Clinical and phenotypic variability in polydactyly families ascertained from Rawalpindi-Islamabad, Pakistan.

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Clinical and phenotypic variability in polydactyly families ascertained from Rawalpindi-Islamabad, Pakistan.

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بسم الله الرحمن الرحيم

CERTIFICATE

This is to certify that dissertation entitled "*Clinical and phenotypic variability in Polydactyly families ascertained from Rawalpindi-Islamabad, Pakistan*" submitted by Huma Fatima is accepted in its present form by the Department of Animal sciences, Quaid-i-Azam University, Islamabad, as satisfying the dissertation requirements for the degree of Master of Philosophy in Human Genetics.

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DECLARATION

I hereby declare that the work presented in this thesis on "Clinical and phenotypic variability in polydactyly families ascertained from Rawalpindi-Islamabad, Pakistan" is my own and no part of the thesis is copied from any other source. Also, it is declared that present work has not been submitted to any other university.

Huma Fatima

Islamabad, 2013

Dedicated to my

Parents

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Abbreviation

A	Affected
B	*Biradari*
CDC	Center for Disease Control and Prevention
CM	Congenital malformations
F	Female
FC	First cousin
GFMER	Geneva Foundation for Medical Education and research
ICD	International Classification of Diseases
M	Male
N	Normal
NCBI	National Center for Biotechnology and Information
OMIM	Online Mendelian Inheritance in Man
PIMS	Pakistan Institute of Medical Sciences
WHO	World Health Organization

Abstract

Polydactyly is a congenital limb defect in which an extra finger or toe is present in the hands or feet, respectively. Polydactyly is the most frequently observed hereditary limb/digit anomaly. It may appear as an isolated anomaly or a part of syndromes. Isolated polydactyly mainly has autosomal dominant mode of inheritance while syndromic polydactylies commonly segregate autosomal recessively. There is a lack of knowledge about the phenotypic spectrum of polydactyly in the Pakistani population. In order to partially fill this information gap the present study was undertaken. During Nov. 2011 to Sep. 2012, field visits were launched at Districts Rawalpindi and Islamabad and families with limb defects were recruited. Twenty families of polydactyly were ascertained but only 17 were included in this study. Sixteen families were depicting non-syndromic polydactyly and one was syndromic, i.e., Ellis-van Creveld syndrome. In the non-syndromic polydactyly cases, there were eleven sporadic and five familial. There were ten preaxial polydactyly and six postaxial polydactyly cases. A broad spectrum of polydactyly phenotype was observed in the recruited families. The most common phenotype was preaxial polydactyly. Different phenotypic manifestation of extra digit was observed, i.e., partially developed to fully develop which were classified according to standard criteria. Among the sporadic cases, there was a preponderance of affected females. The mode of inheritance of sporadic cases cannot be inferred and it was assumed that they may originate due to novel mutations or stochastic factors. In the familial cases, male were more commonly affected and autosomal recessive and X-linked recessive modes of inheritance were observed. This study is an effort to appreciate the clinical spectrum of one of the most common limb anomaly in the Rawalpindi/Islamabad population. This study witnessed a broad phenotypic variability of polydactyly. This information would help in further delineation of sub-types of polydactyly which would be highly beneficial for the affected subjects and their families in terms of genetic counseling and management.

Introduction

1. Introduction

A genetic disorder arises due a different form of a gene known, as a gene variant, or change in the information contained in a gene and its function, called a mutation (Lewis, 2008). Mutation alters the normal protein structure and function, which is essential for regular cellular and physiological functions. Many genetic disorders are transmitted genetically. These mutated or altered genes transmitted from one generation to another and cause the genetic diseases (Medline Plus, 2012). Genetic factors play important role in the etiology of genetic abnormalities or disorders (Shanti, 2001).

Some genetic disorders are congenital and other have late onset. There are approximately 17,000 well-characterized genetic disorders (OMIM, 2012). There are four major classes or types of genetic disorders; single gene disorder, multifactorial disorders, chromosomal abnormalities, mitochondrial diseases (Lewis, 2008).

Single gene disorders are also called Mendelian or monogenic disorders cause by mutation in a single gene e.g. polydactyly. Multifactorial disorders are complex and caused by many factors, for example environment, lifestyle and many genes control these traits, known as polygenic traits, e.g. cleft palate and cancer (Shanti, 2001).

Chromosomal abnormalities are due to gross level changes in the chromosome structure, that cause the genetic information to change and as a result, various chromosomal anomalies occur like Down syndrome and Turner syndrome (Lewis, 2003). Mitochondrial diseases are due to malfunctioning of mitochondria, that is the power house of the cell. Mutations either in mitochondrial genes or in nuclear genes that translate for the internal structure of mitochondria are responsible for the mitochondrial diseases. These mutations can be spontaneous or inherited or due to environmental causes (Scharfe et al., 2009).

Inheritance pattern of genetic disorders depends on whether the gene is located on an autosomal or sex chromosome or either it is present in mitochondrial DNA. A single gene disorder follows the Mendelian inheritance patterns, i.e., autosomal dominant, autosomal recessive, X-linked dominant, X-linked recessive and Y-linked inheritance. Autosomal dominant disorders are due to mutant gene that is coming from one parent (Lewis, 2008). The sibs of two affected individuals may be normal, e.g., Marfan syndrome. Autosomal recessive have many identifying characteristic, e.g., most affected individuals have normal parents. All the children of two affected individuals are affected. Male to female ratio is same, e.g., cystic fibrosis. In X-linked dominant disorders, all the daughters and no son of an affected male are affected and females are more commonly affected, e.g., hypophosphatemia. In X-linked recessive disorders, men are more affected, than females. Hemizygous male and homozygous females are affected, e.g. hemophilia. In Y-linked inheritance only male have Y chromosome so these traits are transmitted directly from father to his son (Cumming, 2009).

Multifactorial disorders do not follow Mendelian segregation because many factors like environment and life style influence them. Segregation pattern of mitochondria disorders is also known as maternal inheritance because during development only the egg cells contribute mitochondria to the developing embryo. Thus only mothers can pass mitochondria disorders to their children (Lewis, 2008).

Prevalence studies of congenital malformation helps to estimate the impact of genetic disorders. The global prevalence of all single gene diseases at birth is approximately 10/1,000 (WHO, 1997). There are the variations in the prevalence of birth defects among different countries.

In Pakistan the incidence of congenital malformation has been investigated by different studies. But there is variation in the prevalence rate of congenital malformations. A study from Liaquat National Hospital, Karachi, reported a prevalence of 15.8/1,000 of total births (Shamim et al., 2010). Similarly another observational study was conducted at Countess Fund Dufferin Hospital Hyderabad, to estimate the frequency of births defects and found to be 15.7/1,000 of total births (Masood et al., 2011).

Marriages among second cousins or closer relatives are known as consanguineous marriages. In many developed countries consanguineous marriages have diminished remarkably. While in the developing countries marriages among blood relatives are norms (Bittles, 1994). According to a study conducted in Lahore Pakistan, the overall incidence of cousin marriages was 46% (Yaqoob et al., 1993). According to another study, a number of Middle-Eastern tribes, Jewish communities, and certain clans in southeast Africa worldwide rate of consanguinity were recorded

as 29% but in Pakistan it was recorded as 60%. Due to this rate of cousins marriage Pakistan is in big trouble in facing the genetic disorders as compare to other populations (Saimon, 2006).

Homozygosity increases in the next generation due to the cousins marriages (Bittles, 1994). Incidence of recessive disorders increases due to marriages among biological kin's that is common in Eastern Mediterranean including Pakistan (Alwan and Modell, 1997).

Some people feel it as a stigma that they have genetic disorder. People who had genetic disorders felt psychological anxiety. But psychological state of the carrier is different from affected individual. People affected with genetic diseases became emotionalized. Many emotional effects can be observed in the individuals affected by genetic disorders for example dejection, sadness, sorrow, anger and anxiety, guilt and uncertainty. They have always affair about the risk of genetic disorders in their children. They are very much conscious about whether their children will suffer from same situation or not. These emotional effects depend upon the expressivity of the genetic disorders and diagnosis (McAllister et al., 2007).

