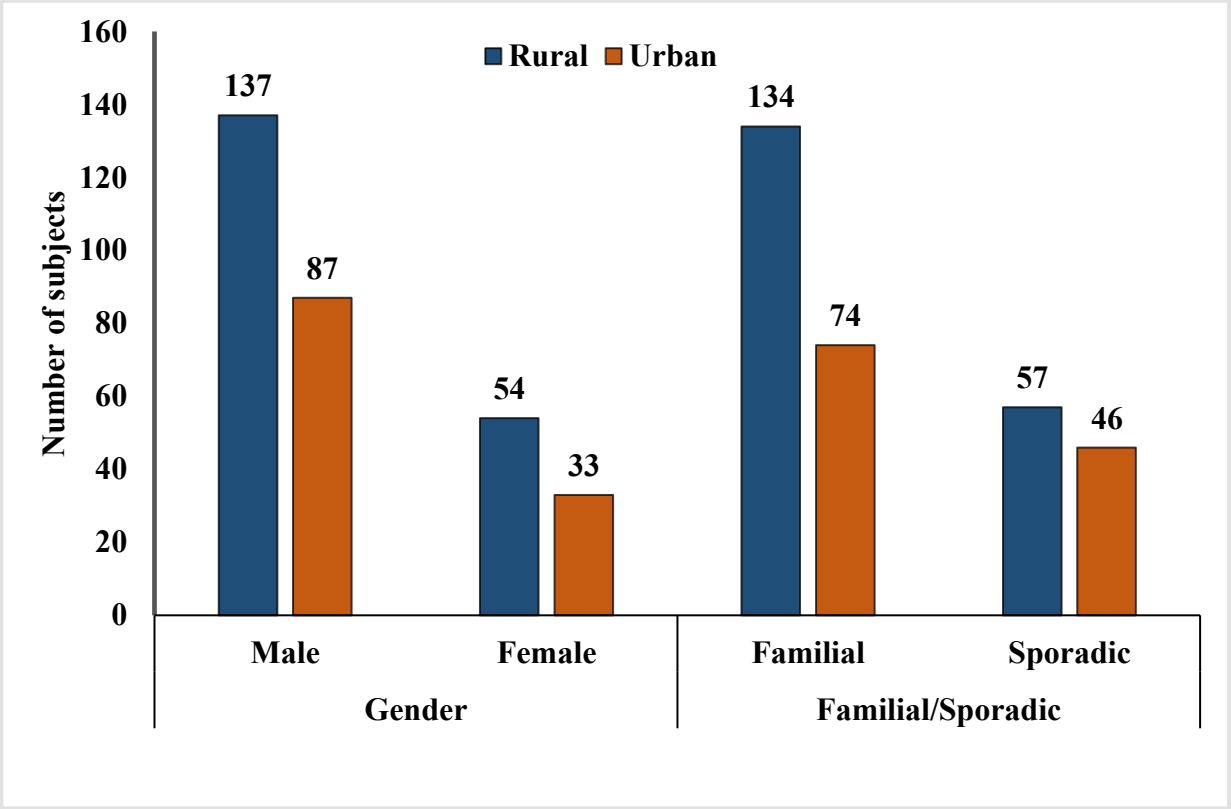

Fig. 3. Distribution of subjects with respect to rural and urban origin

3.1.3 Distribution of subjects with respect to age categories

Subjects were classified into 5 different age categories based on their age. The highest number of cases were found in the age category of >10-20 years with a percentage of 45.3% (n=141). 23.4% cases (n=73) were from the category of age 6-10 years. While 15.7% (n=49) were from the age category of above 30, followed by 8.3% (n=26) from 21-30 years and 7% (n=22) from age category up to 5 years (Fig. 4).

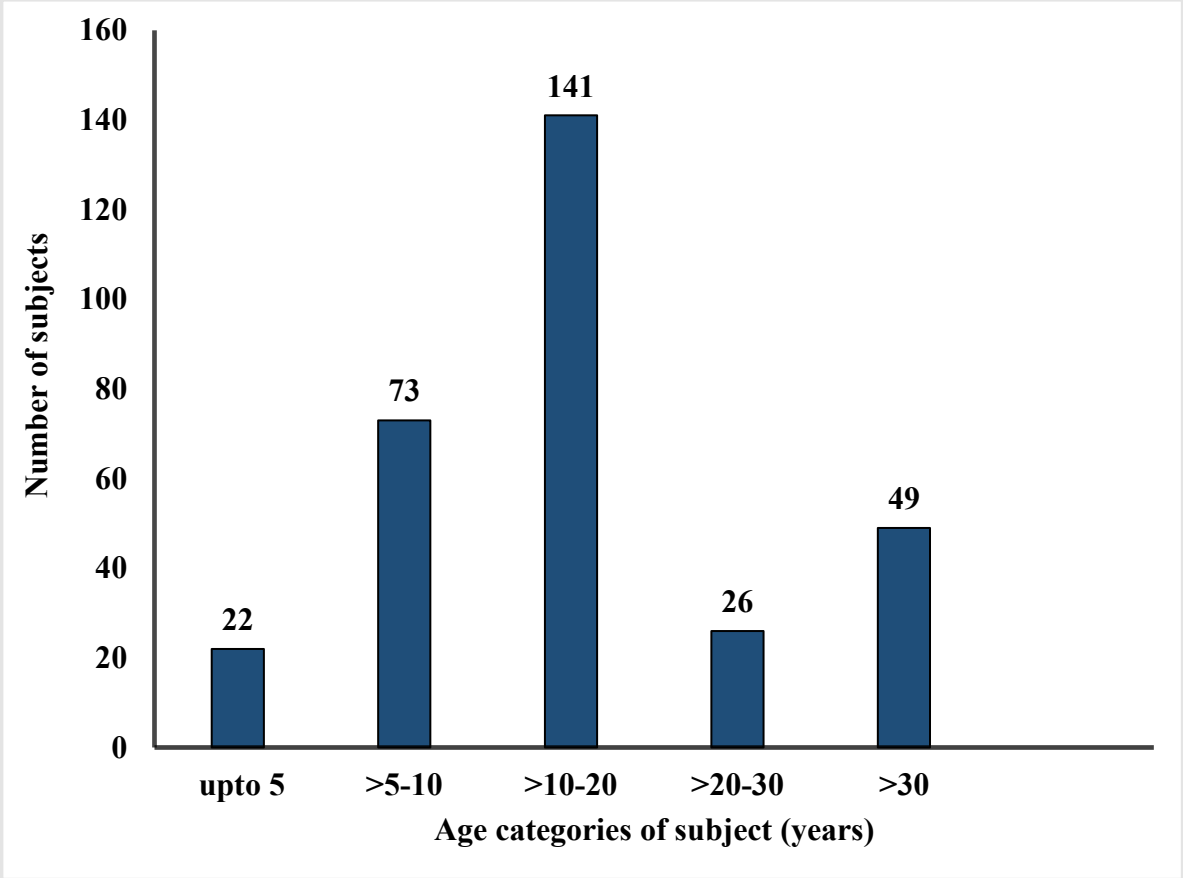

Fig. 4. Distribution of subjects with respect to age categories (years)

3.1.4 Distribution of subjects with respect to literacy level

The subjects up to age 5 category were not included and 93.2% (n=290) were considered for this category of distribution based on literacy level. As most of the index cases were observed in special schools therefore most of the cases were found to be literate and contributed 73.3% (n=228) as compared to the illiterate 21.3% (n=62). From this literate category 74.1% (n=169) were male while 25.8% (n=59) were females. Literate subjects were further divided into four groups based on their level of education Primary schooling, Middle schooling, High-schooling and above High school categories. Primary school category was 45.6% (n=104) followed by Middle schooling 31.5% (n=72), High-schooling 21.9% (n=50) and above high schooling 4.8% (n=11), respectively (Fig. 5).

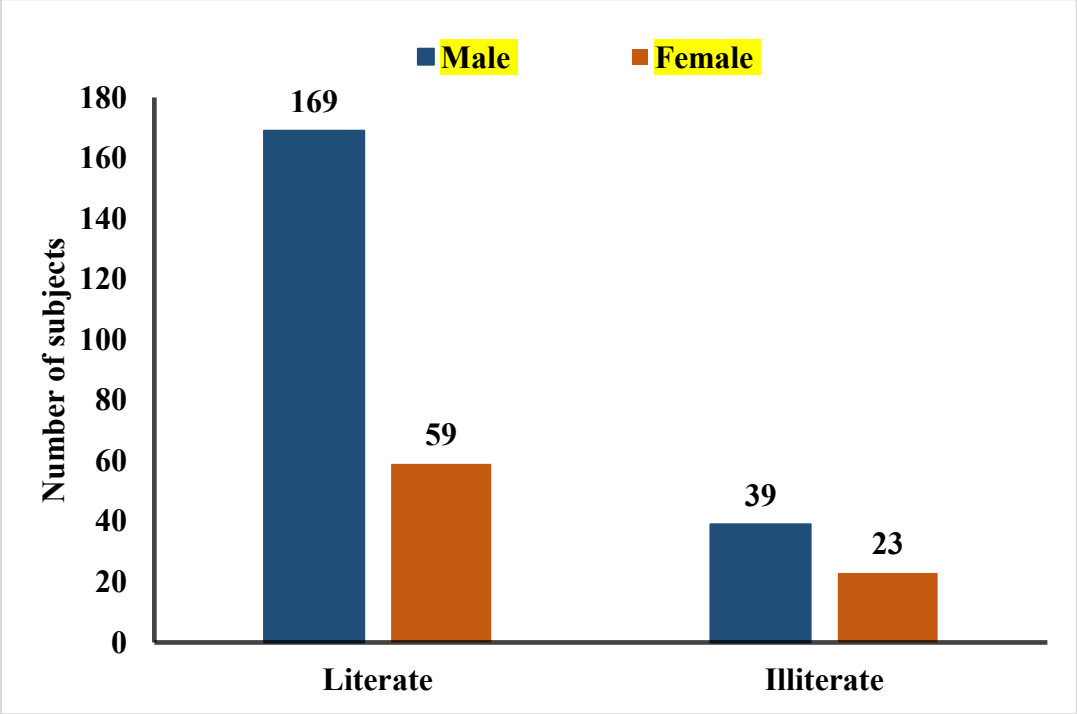

Fig. 5. Distribution of subjects with respect literacy level

3.1.5 Distribution of subjects with respect to their guardian occupation

The occupation of the guardian was considered for this distribution of the index cases. They were divided into 5 categories, Shopkeeper, Labour, Unemployed, employed and others. Shopkeeper were 29.9% (n=93). There were 24.1% (n=75) cases when guardian was found to be Labour. The guardians of the 21.8% (n=68) cases included unemployed. While 17.6% (n=55) were employed. Others categories included Private jobs, deceased and other small businesses (Fig. 6).