Early death of the family members, increases the family grief and the make them conscious about the genetic situation occurring in the family. Genetic conditions and disease are highly variable so their emotion and psychological effects also varies (McAllister et al., 2007). Patients can cope, minimize or overcome the genetic disorders by doing adjustment in the affected family members or by knowing about the risk of recurrence of the genetic diseases, but this can be only possible with the help of genetic counseling (Fraser et al., 2003). Genetic disorders are the cause of 20-30% of infant mortality and morbidity (Berry et al., 1987). According to one study

that was conducted in Pakistan, total estimated infant mortality was 10% and serious birth defects prevalence was 5%. Severe mental retardation prevalence was 1.1 per 100 live births. Birth stressful event or a physical injury and cousin marriages poverty, malnutrition, were common causes of infant mortality and mental retardation in Lahore, Pakistan (Gustavson, 2005).

Some common genetic disorders found in Pakistan are: cystic fibrosis, thalassemia, Down syndrome, mental retardation, Fragile X syndrome, muscular dystrophy. In multifactorial genetic disorders cancer, diabetes, cleft lip and palate are most common. Some common limb genetic disorders found in Pakistan are: congenital dislocation of the hip, Clubfoot, camptodactyly, brachydactyly and polydactyly.

Limb defects can be recognized at the time of birth or before birth. They can be occurring as follows: limb can be increase in size, limb can be small in size or complete absence of limbs, and there can be the alteration in the structure or anatomy i.e. the digit or toes may be extra and digits cannot separate (Wilkie, 2003).

Congenital limb defects are clinically and genetically heterogeneous disorders. They reveal wide spectrum of phenotypic and clinical variability. They can be due to the environmental or genetic causes that affect the normal developmental program (Schwabe and Mundlos, 2004).

Following are the causes or risk factors of limb defects: genetic causes or abnormality, mechanical pressure that affect the baby growth in the uterus and growth retardation, tarotogenic exposure of mother during pregnancy, smoking and medication (Wilkie, 2003). A congenital limb defect in which an additional finger or toe in hand or foot is present respectively, is known as polydactyly. Severity of

polydactyly varies from mere splitting to complete duplicated of digit (Mumoli et al., 2008).

Polydactyly is the most frequent innate abnormality of the hand and foot. It may emerge as an isolated anomaly or as a part of a syndrome. Isolated polydactyly have autosomal dominant mode of inheritance; while syndromic polydactyly commonly has autosomal recessive mode of inheritance (Hosalkar et al., 1999).

It can be classified into three major classes on the basis of position of extra digit medial ray (preaxial), central ray (mesoaxial) and lateral ray (postaxial). In preaxial polydactyly, extra digit is present near thumb or radius. In postaxial polydactyly extra digit is present near fifth finger/toe or near ulnar/fibular side. In mesoaxial polydactyly it is present between small finger and thumb (Mumoli et al., 2008).

According to radio-morphological changes polydactyly divided into five types: distal phalanx, middle phalanx, proximal phalanx, metacarpal or metatarsal, carpal or tarsal. In distal phalanx: additional digit has partial or complete duplication of distal phalanxes. In middle phalanx: complete duplication of distal phalanx and partial or complete duplication of middle phalanx. In proximal phalanx: complete duplication of middle phalanx and partial or complete duplication proximal of phalanxes and similar is the case with remaining two types (Blauth and Olason, 1988).

The most common type of polydactyly is the duplication of the first digital known as preaxial and duplication of fifth digit known as postaxial polydactyly. Less common type of polydactyly is mesoaxial polydactyly. Similarly the partial developed

extra digit is more common as compare to of fully developed extra digit that is originating from wrist (Elliott and Evans, 2006).

According to one group of study the prevalence of preaxial and postaxial polydactyly was calculated as 20% and 10%, respectively (Castilla et al., 1998). Preaxial polydactyly is common and mostly it is sporadic and unilateral. Polydactyly inherits as an autosomal dominant fashion. But it also depends on the condition that is occurring in the family, either that is inheriting in the family (Kozin, 2003).

An estimated 15% of the children born who have polydactyly they are associated with other syndromes (Case31.Polydactyly, 2012). Some Syndromes associated with polydactyly are known as: Mirror hand deformity, Mohr syndrome, Basal cell nevus syndrome, trisomy 13, Oral-facial-digital syndrome, Ellis-van Creveld syndrome and Short rib polydactyly (Medscape, 2012).

Polydactyly is well diagnosable at the time of birth but it can be diagnosed prenatally. When fetus was of 18 weeks, at that time polydactyly can be seen in ultrasound. If the fetus have polydactyly it is very essential to do medical tests, in order to make sure that fetus do not have any syndrome associated with polydactyly. If polydactyly is observed then X-rays and chromosome and enzyme analysis should be done. Family history is helpful in diagnosis that any other member have isolated or syndromic polydactyly. Isolated polydactyly do not have any bad effect on the health and can be treated (Yahoo Health, 2012).

Male sex, low maternal education, twinning, parental consanguinity, and recurrence in first-degree relatives are the other factors that are linked with polydactyly. Postaxial polydactyly is related with parental sub fertility, and bleeding in the first trimester (Medscape, 2012).

Family history is useful in determining the inheritance pattern and risk assessment. Isolated polydactyly have autosomal dominant pattern but due to reduce penetrance sibs of affected parents do not show the phenotypes although they have the mutation. Due to incomplete penetrance, risk assessment of a child of affected person has less than 50% chance of having polydactyly. Ascertainments of complete family history with polydactyly is difficult because extra finger is surgically removed early in life, forgotten and not discussed during family follow up. So the risk assessment of polydactyly is also difficult (Case 31.Polydactyly, 2012).

Temtamy and McKusick (1969, 1978) classified the preaxial polydactyly and post-axial polydactyly in to 4 and 2 classes, respectively. In preaxial polydactyly type I the distal phalanx is partially duplicated; in type II polydactyly, there is triphalangeal thumb; in type III the index finger is replaced by one or more triphalangeal digits; in type IV, there is polydactyly associated with syndactyly.

Wassel (1969) classified the preaxial and post-axial polydactyly in to 7 and 2 classes, respectively. They further classify the preaxial polydactyly into three more classes on the basis of duplication severity of the phalanx, in addition to four classes given by Temtamy and McKusick (1978). Type I; Distal phalanx partially duplicated, Type II; Distal phalanx completely duplicated, Type III; Proximal phalanx partially duplicated, Type IV; Proximal phalanx fully duplicated Type V; Meta carpal partially duplicated, Type VI; Meta carpal completely duplicated, Type VII; Triphalangeal thumb is present. In both classification of Postaxial polydactyly is present. Type A; Extra digit is well developed, Type B; Extra digit is rudimentary.

During four week of embryonic development limb bud starts to develop. The developing limb can be divided into three parts the proximal stylopod, the middle zeugopod and the distal autopod Interaction of gene and molecular factors occur and complete limb developed, that have specific number and appearance. Embryogenesis is critically relied upon the proper signaling for differentiation of developing limb. Contention in these pathways results in innate limb anomalies (Zguricas et al., 1999). Development of limb is very specialized musculoskeletal structure. Muscles, bone and cartilage are the structural components of musculoskeletal are formed by mesoderm. During the 5^{th} to 8^{th} week of embryonic development, limb developed and following events occur. In fifth week limb bud develops. In sixth week digit rays are formed in upper limbs. In seventh week digit rays are seen in lower limb. During eighth week limbs grow in length, and rotate. Elbow, knee, shoulders and knee developed at the end of this week. Digit rays developed into digit. At the end of limb development apoptosis occur and cell are lost between the digits (UNSW, 2012).

Limb development, geometry and patterning occur in three axis's dorsal-ventral, anterior posterior, and proximal distal. Autopod, zeugopod and stylopod are specified by Hox genes (Wellik and Capecchi, 2003). Two important regions apical ectodermal region (AER), and zone of polarizing activity (ZPA). AER is formed by Wnt7a. FGF encoding genes express in apical ectodermal regions responsible for growth and proliferation. Sonic hedgehog (*SHH*) express in posterior mesenchyme region in the zone of polarizing activity, responsible for five digit autopod formations. T-box (*Tbx*) genes are responsible for limb identity. *Tbx4* express in hind limb and *Tbx5* express in forelimb. Bone and limb formed by the process of ossification and chondrogenesis (Gilbert, 2000). Digit numbers are controlled by sonic hedgehog

(Shh). Mutation in the ZPA regulator causes the preaxial polydactyly types II and Preaxial polydactyly types III (Sun et al., 2008).

In order to get an insight into the types and prevalence of hereditary limb defects in the Rawalpindi/Islamabad population, I have carried out a study. This study establishes the types of digit defects which are common in this population, i.e., polydactyly. This thesis covers the phenotypic and clinical aspects of several families and cases with polydactyly.