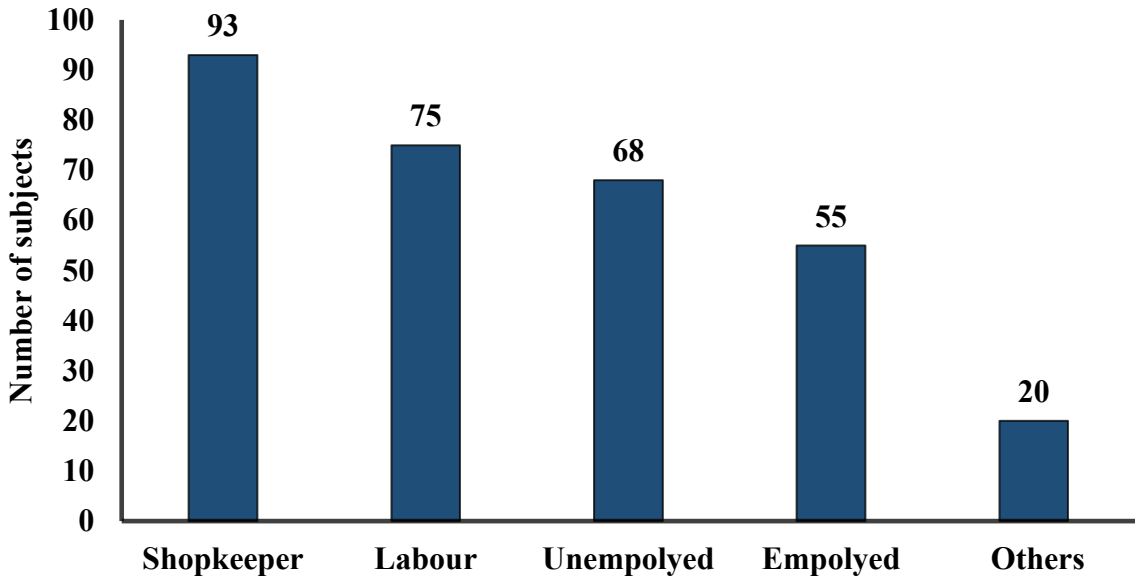

Fig. 6 Distribution of subjects with respect to guardian occupation

3.1.6 Distribution of subjects with respect to marital status and family type

For the description of marital status index cases age above 16 were considered only. Out of 144 subjects 68.7% (n=99) were single and 31.2% (n=45) were married. Another distribution of subjects was made based on their family type whether Nuclear or Extended. According to that distribution, extended family type was dominant contributing 60.7% (n=189) out of total 311 cases while nuclear family type contributed 39.2% (n=122) (Fig. 7).

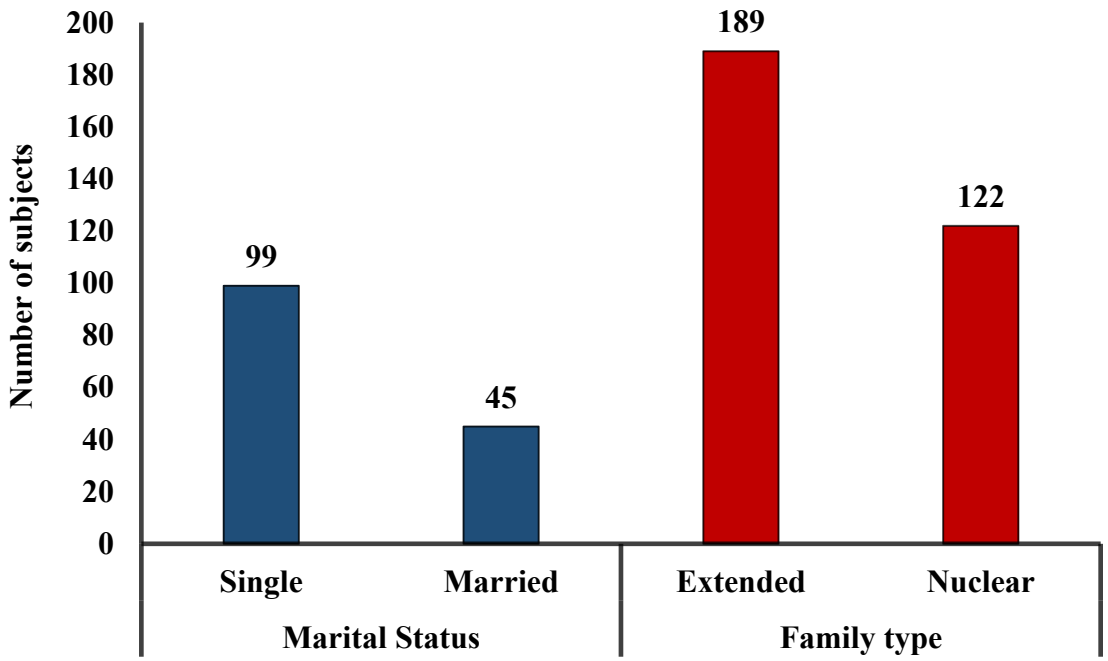

Fig. 7. Distribution of subjects based on their marital status and family type

3.1.7 Distribution of subjects based on their economic status

Index cases were divided into 4 groups because of their self-declared economic status distribution. These were Low, Low-mid, High and High–mid categories. The highest number of cases belonged to the Low category of the economic status with 50.4% (n=157). The low-mid category covered 26.3% (n=82), while High-mid category contributed 18.6% (n=58) and there were only (n=14) 4.5% cases from the high economic status category (Fig. 8).

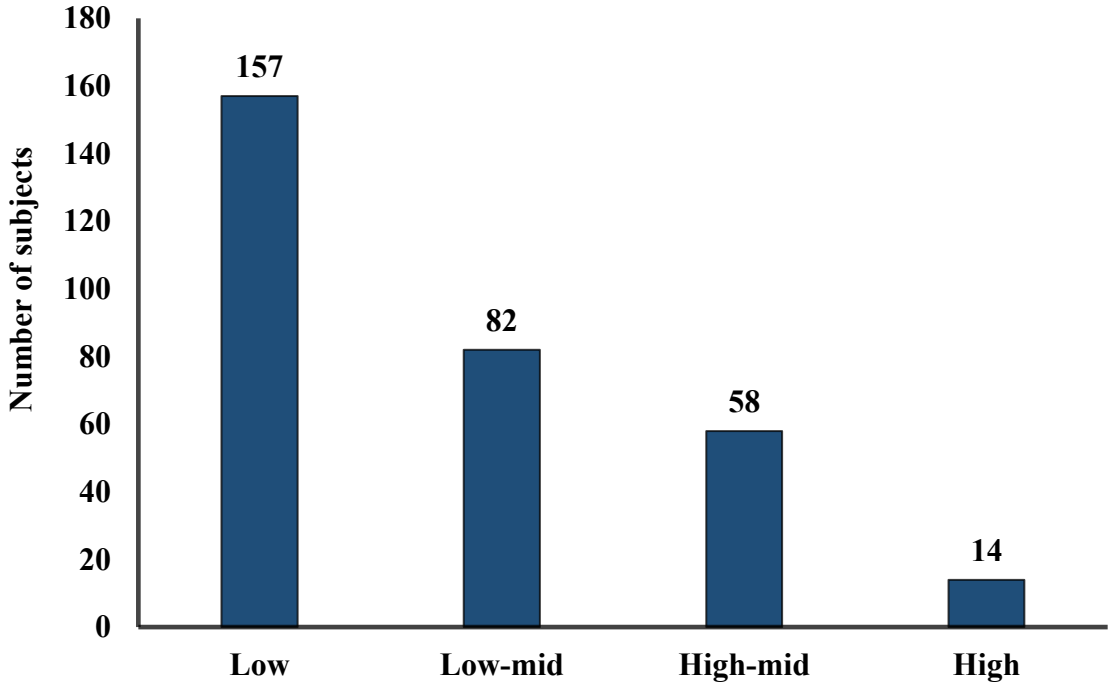

Fig. 8. Distribution of subjects based on their economic status

3.1.8 Distribution of subjects with respect to caste-system

The index cases were collected from subjects of many different castes. As there were so many castes so, the others category was found to be the most dominant one which contributed 50% (n=157). After that, the second most dominant caste system included Balouch with 24% (n=75). Shaikh contributed 11% (n=35) and data collected from Panhwar contributed 9% (n=27). Whereas Syed caste accounted for only 5% (n=17) (Fig. 9).

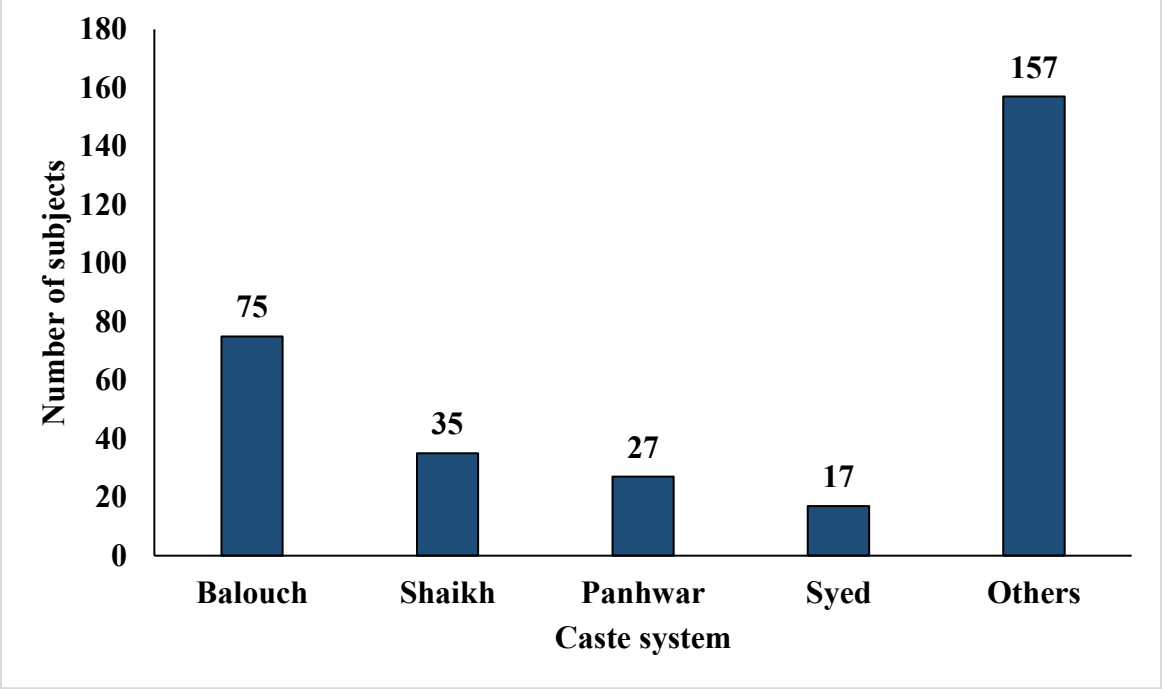

Fig. 9. Distribution of subjects with respect to caste-system

3.1.9 Distribution of subjects with respect to mother-tongue

The Sindhi was found to be the most spoken language and contributed 89.35% (n=278) and there was only a fraction of cases speaking Urdu with 0nly 2.89% (n=12) and other languages accounting 6.75 % (n=21). That indicated the dominance of Sindhi language spoken in that area (Fig. 10).

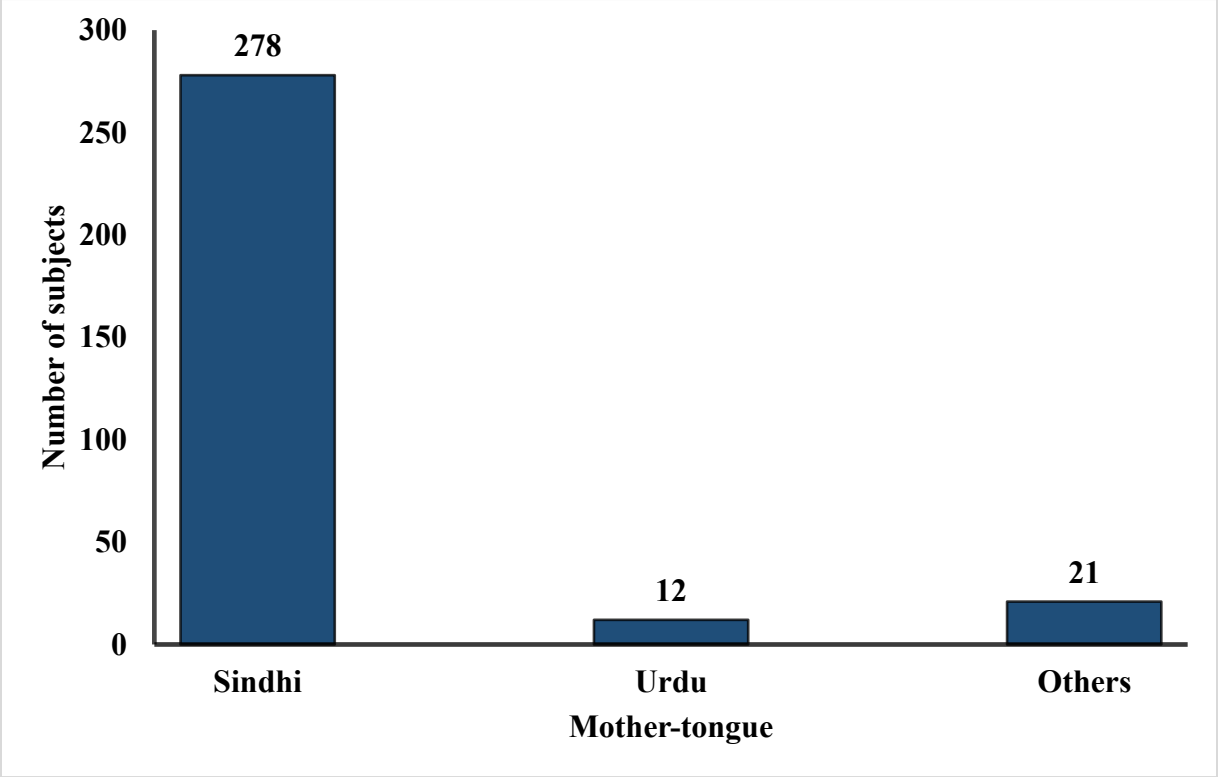

Fig. 10. Distribution of subjects based on their mother –tongue

Table 3. Demographic distributions of 311 index subjects with respect to gender And familial/sporadic

Demographic variables	Gender		Familial/Sporadic		Total, n (%)
	Male, n (%)	Female, n (%)	Familial, n (%)	Sporadic, n (%)	
Origin (n=311)					
Rural	137 (61)	54 (62)	134 (64)	57 (55)	191 (61)
Urban	87 (39)	33 (38)	74 (36)	46 (45)	120 (39)
Total	224 (72)	87(28)	208 (67)	103 (33)	311
	Chi^2=0.0218; df=1; P=0.883		**Chi^2=2.399; df=1; P=0.122**		
Age (years)					
Up to 5	16 (7)	6 (7)	13 (6)	9 (9)	22 (7)
>5 to 10	51 (23)	22 (25)	55 (26)	18 (17)	73 (23)
> 10 to 20	104 (46)	37 (43)	81 (39)	60 (58)	141 (45)
> 20 to 30	22 (10)	4 (5)	24 (12)	2 (2)	26 (8)
>30	31 (14)	18 (21)	35 (17)	14 (14)	49 (16)
	Chi^2=4.299; df=4; P=0.367		**Chi^2=16.67; df=4; P=0.002 Sig.**		
Caste					
Balouch	52 (23)	23 (26)	53 (25)	22 (21)	75(24)
Panhwar	21 (9)	6 (7)	21 (10)	6 (6)	27 (8)
Syed	15 (12)	2 (2)	12 (6)	5 (5)	17 (5)
Shaikh	27 (12)	8 (9)	20 (10)	15 (15)	35 (11)
Others	109 (49)	48 (55)	102(50)	55 (53)	157 (50)
	Chi^2=3.991; df=4; P=0.4181		**Chi^2=3.796; df=4; P=0.4343**		

Guardian occupation					
Shopkeeper	71 (32)	22 (25)	64 (31)	29 (28)	93 (30)
Labour	55 (25)	20 (23)	41 (20)	34 (33)	75 (24)
Unemployed	48 (21)	20 (23)	47 (23)	21(20)	68 (22)
Employed	36 (16)	19 (22)	39 (19)	16 (16)	55(18)
Others	14 (6)	6(7)	17 (8)	3 (3)	20 (6)
	Chi^2=2.214; df=4; P=0.697		**Chi^2=8.730; df=4; P=0.0682**		
Literacy rate (age >5 included n=290)					
Literate	169 (81)	59 (72)	152 (78)	76 (80)	228 (73)
Illiterate	39 (19)	23 (28)	43 (22)	19 (20)	62 (27)
	Chi^2=3.026; df=1; P=0.082		**Chi^2=0.159; df=1; P=0.689**		
Level of education					
Primary schooling	70 (34)	34 (41)	72(37)	32 (34)	104 (33)
Middle schooling	51 (25)	21 (26)	50 (26)	22 (23)	72 (23)
High schooling	45 (22)	5 (6)	29 (15)	21 (22)	50 (16)
Above	8 (4)	3 (4)	9 (5)	2 (2)	11 (4)
	Chi^2=9.283; df=3; P=0.0258 Sig.		**Chi^2=3.352; df=3; P=0.341**		
Economic status					
Low	118(53)	39 (45)	100 (48)	57 (55)	157 (50)
Low-mid	59 (26)	23 (26)	59 (28)	23 (22)	82 (26)
High-mid	37 (17)	21 (24)	40 (19)	18 (17)	58 (19)
High	10 (4)	4 (5)	9 (4)	5 (5)	14 (5)
	Chi^2=2.719; df=3; P=0.4370		**Chi^2=1.828; df=3; P=0.6089**		

Marital status Age 16 or above (n=144)					
Single	85 (77)	14 (42)	60 (63)	39 (80)	99 (69)
Married	26 (23)	19 (57)	35 (37)	10 (20)	45 (31)
	Chi^2=13.81; df=1; P= 0.0002		**Chi^2=4.064; df=1; P= 0.0438**		
Family type					
Extended	135 (60)	54 (62)	132 (64)	57 (55)	189 (61)
Nuclear	89 (40)	33 (38)	76 (36)	46 (45)	122 (39)
	Chi^2=0.085; df=1; P= 0.770		**Chi^2=1.906; df=1; P= 0.167**		
Mother tongue					
Sindhi	200 (89)	78 (90)	184 (88)	94 (91)	278 (89)
Urdu	9 (4)	3 (3)	9 (4)	3 (3)	12 (4)
Others	15 (7)	6 (7)	15 (7)	6 (6)	21 (7)
Total	224	87	208	103	311
	Chi^2=0.057; df=2; P= 0.971		**Chi^2=0.614; df=2; P= 0.736**		

3.2 Distribution of congenital anomalies into major and minor categories

All the index cases were categorized into 5 major groups (Table 4). Sensorineural/ear defects were most common (n=197), followed by limb defects (n=44), visual/eye impairments (n=30), neurological disorders (n=20), and some cases with less than 10 subjects were combined to be kept under the category of others. The pie chart below (Fig.11) explains the percentage of these major anomalies. Minor categories with their classification according to OMIM and ICD-10 databases are figured in the Table 5.

In sensorineural defects, the cases with deaf/mute were the most common accounting 98.9% (n=195) and 1.0% (n=2) were with the only mute category out of total cases. In limb defects, split hand-foot was most frequent with 34.0% (n=15) cases and clubfoot with 31.8% (n=14). Cataract with 66.6% (n=20) cases was the most frequent in visual/eye impairments. In the neurological defects, intellectual disability was the most common with 80% (n=16). While the other category contains few cases related to orofacial defects, musculoskeletal and thyroid disorders.

Table 4. Major groups of congenital anomalies with respect to number of subjects

Congenital Anomaly	No. of Subjects	Proportion	Gender (n)		Familial/ Sporadic (n)	
			Male	Female	Familial	Sporadic
Sensorineural/ear defects	197	0.633	144	53	133	64
Limb defects	44	0.141	34	9	32	12
Visual/eye impairments	30	0.096	16	14	23	7
Neurological defects	20	0.064	12	8	11	9
Others	20	0.064	17	3	9	11
Total	311		224	87	208	103
			Chi^2=9.460; df=4; P= 0.0506		**Chi^2=7.609; df=4; P= 0.1070**	

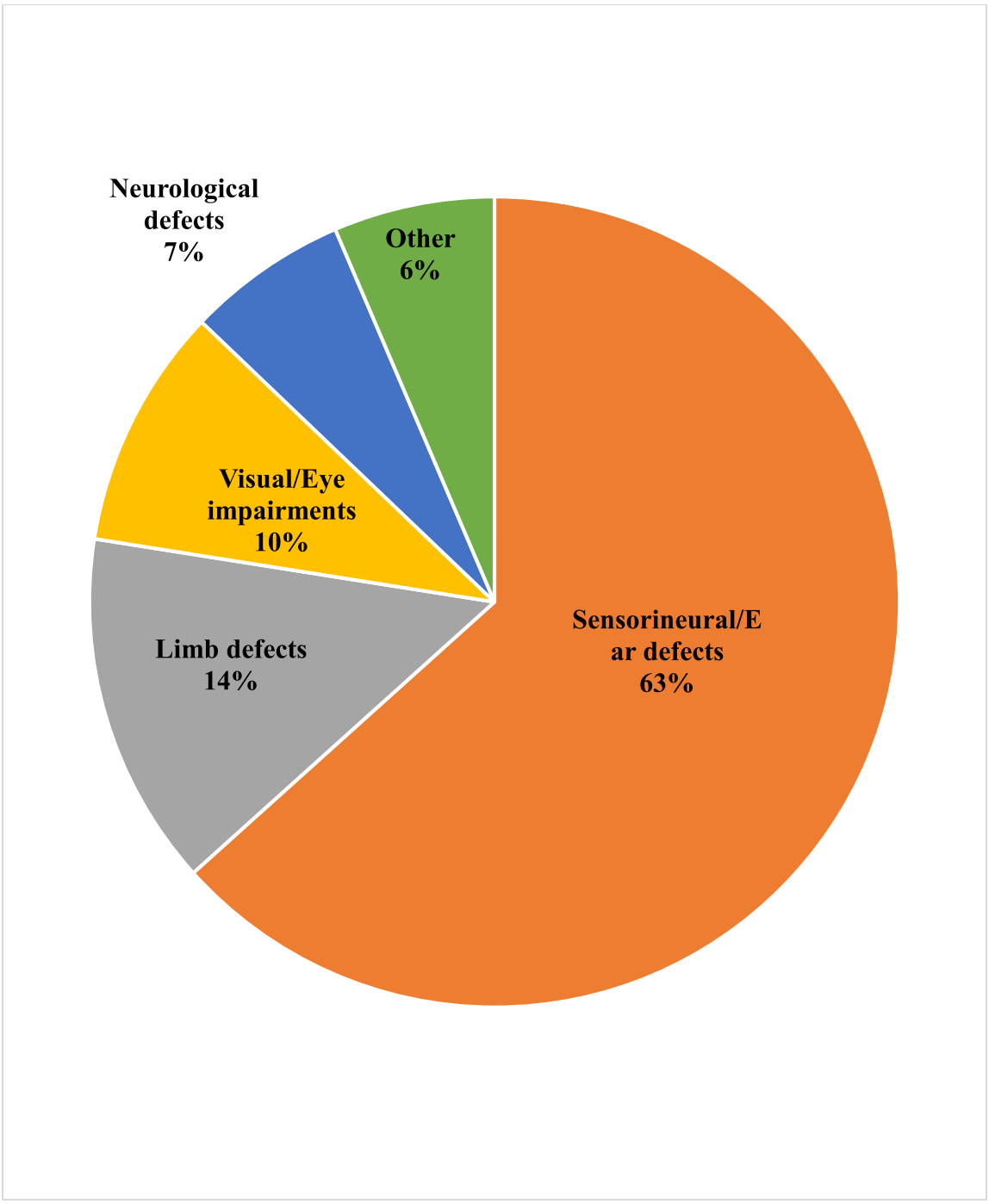

Fig. 11. Major categories of congenital anomalies

Table 5. Major groups of congenital anomalies with respect to number of subjects

Anomaly major/minor	No. of cases	Proportion	OMIM	ICD-10
Sensorineural defects	197	0.633		
Deaf/mute	195	0.627	220290	H91.3
Only mute	2	0.006		
Limb defects	44	0.141		
Split hand-foot	15	0.04		Q 72.7
Clubfoot	14	0.045	119800	Q66.89
Brachedactely	4	0.012	112500	Q71.8
Polydactyly	4	0.012	603596	Q69.9
Camptodactely	1	0.003	114200	
Bifid thumb	3	0.009		
Syndactyly	1	0.003	609815	Q70.9
Clinodactely	2	0.006	114200	
Visual/eye impairments	30	0.096		
Cataract	20	0.064	302200	H 26.9
Blindness	6	0.019		
Night Blindness	1	0.003	310500	H 53.60
Retinitis pigmentosa	1	0.003	300029	H 35.52
Glaucoma	2	0.006	231300	H 40.82

Neurological defects	20	0.064		
Intellectual disability	16	0.051	300243	F71
Epilepsy	4	0.012	245570	G40
Others	20	0.064		
Cleft palate	8	0.025	119540	Q35
Muscular dystrophy	6	0.01		
Dwarfism	3	0.009	100800	E34.3
Hypothyroidism	3	0.009	218700	E03
Total	311			

3.3 Distribution of subjects with respect to genetic attributes

3.3.1 Distribution of anomalies with reference to gender

There was a total number of 311 cases where male cases were 224 making 72% while there were only 28% females (n=87). In all the categories of congenital anomalies observed, male cases were more frequently observed. In sensorineural defects, 73% (n=144) were male and 26.9% (n=53) were female cases. In case of limb defects, male cases were quite dominant and contributed 79.5% (n=35) whereas female cases were only 20.4% (n=9). Male cases were also higher in visual/eye impairments and counted 53.3% (n=16) while female cases were only 46.6% (n=14). In neurological disorders, male cases contributed 60% (n=12) whereas 40% (n=8) were female members. In the others category, 85% (n=17) were male members whereas 15% were female cases (Table 4; Fig. 12).