Aims and Objectives

In the present study 50 families of different limb defects were recruited from Rawalpindi and Islamabad districts. The most common limb defect observed was polydactyly. 20 families of polydactyly were ascertained and 17 families were included in the study. These families were revisited to understand the phenotypic manifestations of hereditary limb anomaly, i.e., polydactyly, in the heterogeneous and multi-linguistic population of Rawalpindi-Islamabad. These families showed a wide range of clinical and phenotypic spectrum.

The specific aims and objectives of the study were as follows:

- To observe the segregation pattern of different polydactyly phenotypes.
- To observe the clinical heterogeneity in polydactyly in the ascertained families.
- To classify the different forms of polydactyly recruited with the help of standard medical/genetic databases and literature survey.
- To provide counseling to the families with genetic disorders i.e. polydactyly
- To provide a basic guideline about the surgery of extra digit as many people do not know what to do with extra digit.

Subjects and Methods

2. Subjects and Methods

2.1 Field visits

In order to investigate and analyze the families with genetic disorders, hospitals rehabilitation centers and different schools were visited. Many families were ascertained during the field work, but 17 fulfilled the inclusion criteria of my research project.

These families belonged to Rawalpindi and Islamabad Districts of Pakistan. Initially the data was collected at Pakistan Institute of Medical Sciences, Islamabad. In the children wards at PIMS consecutive live births were monitored. At second stage data was collected from rehabilitation centers and schools. Then, each family was visited at their residence at least two or three times in order to know about the family history, segregation pattern, and to confirm about the clinical and phenotypic spectrum.

All the available affected and unaffected individuals of the seventeen recruited families were physically examined. Extensive pedigrees of family were constructed to know about the segregation pattern of the disorder. In order to diagnose the anomalies, clinical and detailed phenotypic symptoms of the affected individuals were recorded.

2.2 Consent approval

The study was approved by the Ethical Review Committee of the Department of Animal Sciences, Quaid-e-Azam University Islamabad. Additionally, I got the consent approval from head of each family, either by visiting the family or telephonically.

During the first visit, consent approval about all the realistic and unrealistic expectations about the family study was discussed with the elders of the family. Then during next visits, family study was conducted and data was obtained.

2.3 Pedigree construction

Pedigree was constructed by interviewing the different members and with the help of elders of the families. Information was carefully drawn especially the cousin marriages record and deceased person status in order to make the family study fruitful.

Pedigree was constructed according to the standard method (Bennett et al., 2008). Females were represented by circles, males by squares. Affected females were symbolized by solid circles and affected males by solid squares. The deceased persons were indicated by a slash on the circle in case of the female and slash on the square in case of the male.

A digit enclosed in the diamond shape indicated the number of sibs about which we were not confirmed about the males and females presence. Single line

between male and female showed the marriage among non relatives or in *Biradari* and double line between male and female indicated the consanguineous marriage.

Each generation in the pedigree was numbered in Roman numerals and individual in each generation by Arabic numbers. The persons that were physically examined mark by transverse lines on pedigree symbols.

2.4 Clinical and phenotype examination

During family visits all the available affected and some of the normal persons were physically examined. For clinical examination subjects were taken to nearby hospital or medical clinic. In the hospital or medical centre, the help of doctors was obtained for the clinical evaluation of the trait. With the help of orthopedic surgeons the physical nature of the extra digit was understood and noted down.

All of the families collected had extra digits in hands or feet. Upon physical examination position of the extra digit, bifurcation, movement, and presence of joint was noted. In position it was noted that either it was present near thumb or near fifth finger or present in the middle of the hands or feet. In bifurcation patterning it was noted that the extra digit was originated from metacarpals or metatarsals or either it from proximal middle or distal phalanges. Presence of bone in extra digit was also observed.

Other skeletal parts and characteristics, e.g., extension and movement of other joints were also examined to confirm any other skeletal defect. Arms and legs lengths were measured to check the length discrepancies. Wrist movement and movement at shoulder joints were observed.

During the clinical examination, photographs and radiographs were taken. Subjects were taken to the radiological department and X-rays of hands and feet were obtained. Maximum number of photographs of affected and some normal persons were taken in order to document and diagnose the genetic defect correctly.

Special care was taken during clinical and phonotype examination so that not to neglect any other associated anomaly. Extension and movement of the joint was observed so that associated anomalies could be observed. Digit sizes or lengths were also observed.

2.5 Anthropometric measurements

Anthropometric measurements of all affected and some unaffected individuals were taken in order to check any other associated skeletal and growth abnormality. Data were recorded on a standard Proforma B and following parameters were taken: weight, standing height, sitting height, arm span, head circumference, neck circumference and chest circumference.

2.6 Diagnosis by literature survey and database search

With the help of literature survey and standard medical genetics databases, these seventeen families of polydactyly were diagnosed and classified.

Following online genetic databases and resources were consulted:

Table 2.1 Online databases

Databases	Names	Web address
OMIM	Online Mendelian Inheritance in Man	http://www.ncbi.nlm.nih.gov/omim
ICD	International Classification of Diseases	www.who.int/classifications/icd/en/
Pak Medi Net	Pakistan Medical Journals	www.pakmedinet.com/
Oxford Medical database	London Dysmorphology Database	http://www.lmdatabases.com/
GFMER	Geneva Foundation for Medical Education and research	http://www.gfmer.ch/200_Search_En.htm
NCBI-Pub Med	National Center for Biotechnology and Information	http://www.ncbi.nlm.nih.gov/
CDC	Center for Disease Control and Prevention	http://www.cdc.gov/nchs/icd.html

Results

3 Results

3.1 Family I (with additional digits in hands and feet)

3.1.1 Field visits and the Family

Family I was ascertained from a remote town of Islamabad. Initially this family was studied at the Pakistan Institute of Medical Science, Islamabad and the index subject (IV-5) was observed shortly after birth in the neonatal department. Later, family was visited at their residence and formal consent was acquired from the guardian of the family. With the help of elders, a four generations pedigree was drawn (Fig. 3.1). Pedigree information was confirmed by interviewing the other members of family. Three affected and eight unaffected family persons were physically examined, and photographs of three affected and one unaffected individual were taken.

There were extra digits in hand and feet of three affected individuals. There were no other skeletal or congenital defects observed in the affected subject and other family member.

3.1.2 Pedigree analysis

Pedigree consisted of four generations (Fig. 3.1). Total numbers of individuals in the pedigree were 30 (19 M, 11 F), of which three males were observed to be affected. There were nine marriages in the pedigree of which five were consanguineous and three were in *Biradari*. The affected individuals were observed in two sibships in generations III and IV.

Mode of inheritance in this family was recessive because the affected individuals had unaffected parents (Fig. 3.1). Hence, only males were affected so X-linked inheritance could be the possible pattern. Generally, polydactyly had autosomal dominant mode of inheritance, but the pattern in which disease was segregating in this family did not support the autosomal dominant mode of inheritance, in which affected individual should have one affected parent (Fig. 3.1).

There was extra digit either in the hands or feet of the three affected subjects. These three subjects belonged to the generations III and IV.

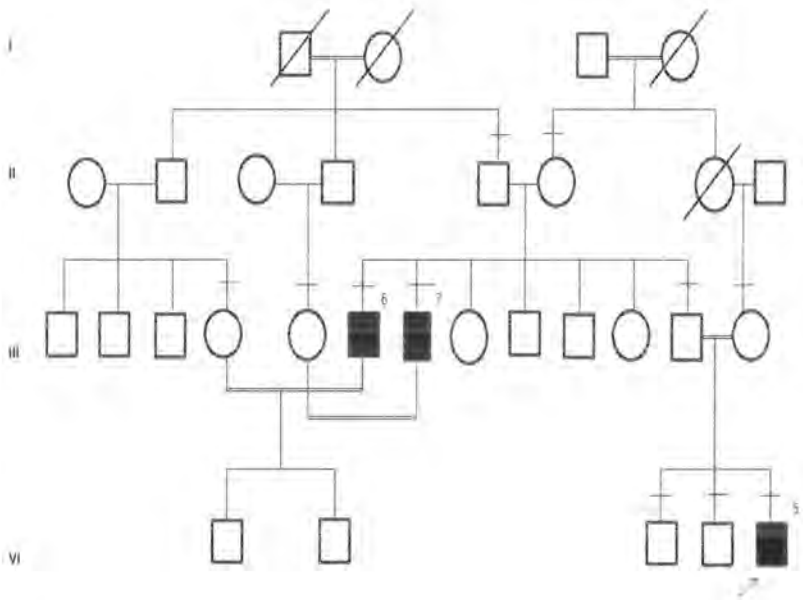

Fig. 3.1 Pedigree of Family 1

* = Horizontal line over the symbols denotes the subjects who were physically examined.