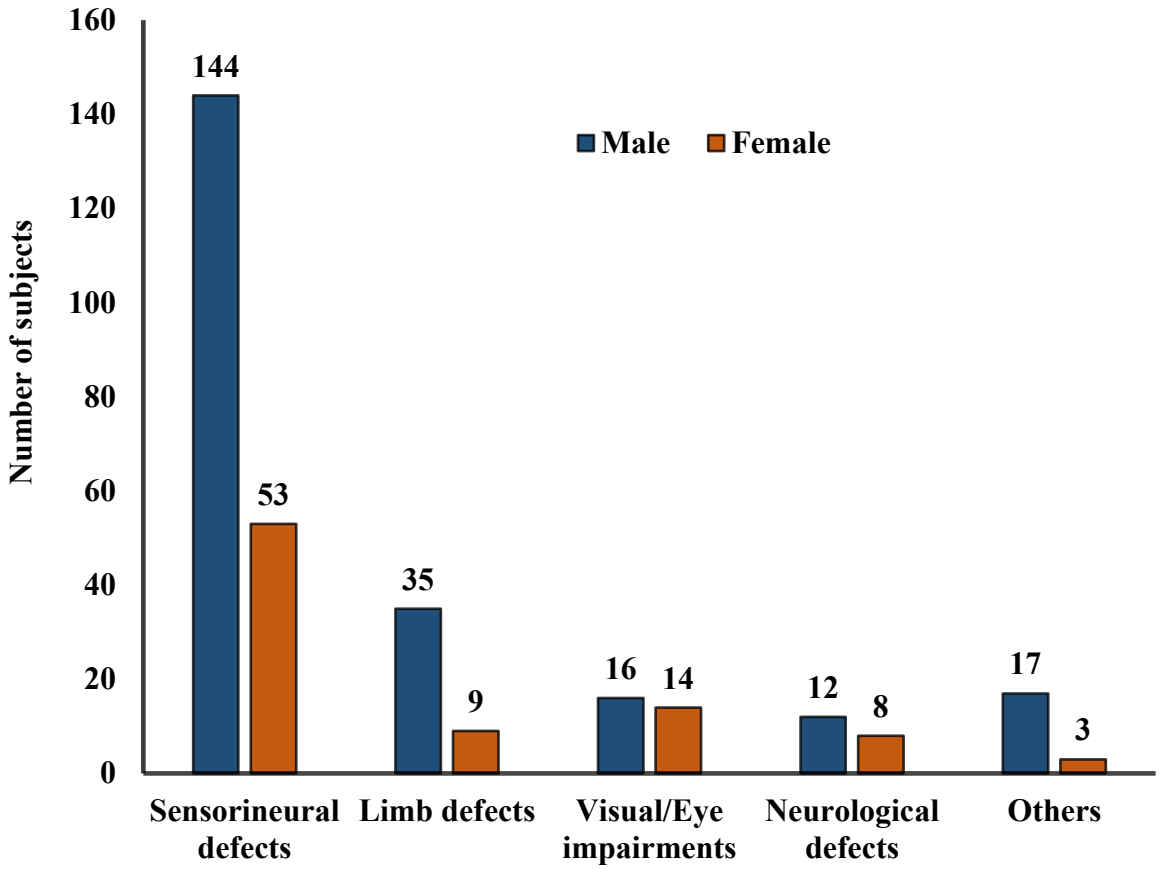

Fig. 12. Distribution of anomalies with reference to gender

3.3.2 Distribution of anomalies with respect to familial/sporadic nature

The total number of familial cases was 208 contributing 66.8% (n=208) whereas sporadic cases were 103 making 33.1% of the total 311 cases. In the sensorineural defects, familial cases were found to be dominant contributing to 67.5% (n=133) where sporadic cases contributed 32.4% (n=64). Familial cases outnumbered those of limb defects with 72.7% (n=32) while sporadic cases were 27.7% (n=12). In visual/eye impairments, similarly, familial cases were frequent with 76.6% (n=23) whereas 23.3% (n=7) were sporadic. In neurological disorders, familial cases were slightly higher contributing 55% (n=11) whereas sporadic cases were slightly less making 45% (n=9). In the others category, sporadic cases were slightly higher contributing 55% (n=11) whereas familial cases were slightly less making 45% (n=9) in the other defect category.

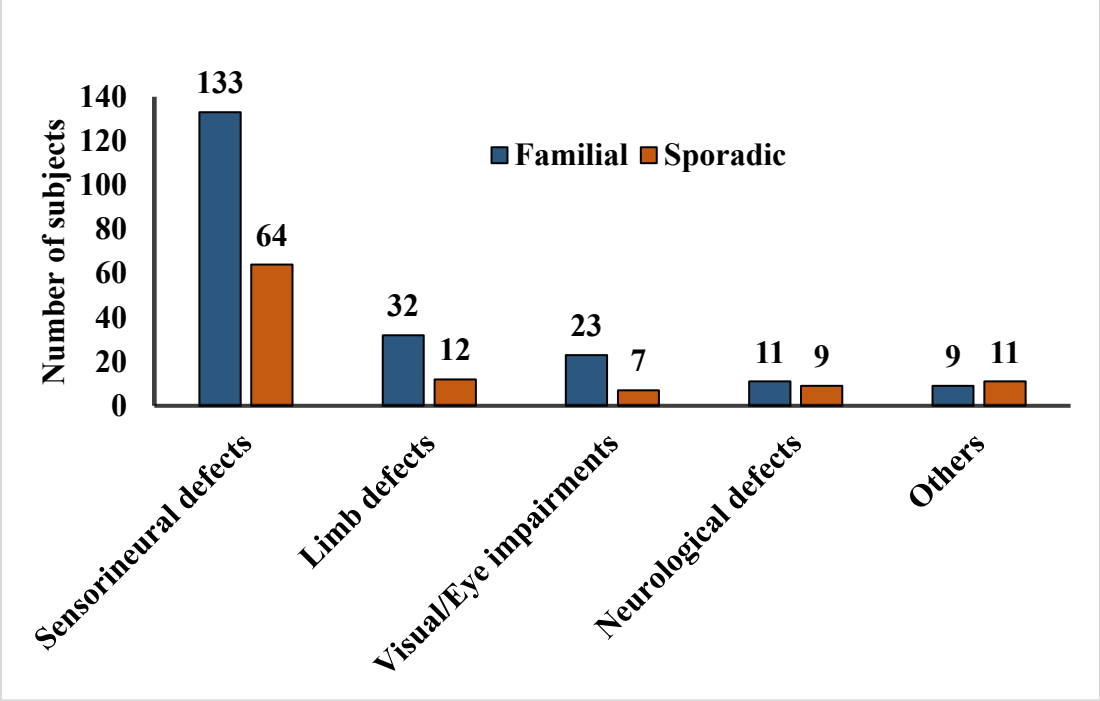

Fig. 13. Distribution of subjects with respect to familial/sporadic nature

Table 6. Distribution of subjects with respect to familial/sporadic nature

Congenital anomaly type	No. of subjects	Sporadic (n)			Familial (n)		
		Male	Female	Both	Male	Female	Both
Sensorineural defects	197	52	12	64	92	41	133
Limb defects	44	9	3	12	26	6	32
Visual/eye impairments	30	4	3	7	12	11	23
Neurological defects	20	6	3	9	6	5	11
Others	20	10	1	11	7	2	9
Total	311	81	22	103	143	65	208
		Chi^2=4.034; df=4; P= 0.4014			**Chi^2=6.654; df=4; P= 0.1553**		

3.3.3 Distribution of parity order in familial cases

Parity order was analyzed to establish any link between the parity and the types of anomalies observed. Out of total 208 familial cases, the highest number of subjects were recorded from the 2nd parity order subject with 62 cases with 30% contribution. After that 1st parity contributed to 24 % cases with (n=49), followed by 3rd with (n=41) and

19.7% cases, whereas above 4th parity accounted for 15.8% (n=33) with (Table 7) with detailed description is present below.

Table 7. Parity order in familial cases (n=208)

Congenital anomaly type	No. of subjects	Parity order in Familial cases (n=208)				
		1st	2nd	3rd	4th	>4th
Sensorineural defects	133	34	44	23	13	19
Visual/Eye impairments	23	7	3	6	3	4
Limb defects	32	3	10	10	5	4
Neurological	11	2	4	1	1	3
Others	9	3	1	1	1	3
Total	208	49	62	41	23	33

3.3.4 Description of number of normal sibs in familial cases

Subjects with 2 normal sibs were the highest in number with 32.2% cases (n=67). Whereas subjects with both 3 and 4 normal sibs were similarly observed (n=37) with 17.7% cases. 15.8% (n=33) cases were reported with 1 normal sibs while number of people with more than 4 normal sibs were 26, contributing to 12.5% of the total familial cases. Least number of cases (n=8) with 3.8% contribution was noted from subjects with no normal sibs were observed (Table 8) explains it in detail.

Table 8. Distribution of number of normal sibs for familial cases (n=208)

Congenital anomaly type	No. of normal sibs for familial cases (n=208)					
	0	**1**	**2**	**3**	**4**	**>4**
Sensorineural defects	3	28	47	22	21	12
Limb defects	1	0	7	10	7	7
Visual/eye impairments	3	1	6	5	4	4
Neurological defects	0	3	4	0	2	2
Others	1	1	3	0	3	1
Total	**8**	**33**	**67**	**37**	**37**	**26**

3.3.5 Distribution of generation with disease for familial cases

To describe the number of generations affected in the familial cases the data was analyzed to know any link between the anomaly type and the number of generations it was affecting. Out of total 208 familial cases 50% (n=104) was found with only 1 generation affected whereas 36% (n=75) cases were found with 2 generations or more than two generations with 14% (n=29) only (Table 9).

Table 9. Distribution of generations with disease in familial cases (n=208)

Congenital anomaly type	No. of cases	Generations with disease (n=208)		
		1	**2**	**3**
Sensorineural/Ear defects	133	74	49	10
Limb defects	32	7	10	15
Visual/Eye impairments	23	7	13	3
Neurological	11	9	1	1
Others	9	7	2	0
Total	**208**	**104**	**75**	**29**
		Chi^2=47.16; df=8; P= 0.0001		

3.3.6 Distribution of affected family members in familial cases

In familial cases, affected family members were divided into 4 categories; with two affected family members, with 3-4 affected family members, with 5-6 affected family members and with more than 6 affected family members. There were 44.2% (n=92) cases when 3-4 family members were affected. There were also 36.5% (n=76)

cases when only 2 subjects were affected. While 12% (n=25) cases were found when 5-6 cases were affected, and only 7.2% (n=15) cases were having more than 6 affected subjects in the family (Table 10).

Table 10. Distribution of affected family members in familial cases

Congenital anomaly type	**No. of cases**	**No. of affected sibs in familial cases (n=208)**			
		2	**3-4**	**5-6**	**>6**
Sensorineural/ Ear defects	133	42	62	18	11
Limb defects	32	13	14	5	0
Visual/eye impairment	23	12	7	1	3
Neurological disorders	11	7	3	0	1
Others	9	2	6	1	0
Total	**208**	**76**	**92**	**25**	**15**

3.4 Classification of sensorineural defects

In this study, sensorineural defects contribute 63.34 % of the total disorders. Sensorineural defects are further classified into two categories of deaf/mute and only mute anomaly types. But deaf/ mute contributed to 98.9 % of the overall sensorineural defects.

3.4.1 Distribution of degree of hearing loss on the basis of gender, familial/sporadic, isolated/syndromic

Deaf/mute is further classified into 4 categories: Mild, Moderate, severe and Profound type. The data is further analyzed with gender, familial/sporadic nature, and isolated /syndromic nature. Out of total 195 cases of deaf/mute 76.4% (n=149) cases were of the profound type whereas 22% (n=42) cases belonged to the severe category. Whereas mild and moderate category contributed only a very small fraction of 2% (n=4) (Fig.14) and (Table 11) explain it in detail.

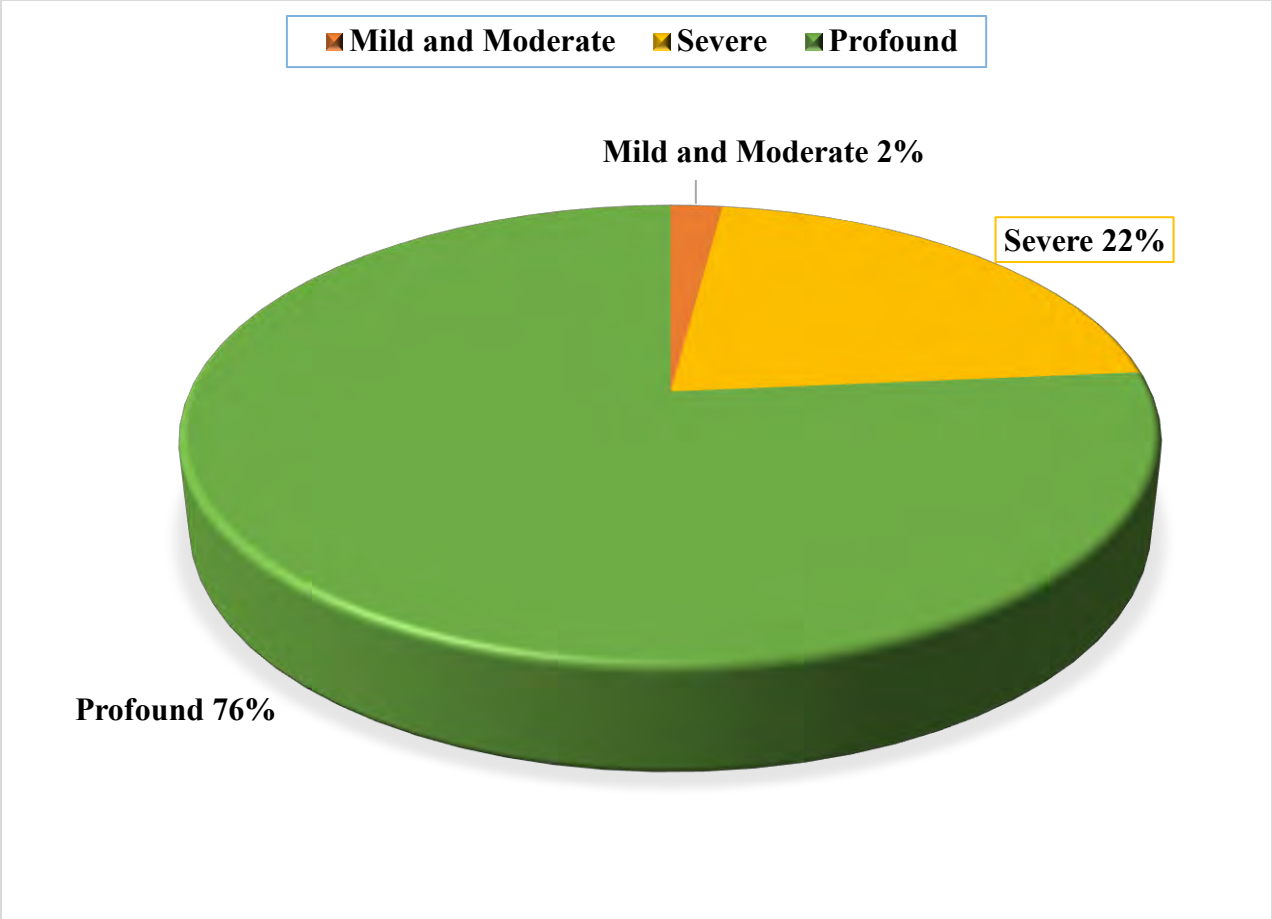

Fig. 14. Distribution of degree of hearing loss

Table 11. Distribution of degree of hearing loss based on gender, familial/sporadic, isolated/syndromic

Deaf/mute (n=195)	Gender (n)		Familial/ Sporadic (n)		Isolated/ Syndromic (n)		Total
	Male	Female	Familial	Sporadic	Isolated	Syndromic	
Mild	0	1	0	1	1	0	1
Moderate	3	0	3	0	3	0	3
Severe	30	12	20	22	39	3	42
Profound	111	38	108	41	145	4	149
Total	**144**	**51**	**131**	**64**	188	7	195
	Chi^2=4.046; df=3; P= 0.2566		**Chi^2=12.70; df=3; P= 0.0053**		**Chi^2=2.034; df=3; P= 0.5654**		

3.5 Limb defects

3.5.1 Distribution of limb defects

In Limb defects, there were 80% (n=35) male subjects there were only 20.4% (n=9) female subjects. The familial cases were contributing 72% (n=32) while sporadic cases only contributed 28% (n=12). In split hand-foot, male category was dominant with 86.6% (n=13) whereas there were only 13.3% (n=2) female subjects. 100% (n=15) cases of this category were familial and no one sporadic case was observed. Whereas 92.8% (n=13) cases in clubfoot were of male subjects and there was only 7.1% female subjects. Isolated cases were 95.4% (n=42) and syndromic cases with only 4.5% (n=2). Details are shown below (Fig. 15) (Table 12).

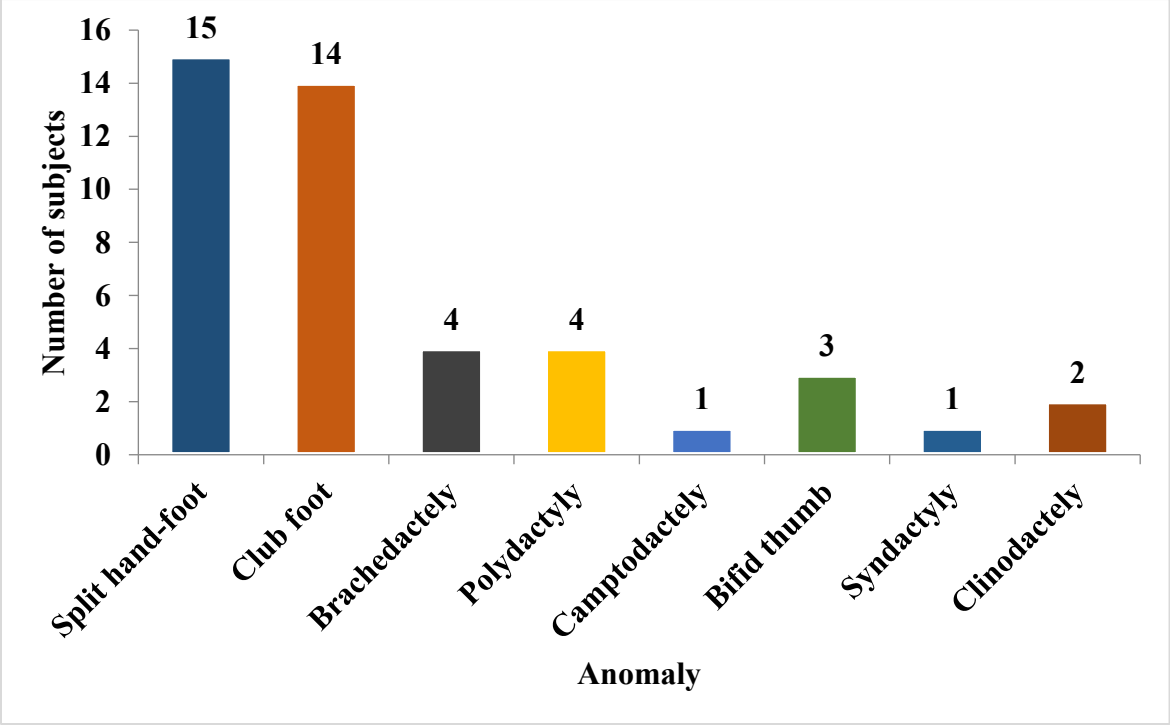

Fig. 15. Distribution of limb defects into minor categories

Table 12. Distribution of Limb defects with respect to gender, familial/sporadic and isolated/syndromic nature

Anomaly	Gender (n)		Familial/Sporadic (n)		Isolated/Syndromic (n)	
	Male	Female	Familial	Sporadic	Isolated	Syndromic
Split hand foot	13	2	15	0	15	0
Clubfoot	13	1	5	9	14	0
Brachedactely	3	1	4	0	4	0
Polydactyly	2	2	2	2	4	0
Camptodactely	1	0	1	0	1	0
Bifid thumb	1	2	3	0	2	1
Syndactyly	0	1	0	1	0	1
Clinodactely	2	0	2	0	2	0
Total	35	9	32	12	42	2
	Chi^2=12.79; df=7; P= 0.0775		**Chi^2=22.75; df=7; P= 0.0019**		**Chi^2=28.63; df=7; P= 0.0002**	

3.6 Classification of Visual/eye Impairments

Visual/eye impairments contributed 10% (n=30) of the total congenital anomalies. They were further subdivided into 3 minor categories of cataract, blindness and others. Cataract contributed 66.6% (n=20) of the total Visual/eye impairments. Whereas blindness contributed 20% (n=6) of the Visual/eye impairments. Others contributed 13.3% (n=4) of the subjects.

3.6.1 Classification of visual/eye impairments based on gender and familial/sporadic nature

In cataract, there were 40% (n=8) male subjects and 60% (n=12) female subjects. The familial cases were contributing 70% (n=14) while sporadic cases only contributed 30% (n=6). In blindness, male category was dominant with 83.3% (n=5) whereas there were only 16.6% (n=1) female subjects. 83.3% (n=5) cases of this category were familial in nature whereas only 16.6% (n=1) subject was sporadic. 75% (n=3) cases in others were of male subjects and there was only 25% (n=1) female subject. 100% (n=4) cases were familial, and no case was sporadic in nature for this category (Fig.16) (Table 13).