3.1.3 Clinical and phenotypic description

The affected subject III-6 had an extra digit near fifth toe in his right foot that was partially fused with the fifth toe. On close examination it was observed that extra digit contained bone and a separate nail which were partially fused with the fifth toe. He had normal hands and left foot (Fig. 3.2 A3). Subject III-7 had an extra node like out growth on small finger in his left hand but the right hand and feet were normal (Fig. 3.2 B2).

The index subject IV-5 had an extra toe close to fifth toe in his left foot that also contained bone and nail and was fully developed, his right foot and hands were normal (Fig. 3.2 C3). All these subjects and the other unaffected persons had normal gait, extension and movement of joints. The summary of the phenotypic data of this family is presented in Table. 3.1.

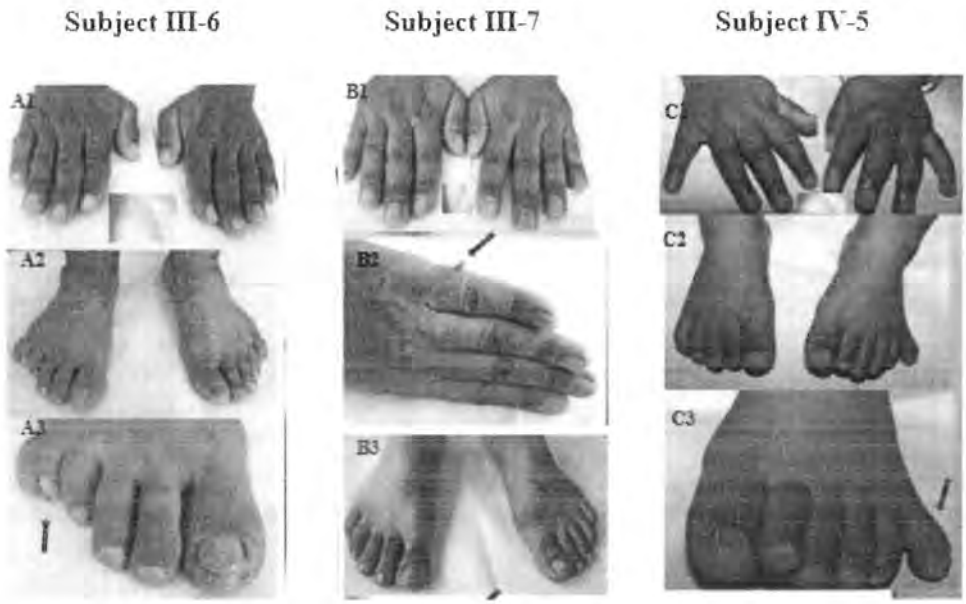

Fig. 3.2 Clinical spectrum of polydactyly in Family I

A1- Normal hands, **A2-3**-An extra toe close to fifth toe in the right foot that is partially fused with fifth toe. **B1-2** An extra spine like out growth on lateral aspect of small finger in the left hand, **B3**- Feet are unaffected.**C1**- Hands are normal, **C2-3** Extra digit near fifth toe in left foot.

Table.3.1 Clinical and phenotypic spectrum of polydactyly of Family I

Subject I.D	Affection status	Right hand	Left hand	Right foot	Left foot	Other symptoms	Fig. No.	Diagnosis
III-6	A	-	-	Postaxial polydactyly	-	Extra toe fused with 5th toe	3.2 A3	Postaxial type-A
III-7	A	-	Postaxial polydactyly	-	-	Extra digit node like	3.2 B2	Postaxial type-B
IV-5	A	-	-	-	Postaxial polydactyly	Extra toe fully developed	3.2 C3	Postaxial type-A
III-12	N	-	-	-	-	-	-	-

3.1.4 Diagnosis and classification

The literature survey and review of reported cases in the OMIM database showed that clinical symptoms in Family I was consistent with postaxial polydactyly type A (OMIM 174200). According to Temtamy and McKusick (1969, 1978) scheme, it was classified as postaxial polydactyly type-A, According to classification by Al-Qattan et al., (2008) it was postaxial polydactyly type-III. For molecular diagnosis, we need to check the mutation in *GLI3* (OMIM 165240) on chromosome 7p because postaxial polydactyly A and B are known to be associated with this gene (OMIM, 2012).

The family belongs to rural area and consanguineous marriages are common as a tradition. In this family, the occurrence of additional ulnar or fibular digits in hands and feet of three affected subjects were witnessed.

Postaxial polydactyly had two major types, type A and type B. Postaxial polydactyly type A that was fully developed and in postaxial polydactyly type B the addition digit was rudimentary. According to the literature survey and review of reported cases phenotypic spectrum of this family was similar with postaxial polydactyly type-A (OMIM, 2012).

The most common mode of inheritance for this anomaly was autosomal dominant. Penetrance rates for types A and B have been estimated to be 0.68 and 0.43, respectively, even higher estimates had been published (Castilla et al., 1973).

Postaxial polydactyly could occur as an isolated anomaly or associated with other anomalies. Associated anomalies could be confined to limbs (Aggarwal et al., 2009). Like in this family the affected subject III-6 had an extra toe close to fifth toe in the right foot that was partially fused with fifth toe and had separate nail.

Zhao et al., (2002) described a familial family of post axial polydactyly. In their reported family sixteen members were affected in six generations with variable phenotype of polydactyly type A and B. In my reported family only three males were affected. Kucheria et al., (1981) reported a family in which many subjects had postaxial polydactyly type A, and few subjects had postaxial polydactyly type B like in this family. One subject III-7 also have postaxial polydactyly type B. Ventruto et al., (1980) also reported a family in which both postaxial polydactyly types, i.e., A and B were present.

3.2 Family II (with additional digits in hands and feet)

3.2.1 Field visits and the Family

Family II was studied from Islamabad; one loop of family was settled in Murree. Initially the family was ascertained at Pakistan Institute of Medical Science. Family was visited at their residence and the formal consent was acquired from the elders of the family. With the help of mother of the index person, a five generations pedigree was drawn (Fig. 3.3). Pedigree information was drawn and confirmed in several visits. Each loop was studied at their residence; only one loop was studied at PIMS, Islamabad. Two affected and three normal persons were physically observed, and photographs of two affected and one normal individual were taken.

There were extra digits in hand and feet of four affected individuals. There was no other skeleton and congenital defect observed in affected as well as in normal persons.

3.2.2 Pedigree analysis

Pedigree comprised of five generations (Fig. 3.3). There were nine marriages in the pedigree of which three were consanguineous and six were in *Biradari*. Total number of individuals in the pedigree was 22 of which four were affected (2M, 2F) and 18 were normal (8M, 10F). Individual II-4 had an extra digit near small finger in both hands and feet. Subject IV-3 had an extra digit near small finger in left foot, while subject IV-4 had extra digit near small finger in left hand. The subject V-2 had extra digits in both hands and in left foot. The affected subjects were segregating in

three sibships in generations II, IV and V. All affected subjects had unaffected parents.

This situation did not support the autosomal dominant segregation pattern, in which affected subjects should have at least one affected parent. Mostly probably the mode of inheritance can be autosomal recessive because the parents of affected individuals were unaffected; there were consanguineous marriages and a skip generation i.e., generation III. It was autosomal because male and females were equally affected.