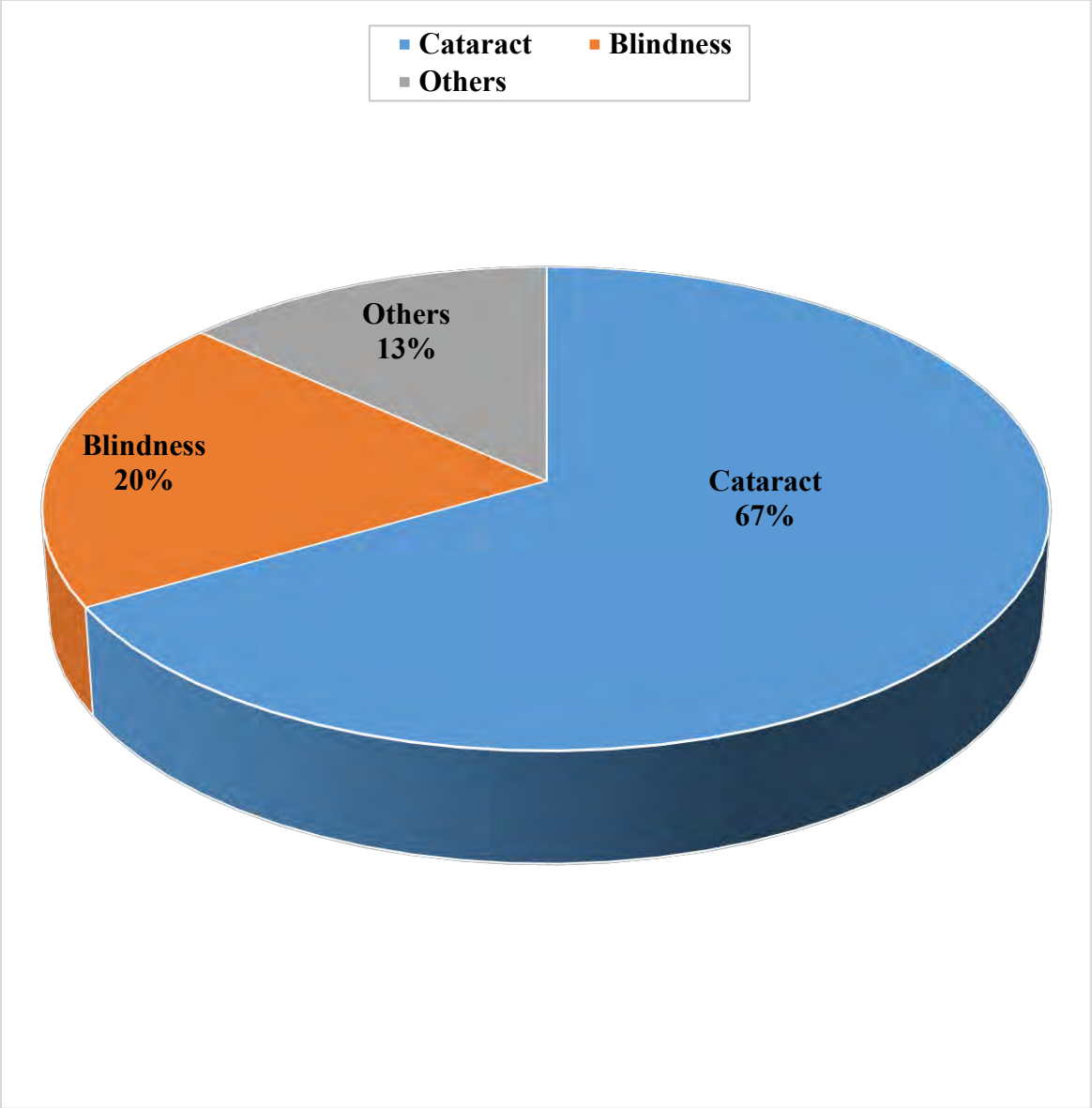

Fig. 16. Distribution of visual/eye impairments

Table 13. Distribution of visual/eye impairments based on gender and familial /sporadic nature

Visual/Eye impairments	Gender		Familial/Sporadic		Total	%
	Male	Female	Familial	Sporadic		
Cataract	8	12	14	6	20	66.6
Blindness	5	1	5	1	6	20
Others	3	1	4	0	4	13.3
Total	16	14	23	7	30	100
	Chi^2=4.353; df=2; P= 0.1135		**Chi^2=1.863; df=2; P= 0.3939**			

3.7 Parental parameters

3.7.1 Parental consanguinity

To find out the marriage types among the parents of index cases, data was analyzed, and it indicated that there were 70.4% (n=219) cases when consanguineous marriage type was found whereas non-consanguineous marriage were found in only 29.5% (n=92) cases (Fig.17). When different categories of congenital anomalies were taken along the parental marriage types, consanguineous marriage type was dominant (Table 14) has the complete detail.

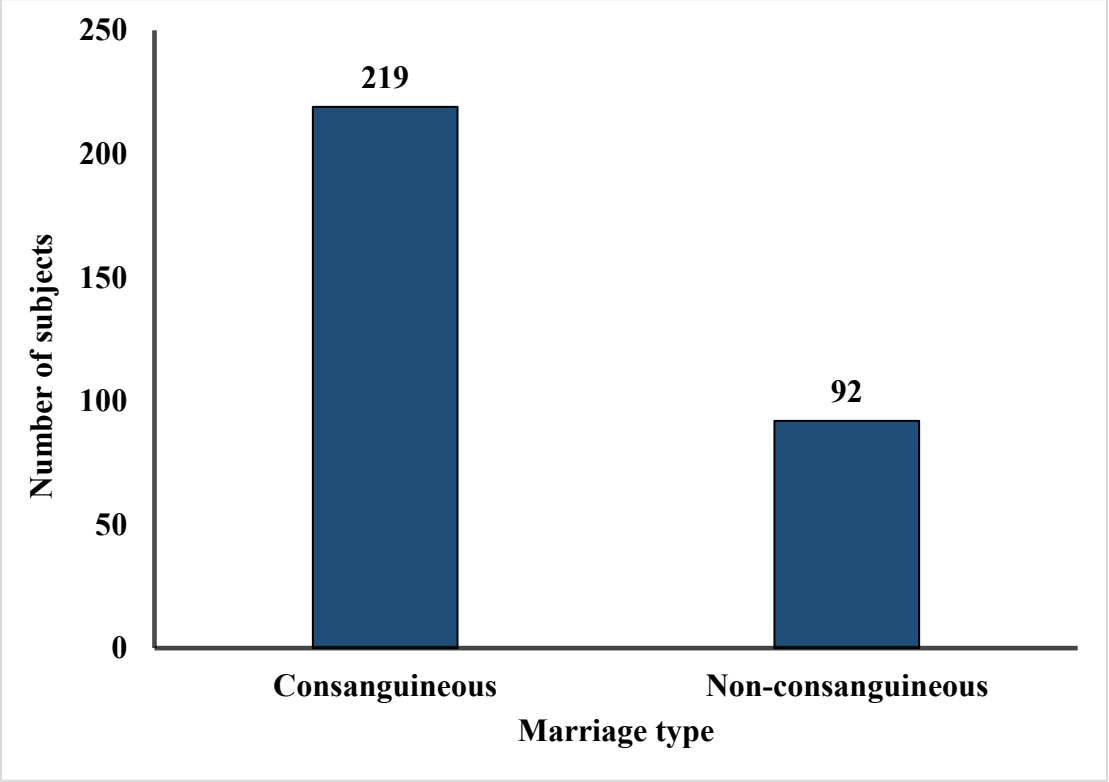

Fig. 17. Distribution of marriage types among parents of index subjects

Table 14. Distribution of anomalies with respect to parental marriage types

Congenital Anomaly	Consanguineous	Non-consanguineous	Total
Sensorineural/ear defects	144	53	197
Limb defects	31	13	44
Visual/eye impairments	11	19	30
Neurological defects	15	5	20
Others	18	2	20
Total	**219**	**92**	**311**
	Chi^2=20.97; df=4; P= 0.0003		

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

Consanguineous marriage type was dominant in males as there were (n=160) consanguineous males as compared to the (n=64) non-consanguineous males. In females, consanguineous marriage type was dominant with (n=59) cases as compared to (n=28) non-consanguineous females. Familial consanguineous cases (n=137) were more frequent as compared to familial non-consanguineous cases (n=71). Sporadic

consanguineous cases were also more frequent with (n=82) as compared to sporadic non-consanguineous cases (n=21) (Table 15).

Table 15. Parental consanguinity with respect to gender and familial/sporadic

Variable	Consanguineous	Non-consanguineous	Total
Male	160	64	224
Female	59	28	87
Chi^2= 0.3926; df=1; P= 0.5310			
Familial	137	71	208
Sporadic	82	21	103
Chi^2= 6.249; df=1; P= 0.0124			

3.7.3 Parental age at the birth of index subjects

For each anomaly type, average paternal and maternal age was calculated and data indicated that it was found highest in other defects category i.e. 34.8 and 31.3 years, respectively. In neurological disorders, the average paternal age was 34.2 years whereas the average maternal age was 29.9 years (Table 16) below explains the details about each anomaly type.

Table 16. Average parental age at birth of index subject

Congenital Anomaly	No. of cases	Average parental age at birth	
		Paternal age (years)	Maternal age (years)
Sensorineural defects	197	31.9	28.8
Limb defects	44	31.6	26.7
Visual/eye impairments	30	30.2	24.7
Neurological defects	20	34.2	29.9
Others	20	34.8	31.3
Average		32.54	28.28

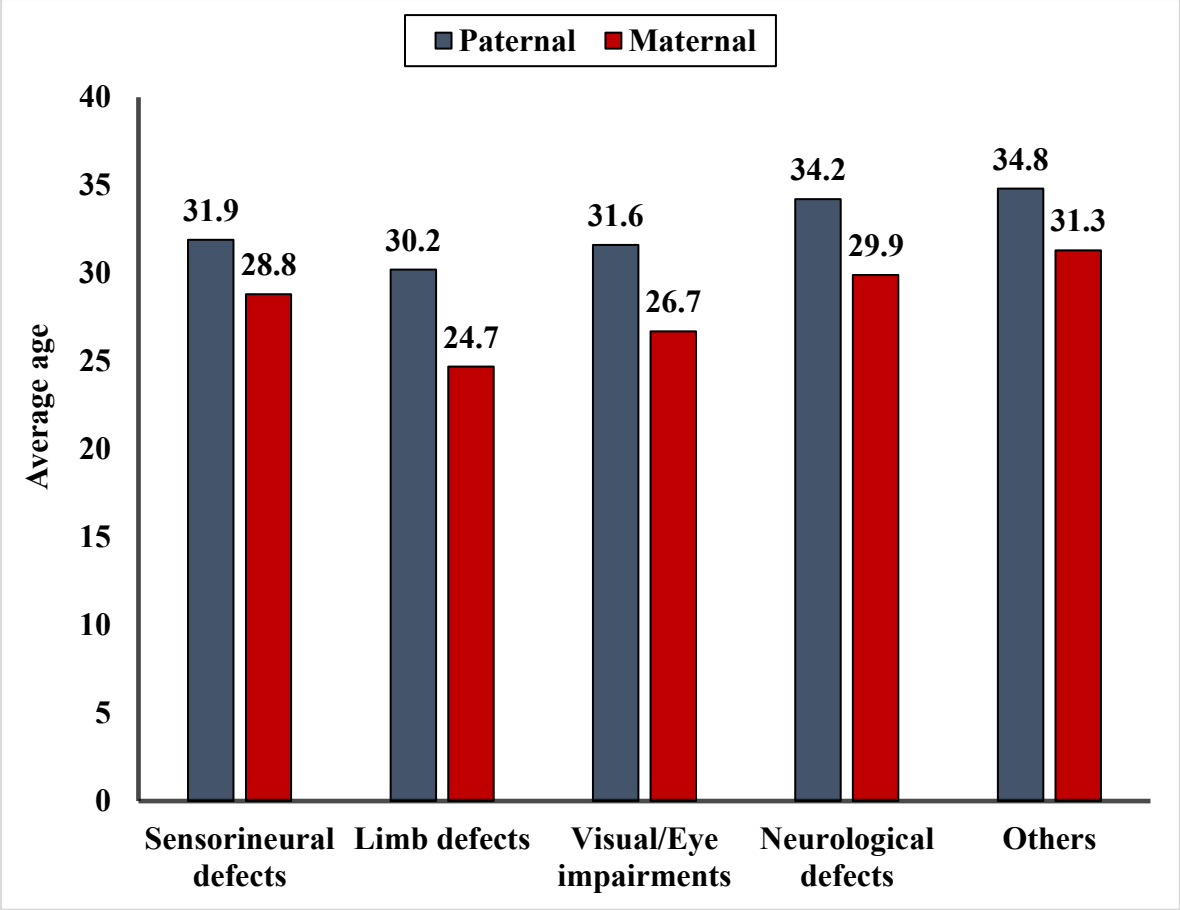

Fig. 18. Average parental age at birth of index subjects

3.8 Among the total 311 index cases, which were categorized into major and minor congenital anomalies, almost 67% were observed to be familial in nature. Three representative familial pedigrees are shown below:

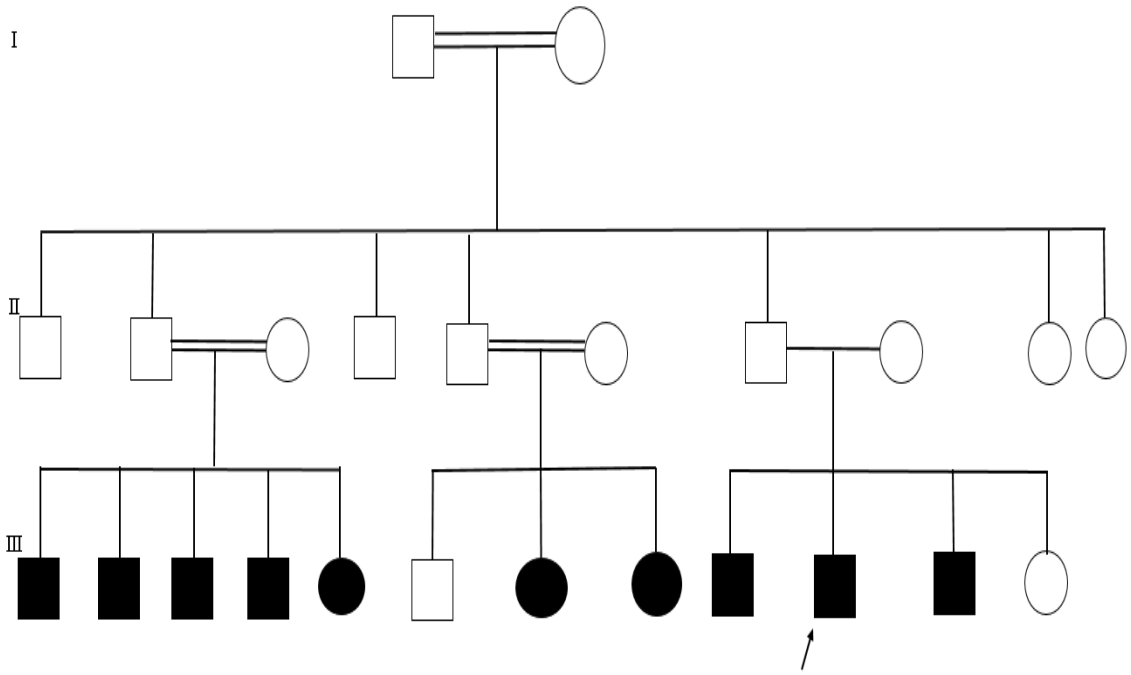

Fig. 19. Pedigree of family showing the segregation of Deaf/mute anomaly. Arrow indicates the index case

(Three loops in which unaffected parents showing affected children and nearly all parents showing consanguinity).

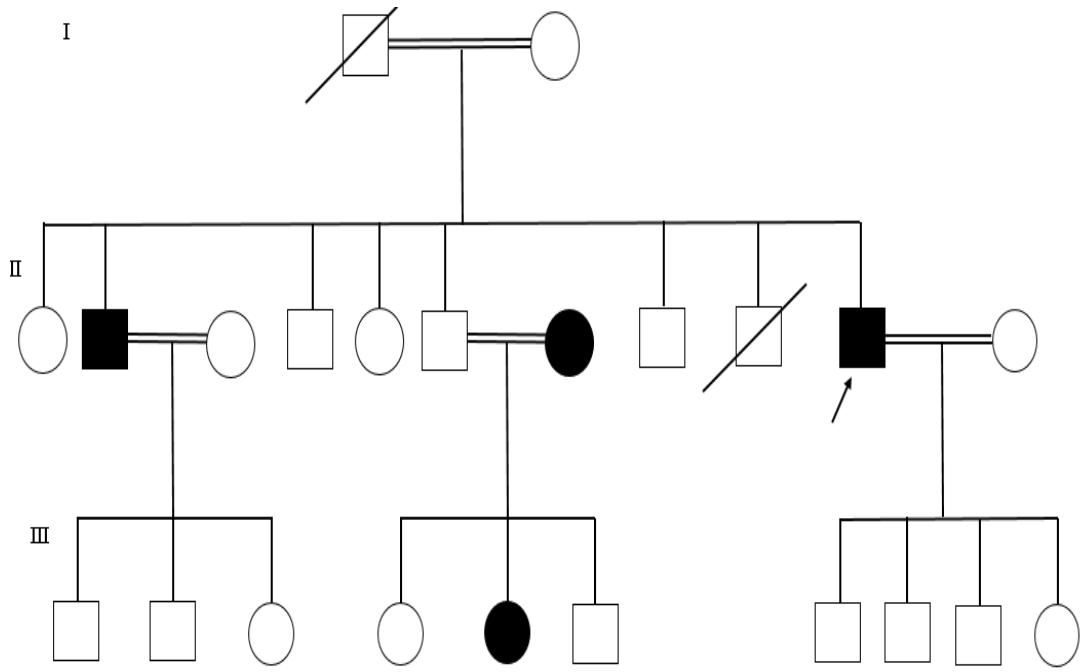

Fig. 20. Pedigree with bifid thumb, polydactyly and brachedactely, arrow indicates the index case

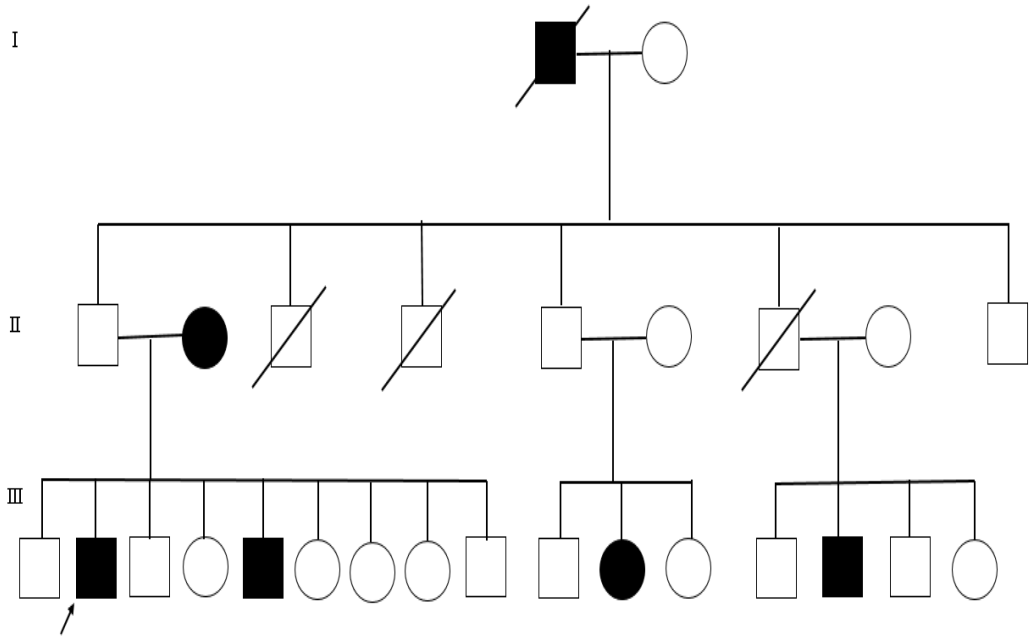

Fig. 21. Pedigree with Brachedactely, arrow indicates the index case and the trait is segregating in nearly all generations.

3.9 Representation of some hereditary anomalies which were classified into major and minor categories have been shown below:

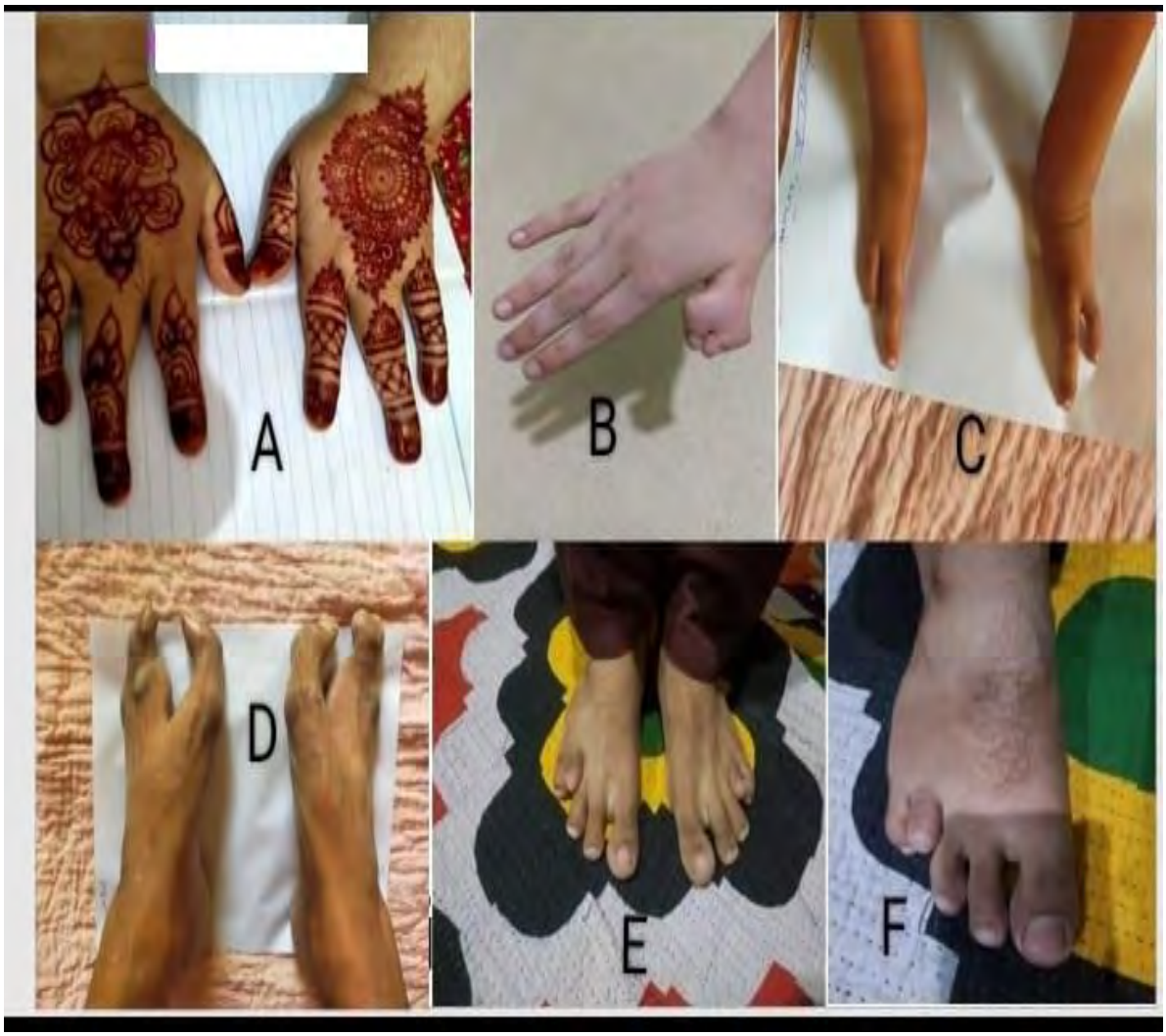

Fig. 22. (A). Syndactyly (B). Bifid thumb (C). Split hand (D). Split foot (E/F). Brachedactely

Fig. 23. (A). Polydactyly of foot (B). Polydactyly of hands (C). Club foot (D). Split hand

CHAPTER 4

DISCUSSIONS

Genetic disorders continue to remain a major concern to geneticists and a major anxiety to expectant women. Individuals with genetic disorders face number of difficulties in performing routine activities. They require extra parental care and become an economic burden on their respective families as well as on the society they usually can not avail job opportunities with respect to normal individuals. They also face socio-psychological barriers in participating as an equal member of the society. Therefore, the management of genetic disorders is a hard challenge for the health care delivering systems because they require lifelong medical attention, expensive, supportive and symptomatic therapy, and specialists care.

Studies on discovering the spectrum of genetic disorders are useful to establish baseline rates, to document changes over time, and to identify clues to etiology. They are also important for development and assessing prenatal screening for congenital anomalies, particularly in high risk populations. Understanding the spectrum of genetic disorders, existing in our populations would help in developing health care systems, and estimating any possible future increase or decrease in the burden of congenital anomalies.