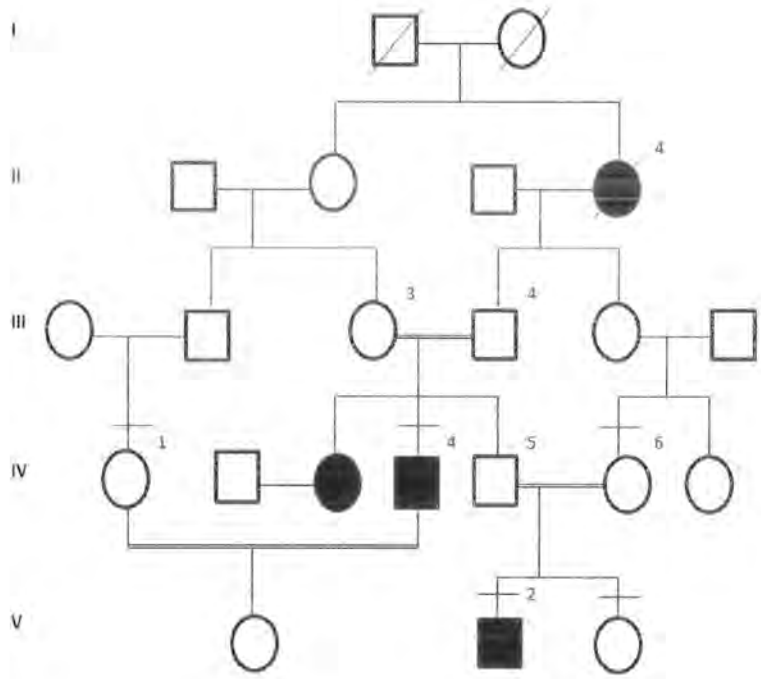

Fig. 3.3 Pedigree of Family II

3.2.3 Clinical and phenotypic description

The deceased subject II-4 had an extra digit near small finger and small toe in both hands and feet, respectively. It was evidenced that extra digit contain bone and separate nail. Subject IV-3 had an extra digit near small toe in left foot, extra digit contained bone and nail. Subject IV-4 had extra digit near small finger in left hand that was partially developed and operated.

Subject V-2 had extra finger in both hand near small finger and extra digit near fifth toe in left foot. In left foot and right hand digits did not contain bone and had been operated, while in left hand extra finger contained bone and did not operated. The summary of the phenotypic and clinical data of the family is presented in Table 3.2.

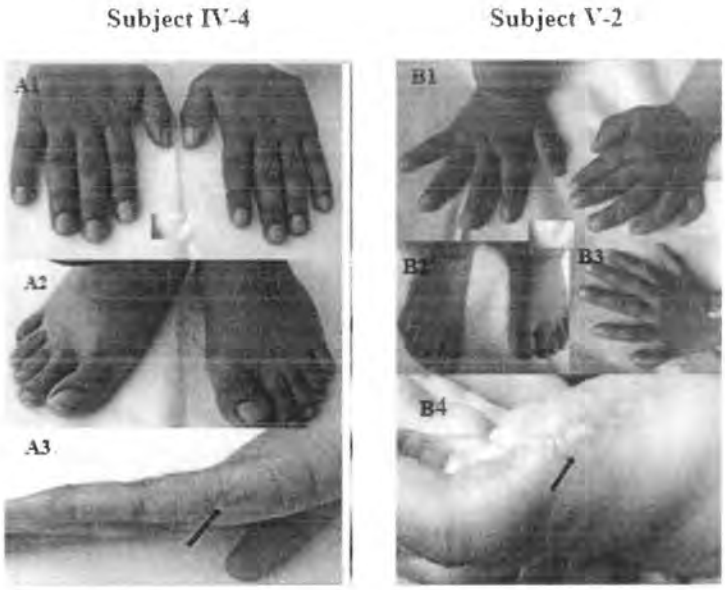

Fig. 3.4 Clinical spectrum of polydactyly in Family II

A1-3-An extra digit near fifth finger in the left hand that is operated and there is a mark of extra finger at this site **A2**- Normal feet. **B1-3** An extra digit in the left hand close to small finger in the left hand, **B2**- Right foot is unaffected while left foot has extra toe near fifth toe. **B-4**- An extra digit near fifth finger in the right hand that is operated and there is a mark of extra finger at this site.

Table 3.2 Clinical and phenotypic spectrum in Family II

Subject I.D	Affection status	Right hand	Left hand	Right foot	Left Foot	Other symptoms	Fig. No	Diagnosis
II-4	A	Postaxial polydactyly	Postaxial polydactyly	Postaxial polydactyly	Postaxial polydactyly	In left foot pedunculated extra digits present	-	Postaxial type-A
IV-3	A	-	-	-	Postaxial polydactyly	Extra toe fully developed	-	Postaxial type-A
IV-4	A	-	Postaxial polydactyly	-	-	Extra toe partially developed	3.4 A3	Postaxial type-A
V-2	A	Postaxial polydactyly	Postaxial polydactyly	-	Postaxial polydactyly	Extra digits in right hand and left foot was not fully developed and operated	3.4 B3& B4	Postaxial type-A

3.2.4 Diagnosis and classification

The literature survey and review of reported cases in the OMIM database showed that clinical symptoms in this family II were consistent with postaxial polydactyly type A (OMIM 174200). According to Temtamy and McKusick (1969, 1978) classification it was classified as postaxial polydactyly type-A. According to classification by Al-Qattan et al., (2008) it was postaxial polydactyly type-III.

The physical and clinical examination of affected individuals in this family showed the fully developed extra digits in the hands and feet. Partially developed extra toe was also present in the left hand of subject IV-4 and in the left foot and right hand of subject V-2 that was operated. There was extra digit but no associated manifestation of I.Q. level, skin, nail, hair, teeth, and other limb defect was observed. So it is an isolated anomaly.

Four affected subjects were witnessed with the incidence of additional ulnar or fibular digits in hands and feet. According to the literature survey and review of reported cases phenotypic spectrum of this family was similar with postaxial polydactyly type-A (OMIM 174200). Ventruto et al., (1980) also reported a family in which both postaxial polydactyly types A and B were present. Zhao et al., (2002) described a family with similar phenotype. Mollica et al., (1978) reported a family of postaxial polydactyly A with autosomal recessive mode of inheritance. In my reported family the same mode of inheritance was observed.

3.3 Family III (with additional digits/thumb in hand)

3.3.1 Field visits and the Family

Family III was studied from a remote town of Rawalpindi. Field visit was conducted with the help of a colleague. Formal consent from the guardian of the family was obtained. During next visits three generations pedigree was constructed and clinical information was collected. One affected and two normal persons were physically observed, and photographs of one affected individual were taken.

There was extra thumb in right hand of individuals III-1 and III-11.There was no other defect of bones or innate defect observed in the subject.

3.3.2 Pedigree analysis

The pedigree comprised of three generations (Fig. 3.5). Total numbers of persons in the family were 19 of which two males (III-1 and III-11) were affected. There were four marriages in the pedigree which one was in the *Biradari* three were consanguineous between I-3 and I-4, between II-1 and II-2 and II-3 and II-4.

The mode of inheritance could be autosomal recessive because there were consanguineous marriages and the parents of affected individual III-1 (II-1 and II-2) and III-11 (II-3 and II-2) were unaffected. Only males were affected so it shows the possibility of X-linked inheritance but if mother was carrier than she should transmit the trait in at least 50% in her male children. Therefore the more likely inheritance pattern would be autosomal recessive.

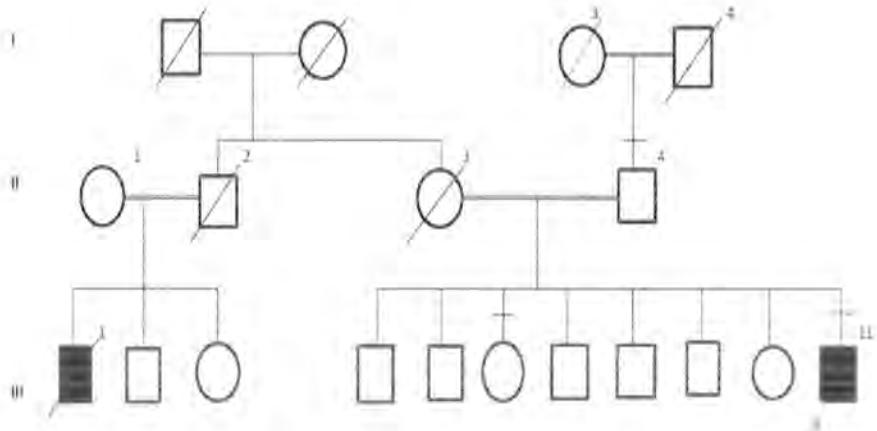

Fig.3.5 Pedigree of Family III

* = Horizontal line over the symbols, denotes the subjects who were physically examined.

3.3.3 Clinical and phenotypic description

The subject III-11, a male of thirty three years was a school teacher. He had incompletely developed extra thumb in his right hand. On close examination it was observed that extra thumb contained bone joint and nail (Fig. 3.6). Extra digit was not independently moveable. Extra thumb was bifurcated from proximal phalangeal joint. Feet were normal. No other notable symptoms related to gait, extension and movement of joints was observed.

It was evidenced that the subject III-1 was 59 years old and also had extra thumb in his right hand that was also partially developed. The phenotypic and clinical data summery of the family is presented in Table. 3.3.

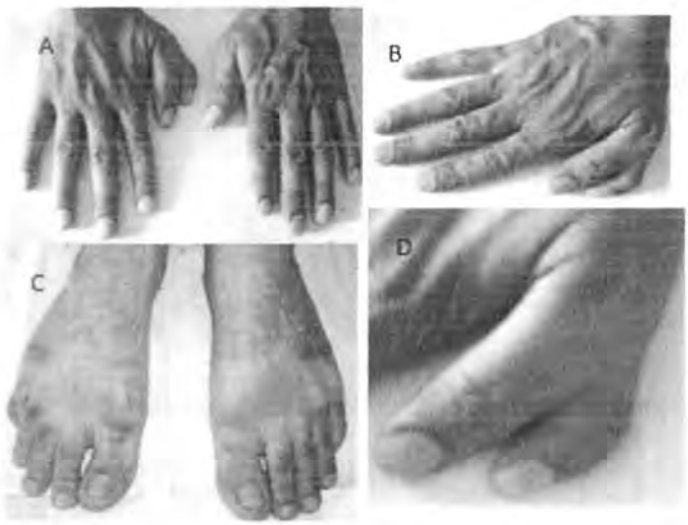

Fig. 3.6 Photographs of hand and feet of Subject III-11.

A, B & D- Extra thumb bifurcating from proximal phalangeal joint in the right hand.

C- Feet were normal.

Table 3.3 Clinical and phenotypic spectrum in Family III

Subject I.D	Affected status	Right hand	Left hand	Right Foot	Left Foot	Other symptoms	Fig. No	Diagnosis
III-1	A	Preaxial polydactyly	-	-	-	Proximal phalangeal joint partially developed .	-	Preaxial type-1
III-6	N	-	-	-	-		-	
III-11	A	Preaxial polydactyly	-	-	-	Proximal phalangeal joint partially developed	3.6 D	Preaxial type-1

3.3.4 Diagnosis and classification

The literature study and analysis of reported cases in the OMIM data base showed that clinical symptoms were consistent with preaxial polydactyly type I (OMIM 174400). According to Temtamy and McKusick (1969) categorization it was classified as preaxial polydactyly type-I, but according to Wassel (1969), Miura (1976), Wood (1978) and Zuidam et al., (2008) classified as preaxial polydactyly type-III. Although Zuidam et al., modify the previous classification schemes.

Family belonged to countryside area and due to custom, consanguineous marriages were practiced commonly. Subject III-1 and III- 11 almost have similar phenotype.

Mumoli et al., (2008) reported a sporadic family in which a female was affected and her extra thumb was bifurcated from metacarpal while the subject of my family the extra thumbs were bifurcated from proximal phalangeal joint.

Radhakrishna et al., (1993) reported a very far-reaching family from India. In this family many members showed preaxial polydactyly with a well-developed extra digit, duplication of the big toes and triphalangeal thumbs. In the present family no duplication of thumb of foot and triphalangeal thumb was observed.

3.4 Family IV (with additional digit and thumb in hands)

3.4.1 Field visits and the Family

Family IV was the resident of a small town of Rawalpindi. One of the family members was my friend; with her collaboration family was recruited. Detailed history about the pedigree information, and clinical symptoms were collected and recorded. Two loops of the family were settled in different villages. Each loop was visited at its residence and clinical and phenotypic details were collected in several visits. Two affected individual and the all the available normal persons were physically observed, and photographs of two affected and one normal individual were collected.

There was extra thumb in right hand of individual III-12 and extra tag like digit in left hand of individual III-12. There was no other skeletal and congenital defect observed in affected and other family members.

3.4.2 Pedigree analysis

Pedigree comprised of four generations (Fig. 3.7). Total number of individuals in the pedigree was 23 (11M, 12F), of which only two males III-5 and III-12 were affected. There were five marriages in the pedigree only one was consanguineous. Individual III-12 was the product of consanguineous marriage, while the subject III-5 was not the product of consanguinity both had an extra digit in his their one hand. The mode of inheritance could be autosomal recessive because the parents of affected individual III-5 (II-1 and II-2) and III-12 (II-3 and II-2) were unaffected. Another

possible explanation can be X-linked inheritance pattern because only males were affected.

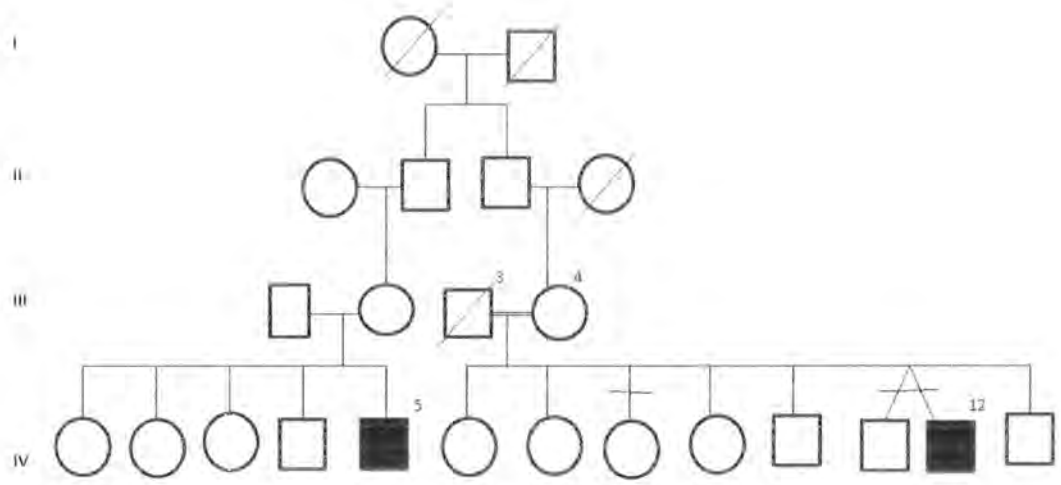

Fig. 3.7 Pedigree of Family IV

* = Horizontal line over the symbols, denotes the subjects who were physically examined.

3.4.3 Clinical and phenotypic description

The subject IV-12, male of 21 years of age, was neurologically abnormal, he was found to have extra thumb in right hand (Fig. 3.8). On close examination it was observed that extra thumb was partially developed and bifurcated near proximal phalangeal joint. The movement of extra digit was not independent.

The subject III-5 had non functional pedunculated digit attached with narrow pedicle near lateral side of fifth finger in left hand. Feet were normal in both affected subjects. No remarkable symptoms related to gait, extension and movement of joint was observed. The summary of the phenotypic and clinical data of the family were presented in Table. 3.4

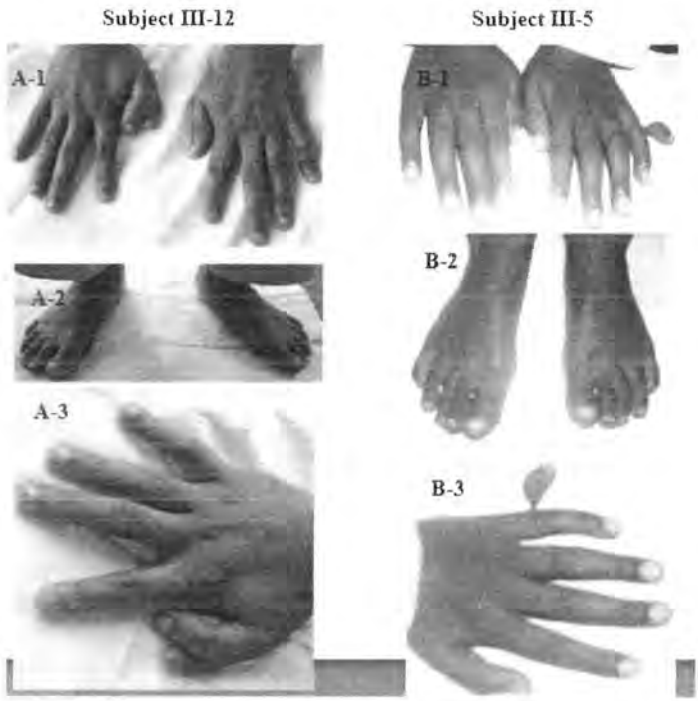

Fig. 3.8 Clinical spectrum of polydactyly in Family IV

A1-3- An extra partially grown thumb right hand **A2-** Normal feet **B1-3** An extra non functional pedunculated digit in the left hand near small finger in the left hand that was attaches to the hand with the help of small pedicle. **B2-** Feet are unaffected.