The present study is conducted in the Sukkur region. The study area is in southern east of Pakistan and on the western bank of the river Indus, with harsh climatic condition which makes this area one of the hottest area in Pakistan. Sukkur witness a high prevalence of congenital and hereditary anomalies due to high rate of consanguineous marriages, poor health care system, lack of attention to expectant women, maternal self-medication, no family planning, exposure to teratogenic, low socio-economic conditions, maternal illnesses, late and early marriages. The health care system is unable to deliver proper management and support for the subject/families affected with certain congenital and hereditary anomalies, as a result

the families and society at large, suffers economically, socially, and psychologically. Proper documentation of births and congenital malformation is deficient in the said area due to the poor infrastructure of health facilities and staff. Congenital anomalies have been reported globally to account for approximately 20% of infant mortality (Chung *et al.*, 2013).

This study is also conducted to assess the prevalence of congenital malformations in the Sukkur region population and the risk factors associated with these defects. The deformity might be reduced by addressing these risk factors including, high rate of consanguinity, radiations and teratogen exposure, advanced maternal age, malnutrition, and maternal diseases are also risk factors. Additionally, screening approaches like as maternal blood marker determination, ultrasonography, amniocentesis, and chorionic villus collection can be utilized to detect and manage high-risk pregnancies.

The results showed that most congenital anomalies were sensorineural/ear defects (63%), followed by limb defects (14%), visual/ eye impairments (10%), neurological disorders (6%) and last category others also accounted for (6%). All the reported subjects, in the current study, were not self-sufficient and required assistance from family members for basic necessities and routine tasks. It was straightforward to locate such patients because almost everyone in the neighborhood knew their identities. Hence it paved an easy way to approach them. While the subjects with sensorineural/ear defects were attending special schools. Therefore the parents of these subjects were approached through school administration.

Congenital hearing loss is most prominent in children caused by environmental and prenatal factors (Korver *et al.,* 2017). Globally the prevalence of

congenital hearing loss is 1- 2/1000 live births (Salvago *et al.,* 2013). Congenital hearing loss is considered as a leading cause of disease burden and the population-based study of congenital hearing loss is not common in the literature. Worldwide prevalence of hearing defects was 1.4% of children under age 15 years, 10% of females over age 15 years, and 12% of males over 15 age years in 2008 (Stevens *et al.,* 2013).

In the present study sensorineural/ear defects were most common congenital anomaly in this study and constitute 63% (n=195) of all anomalies. Due to availability of medical and audiology reports of some cases under study it was bit easy to predict severity level. According to severity level of hearing loss all the 198 cases were categorized into 4 categories i.e. profound, severe, moderate and mild.

In the present study profound deafness prevails and constitutes about 76%. While the severe deafness accounted for 22% and Moderate to mild level of hearing impairment constitutes only a small fraction of about 2% of total anomalies. Furthermore, it was also observed in our findings that the rate of consanguineous marriages and this increased ratio is linked with increase prevalence of profound deafness cases.

A study was conducted in Peshawar district of Khyber Pukhtoon-Khuwa, Pakistan. 140 school going pupils were recruited in the study. Careful analysis of these subjects reveals high ratio of profound deafness with parental consanguinity. These results are consistent with our findings (Sajjad *et al.,* 2008). According to another study by (Bubbico *et al.,* 2007) showed that consanguineous marriages are linked with prelingual profound deafness.

Most of cases about 96% (n=188) were isolated and only 4% cases presented syndromic nature of disease. It is consistent with study conducted by (Stallings *et al.,* 2018) in which ear and eye defects were examined for isolated and syndromic nature and or all these isolated cases were more prevalent than syndromic in studied population. Another study reveals isolated sensorineural hearing loss is the most common sensorineural disorder accounting for 70% of congenital hearing loss of which 80% have an autosomal recessive mode of inheritance (Motavaf *et al.,* 2017). It is also consistent with our findings that non syndromic cases predominate in all cases of deafness.

In the present study limb defects were the second highest in number. 42 cases were isolated in and 2 were syndromic in nature. The limb defects were further classified into minor groups. Split hand-foot cases were highest in number (34%), followed by talipes (32%), Brachedactely and polydactyly (9%), bifid thumb (7%), clinodactely (5%) and syndactyly with only (2%).

Our findings were comparable to those of (Bhatti *et al.,* 2017), who found that limb defects were the most prevalent group (47%) followed by neurological disorders (31%), musculoskeletal defects (9%), and neuromuscular anomalies (4%). The study carried out by (Zahra *et al.,* 2016) also reported that limbs defects were the third most common congenital anomalies (21%) after neurological disorders (34%) and musculoskeletal defects (23%).

Moreover, it was also observed in congenital limb defects that 95% cases were isolated in nature in comparison to syndromic nature with only 5%. This finding contradicts the (Patton *et al.,* 2010) who reported the maximum number of syndromic cases. One possible etiological reason behind the high prevalence of isolated limb

defects in this study is because of genetic non-genetic, environmental and stochastic factors all have a role in the etiology of limb defects.

The third prevalent congenital anomalies were visual/eye impairments. The visual/eye impairments contributed 10% of the congenital anomalies in the present study. Which included cataract with the highest contribution of 67%. The high prevalence of cataract is in line with one of the study carried out in Ghana which reported cataract as the most common congenital abnormality overall (Ilechie *et al.,* 2014). Blindness contributed 20% and others categories of visual/eye impairments accounted for only 13%.

The 311 index cases were analyzed based on familial and sporadic nature. In the case of sensorineural defects majority of the cases were familial showing 68% and only 32% cases were sporadic. The familial cases of sensorineural/ear defects are concordant to the study carried out by (Zahra *et al.,* 2016), their findings in sensorineural/ear defects category also depict the highest number of familial cases with 72% and sporadic 28%. In the case of limb defects majority of the cases were familial contributing 73% and only 27% cases were sporadic. The present study contradicts with the study carried out by (Ullah *et al.,* 2015) their findings depict the highest number of sporadic cases (n=120) and familial (n=33) in limb defects.

One of the most important factor behind the highest number of familial cases in the current study is the socio-cultural norms of the region which includes high rate of cousin marriages and certain myths persisting in the minds of local population of the region. Secondly, most of the parents of affected subjects, belong to rural areas where a great number of expectant women is bound to work in fields which increases the high risks chemical exposure thereby, leaving the familial history of congenital

anomalies during every gestation period of expectant women. These findings are consistent with the findings of (Sozan *et al.,* 2018), depicting that familial history of congenital anomalies in the mother, parental consanguinity, and a history of physical illnesses were all significantly associated with an increased risk of congenital anomalies.

In the present study, there was a great representation of affected male subjects as compared to female subjects. Males were (72%) and females were (28%). The low ratio of female subjects in the present study was due to the socio-cultural norm of Pakistani society especially in rural areas where proper consent is needed to approach female subjects and female is restricted in their proper jurisdiction and difficult to find female subjects in the public areas where most of the male subjects were ascertained.

The present study correlates with other epidemiological studies where a high ratio of male subjects was recruited. In a study carried out on congenital and hereditary anomalies in the Sialkot district of Pakistan where the frequency of male subjects was (75%) and females were (25%). The ratio of male subjects was higher than female subjects and was consistent with the present study (Bhatti et al., 2019). Our results are also consistent with the finding of (Zahra *et al.,* 2016) who reported a greater percentage of affected males (54%) than female (46%). Another study conducted by (Ochoga *et al.,* 2018) reported a high ratio of male subjects (60%) than female (40%) affected with congenital anomalies. Our findings are likewise in line with those of (Baruah *et al.,* 2019), who conducted research in Assam, India, and found that the ratio of affected males (58%) was significantly greater than the female patients (48%). In the study of (Hemonta *et al.,* 2010), conducted in Assam India, the ratio of affected males was 66% higher than females 35%. This finding was following the present study where the ratio of males was higher than females.

In the present study, congenital and hereditary anomalies were analyzed based on age group in the index subjects. The highest number of cases were found in the age category >10-20 years with a percentage of 45.3% (n=141), followed by age group 6-10 with 23% (n=73).

While the age group 21-30 have a small fraction of only 8% (n=22). The present study finding is in accordance with a previous study conducted by (Taye *et al.,* 2019). Where a majority of the subjects with congenital anomalies have an age group of up to 17 years (Bhatti *et al.,* 2019), also consistent with the present study finding where most subjects have an age group of 9-19 years. (Zahra *et al.,* 2017) reported that the majority of subjects with anomalies have an age group 10-19 which are also in line with the present finding where most index subjects have an age category of >10-20 years.

The 311 cases were also analyzed based on the socio-economic status of families, most of the subjects belong to the low category 50%, followed by low-mid-26%, while High-mid category contributed 18.6% and there were only 4.5% cases from the high economic status category. According to a study conducted by (Taye *et al.,* 2019), the majority with 49% of the families fall in the middle-income family followed by low-income families (43%), their finding contrasts with the present study results.

The 311 index subjects with congenital and hereditary anomalies were analyzed based on parity. A total of 31% had 2nd parity followed by 1st parity 28% then 18% third parity. Our results are in contrast to (Mahela, 2016) who reported the highest prevalence in the first parity 31% followed by second parity 18%.

The total enlisted subjects were also examined regarding generation with the disease. Most of the cases in the present study segregating in one generation (66%) followed by the anomalies segregating in two and more than two generations (24%) and (10%) respectively. The present study result is consistent with the (Zahra *et al.,* 2016) that reported the maximum number of diseases segregating in one generation.

This study also examined closely at the role of parental factors in the development of birth defects. Parental parameters act as high risk factors, increasing the likelihood of a foetus being born with any type of congenital or hereditary anomaly. Consanguinity between parents and average maternal and paternal age were the parental attributes examined in this study. Many studies have shown that consanguinity is associated with a higher rate of birth defects. Maternal and paternal age is linked to a variety of fetal anomalies.

Consanguineous marriages were more common, according to a careful examination of 311 cases of congenital and hereditary anomalies. Consanguinity was found in 219 (70%) of the cases studied. Non-consanguineous marriages accounted for 30% (n=92). The proportion of marriages involved first and second cousins among consanguineous marriages. As a result, consanguinity is a high risk factor for birth defects. According to a study by (Jabeen & Malik, 2014), consanguineous marriages accounted for 62% of the studied population, while first cousin marriages accounted for approximately 50%. These findings are consistent with ours. According to (Corry, 2014), 30% of major childhood disabilities in Bradford were linked to the Pakistani community showing consanguinity. The Indian and Bangladeshi communities accounted for 5% of all births. The increased ratio was attributed to the high prevalence of consanguineous marriages in these communities. Another study conducted by (Akram, 2008), more than 80% of all parents in Pakistan are first

cousins, 7% are blood relatives, 6% belong to the same caste, and only 4% are outsider marriages.

Maternal and paternal ages were also determined in each case, with the average paternal age in each case being 35 years and the average maternal age being 31 years. The average paternal and maternal ages in cases of ear defects were 32 and 29 years, respectively. In cases of neurological defects, the average paternal and maternal ages were 34 and 30, respectively.

Study Limitations

The distribution and prevalence of congenital and hereditary anomalies reported in this study may differ from those reported in other studies. Many factors, such as the demographic distribution of that restricted population and their values, contribute to this changed prevalence. Another consideration is the method of data collection used during the study. Limiting factors include ethnicity, social and moral norms, and the size of the population under study.

Conclusion

The current study observed high incidence of sensorineural/ear defects and limb defects among 311 cases of congenital anomalies. High prevalence of familial cases suggest that high level of consanguinity, ethnicity, socio-cultural norms and certain environmental factors have an important etiological roots in the study area.

Recommendations

There is a scarcity of demographic and genetic data on congenital and hereditary anomalies in the Sukkur region. Because there is very little literature available on sensorineural/ear defects in the selected area, this study will be useful in predicting the distribution pattern of sensorineural/ear defects and other congenital and hereditary anomalies in Sukkur region.

CHAPTER. 5

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