Table 3.4 Clinical and phenotypic spectrum in Family IV

Subject I.D	Affection status	Right hand	Left hand	Right Foot	Left foot	Other symptoms	Fig. No	Diagnosis
III-5	A	-	Postaxial polydactyly	-	-	Extra toe partially developed	3.8 B	Postaxial type-B
III-12	A	Preaxial polydactyly	-	-	-	Extra digits partially developed	3.8 A	Preaxial type-I
III-4	N	-	-	-	-	-	-	-

3.4.4 Diagnosis and classification

The literature review and analysis of reported cases in the OMIM database showed that clinical symptoms in subject III-12 were consistent with preaxial polydactyly type I (OMIM 174400). According to Temtamy and McKusick (1969, 1978) classification it was classified as preaxial polydactyly type-I.

The mutation in the *SHH* (OMIM 600725) regulatory element *ZRS* that present in intron 5 of the *LMBR1* (OMIM 605522) on chromosome 7p because preaxial polydactyly type I can be caused by mutation in this gene. For molecular analysis we can check the mutation in this gene. For molecular analysis, we need to confirm the mutation in *GLI3* gene (OMIM 165240) on chromosome 7p because postaxial polydactyly type A and type B are known to be caused by mutations in this gene.

Wassel (1969) categorized it as preaxial polydactyly type-III. Miura (1976), wood (1978) classified it similarly although they gave extension to the Wassel scheme. Zuidam et al., (2008) reported a similar case and classified it as preaxial

polydactyly type-III because there is the complete duplication of distal phalanx and partial duplication of proximal phalanx.

But the clinical symptoms in the subject III-5 were consistent with postaxial polydactyly type B (OMIM 174200) and Temtamy and McKusick (1969, 1978) classified it as postaxial polydactyly type-B. But according to Al-Qattan et al., (2008) who further classified the cases it was postaxial polydactyly type-II-B.

VanderMeer et al., (2012) described and found out the mutation in ZRS the enhancer of *SHH* in a family responsible for preaxial polydactyly, triphalangeal thumb and postaxial polydactyly. While in my respective family preaxial and postaxial polydactyly was found in the same family but no triphalangeal thumb and syndactyly was observed. Same mutation can be responsible for the phenotype observed in this family.

3.5 Family V (with additional digits in hands and feet)

3.5.1 Field visit and the Family/subject

The Family was studied from Pakistan Institute of Medical Sciences (PIMS), Islamabad. Basically the family originated from Rawalpindi. The subject III-1 was born in the guinea ward at PIMS. Family also came to PIMS for medical checkup so the complete clinical and phenotypic information was collected in several visits to the hospital and their residence. Three generation pedigree was constructed. Three normal and one affected individual was physically observed. Photographs of one affected and one normal person were taken. Radiographs of affected subject III-1 was also taken. In individual III-1, there was a bilateral digit addition near ulnar side in both hand and fibular side in both feet. Subject III-3 had extra thumb in right hand that was bifurcated near proximal phalangeal joint.

3.5.2 Pedigree analysis

The pedigree comprised of three generations (Fig. 3.9). Total number of individual in the family was twenty four of which only two male were affected. There were six marriages all were consanguineous between (subjects I-1 and I-2, I-3 and I-4, I-5 and 1-6, 1-7 and I-8, II-4 and II-5, and II-10 and II-11). Subject III-1 and III-3 was also the product of consanguinity.

The mode of inheritance could be autosomal recessive because there were consanguineous marriages and the parents of affected individual III-1 (II-4 and II-5)

and III-3 (II-10 and II-11) were unaffected and there were consanguinity. Although X-linked inheritance can also operate here as inheritance pattern because only male were affected.

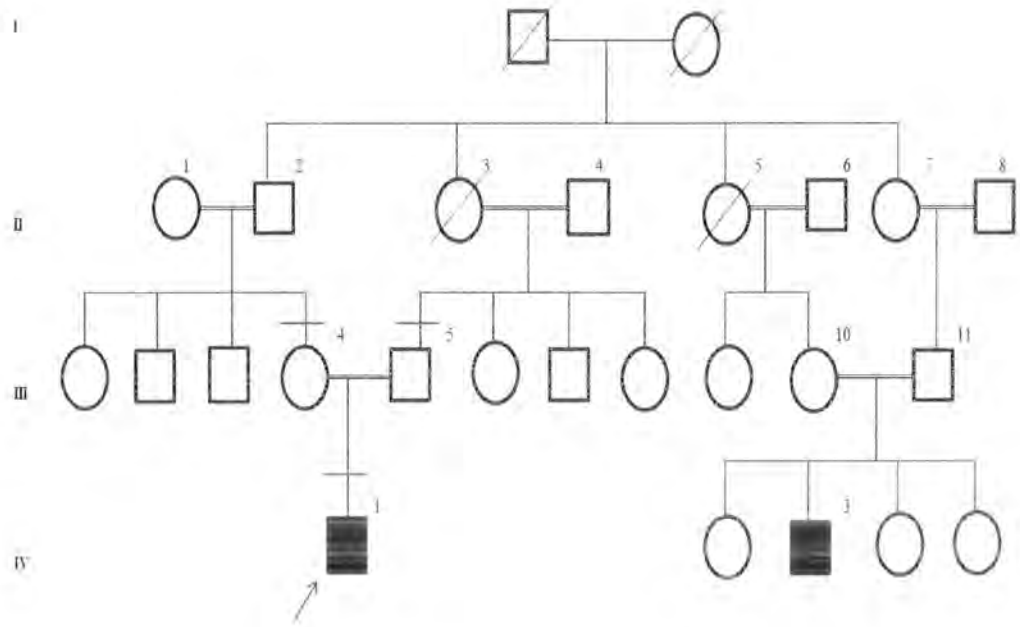

Fig. 3.9 Pedigree of Family V

* = horizontal line over the symbols denotes the subjects who were physically examined.

3.5.3 Clinical and phenotypic description

The subject IV-1 was a male that was one year old. He had extra digits in both hands and feet near fifth finger and toe respectively. Physical examination showed that extra digits contained bone joint and a nail and was fully developed (Fig. 3.10). Extra digits originated from carpals and it was independently moveable. While subject III-3 had extra thumb in his right hand that was partially developed and originated from proximal phalangeal joint.

Extension and movement of joint was normal. Limbs sizes were also normal in both subjects. No other remarkable symptom related to teeth, skin, nail and hairs was observed.

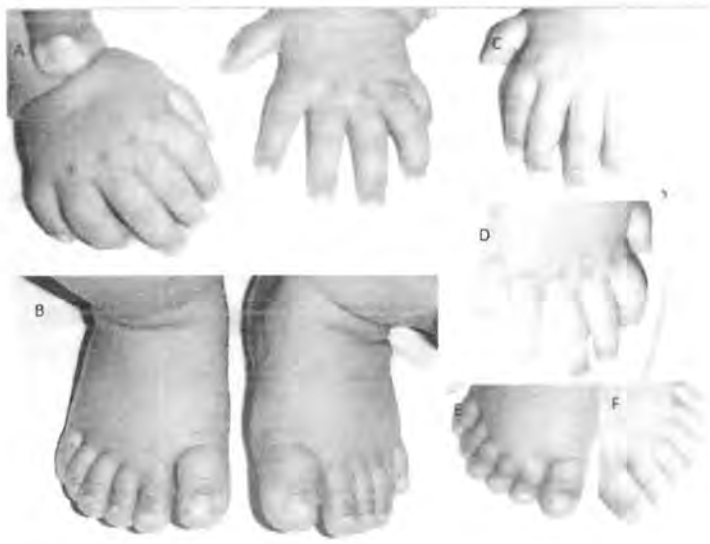

Fig. 3.10 Photographs of hands and feet of Subject III-1

A. Extra fully developed fingers near ulnar side in both right and left hands of individual III-1. **B.** Extra fully developed toe near fibular side in both right and left feet of individual III-1. **C- F.** Magnified image of hands and feet of individual III-1

Table 3.5 Clinical and phenotypic spectrum in Family V

Subject I.D	Affection status	Right hand	Left hand	Right foot	Left Foot	Other symptoms	Fig. No	Diagnosis
III-1	A	Postaxial polydactyly	Postaxial polydactyly	Postaxial polydactyly	Postaxial polydactyly	Extra toe fully developed	3.10 B	Postaxial type-A
III-3	A	Preaxial polydactyly	-	-	-	Extra thumb partially developed	-	Preaxial type-1
II-5	N	-	-	-	-	-	-	-

3.5.4 Radiograph analysis

Roentgenograms of subject III-1 is showed in (Fig. 3.11). In right and left hand the 6th metacarpal fuse with 5th metacarpal and look like y-shape. Remaining metacarpals and phalanges were normal (Fig. 3.11 A,B). Roentgenograms of feet showed six digits with completely developed 6TH metatarsal and normal phalanges (Fig. 3.11 C,D).

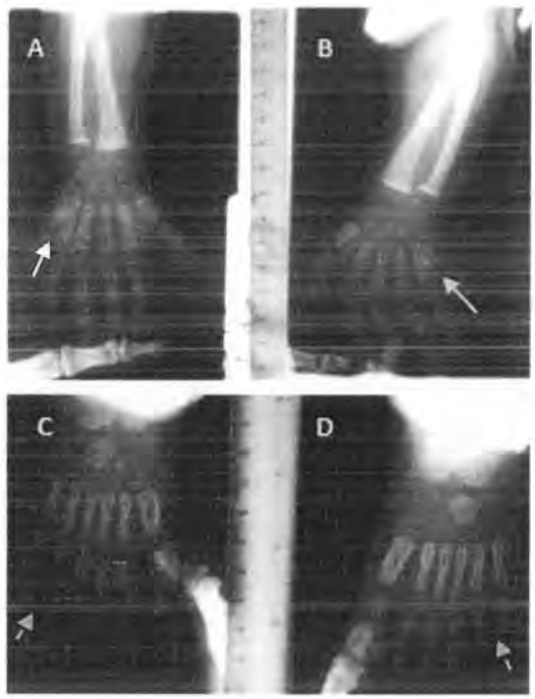

Fig. 3.11 Radiographs of hands and feet of Subject III-1

A-B Radiographs of hands. White and purple arrow shows the 6th metacarpal fuse with 5th metacarpals and look like y-shape metacarpals in both hands. **C-D** Radiographs of feet. 6th metatarsals in both feet are fully developed.

3.5.5 Diagnosis and classification

The literature survey and review of reported cases in the OMIM data base showed that clinical symptoms in the subject III-1 were similar with postaxial polydactyly type A (OMIM 174200) and according to Temtamy and McKusick classification (1969) who also classified it as postaxial polydactyly type-A because the extra digit was fully developed and functional. But according to Al-Qattan et al., (2008) who further classified the cases it was postaxial polydactyly type-III-A.

The clinical symptoms in the subject III-1 are similar with postaxial polydactyly but according to the scheme introduced by Al-Qattan et al., (2008) it was classified as postaxial polydactyly type-III. They report a case with similar phenotype i.e. there was bilateral fully functioning digit was present that is similar to subject III-1 of present study.

But in subject III-12 clinical symptoms are consistent with preaxial polydactyly type I (OMIM 174400). According to Temtamy and McKusick (1969,1978) classification it was classified as preaxial polydactyly type-I but according to Wassel (1969), Miura (1976), Wood (1978) and Zuidam et al., (2008) classifications who purposed extension to Temtamy and McKusick (1978) scheme it was classified as preaxial polydactyly type-III because there is the complete duplication of distal phalanx and partial duplication of proximal phalanx.

Chakraborty et al., (2007) described a family with two members affected; each had an extra digit near ulnar and fibular side in both hand and feet respectively. But the bifurcation, size and duplication of extra fingers of their case were different from my case. In case -I of their family in left hand extra digit bifurcate from metacarpal and had Y shape. In right hand size of the extra digit was small. Extra toes in both feet were similar with my reported family. As per my case the extra digits of both were symmetrical with the arrangement of the digits of the hand and feet and were of normal size and bifid metacarpal was present.

Robert and Blereau (2009) also reported a case in which other family members have extra digits but one subject involved the four extremities. In my family additional subject III-3 had preaxial polydactyly. But in their subject the type of extra digit in hands was different from my subject as it was type II postaxial polydactyly and extra toes were similar to subject III-1 of the present family.

Table.3.6 General and demographic information of familial polydactyly cases

I-V

Family ID	Subject ID	Gender	Age (years)	Location	Parity	Number of normal sibs	Number of normal kids	Parental consanguinity
I	III-6	Male	54	Islamabad	1	5	2	B
	III-7	Male	50	Islamabad	2	5	-	B
	IV-5	Male	1	Islamabad	3	1	-	FC
II	IV-4	Male	32	Islamabad	2	1	1	FC
	V-2	Male	3	Islamabad	1	1	-	FC
III	III-11	Male	33	Rawalpindi	11	10	-	FC
IV	IV-5	Male	4	Rawalpindi	5	4	-	B
	IV-11	Male	21	Rawalpindi	7	7	-	FC
V	III-1	Male	1	Rawalpindi	1	-	-	FC

Key: FC= first cousin; B= *biradari.*

3.6 Sporadic cases of preaxial and postaxial polydactyly (n=12)

3.6.1 Field visit and the subjects

Family/subjects VI to XVII with congenital limb defect were recruited from Rawalpindi-Islamabad. Family VI and VII belonged to Islamabad and family VIII to XVII originated from Rawalpindi.

There was a unilateral additional digit (extra thumb) in the subject VI to XIV. There was an extra digit near fifth finger in left foot of subject XV and she had low I.Q. The Family/subject XVI had bilateral digit addition near ulnar side. She had short stature due to comparative short limbs. In the feet, the third and fourth toes were small and equal to the fifth toe.

There were extra digits in both hand of subject XVII that were present near ulnar side. The extra digit was not fully developed and was non-functional and it had wide pedicle. It was like a node and did not contain bone but had nail. Extra digit in left hand was thread like and under developed. She had been operated for the extra digits.

There was no other skeletal or congenital defect observed in these subjects and there was no family history of any other genetic defect. Pedigree, clinical and phenotypic details are mentioned in Tables 3.7 and 3.8. The phenotypes of these cases are depicted in Figs. 3.12, 3.13 and 3.14.

Table.3.7 General and demographic information of sporadic polydactyly families/subjects VI-XVII

Family/ Subject ID	Gender	Age (years)	Location	Parity	Number of normal sibs	Number of normal kids	Parental consanguinity
VI	Female	1	Islamabad	2	1	-	FC
VII	Female	22	Islamabad	1	2	2	FC
VIII	Female	4	Rawalpindi	2	1	-	FC
IX	Female	22	Rawalpindi	2	2	-	B
X	Female	6	Rawalpindi	4	4	-	FC
XI	Female	4	Rawalpindi	4	3	-	FC
XII	Male	1	Islamabad	1	-	-	FC
XIII	Female	16	Rawalpindi	2	3	-	FC
XIV	Female	5	Rawalpindi	4	3	-	FC
XV	Female	18	Rawalpindi	2	3	-	FC
XVI	Female	32	Rawalpindi	1	1	-	NR
XVII	Female	9	Rawalpindi	4	3	-	B

Key: NR=non-related; FC= first cousin; B= *biradari.*

Table.3.8 Clinical and phenotypic spectrum of sporadic polydactyly families/subjects VI-XVII

Family/subjects I.D	Right hand	Left hand	Right foot	Left foot	Other symptoms	Fig. No.	Diagnosis by Temtamy and McKusick	Diagnosis by Wassel, Miura and Wood
VI	Preaxial polydactyly	-	-	-	Knob like t partially developed	3.12 A	Preaxial type-I	Preaxial type-I
VII	Preaxial polydactyly	-	-	-	Duplication of distal phalanx	3.12 B	Preaxial type-I	Preaxial type-II
VIII	Preaxial polydactyly	-	-	-	Proximal phalanx partially developed	3.12 C	Preaxial type-I	Preaxial type-III
IX	Preaxial polydactyly	-	-	-	Distal phalanx Partially developed	3.12 D	Preaxial type-I	Preaxial type-I
X	-	Preaxial polydactyly	-	-	Proximal phalanx partially developed	3.13 A	Preaxial type-I	Preaxial type-III
XI	Preaxial polydactyly	-	-	-	Proximal phalanx partially developed	3.13 B	Preaxial type-I	Preaxial type-III
XII	Preaxial polydactyly	-	-	-	Proximal phalanx partially developed	3.13 C	Preaxial type-I	Preaxial type-III
XIII	Preaxial polydactyly	-	-	-	Proximal phalanx partially developed	3.13 D	Preaxial type-I	Preaxial type-III
XIV	-	Preaxial polydactyly	-	-	Duplicated distal phalanx and fused	3.14 A	Preaxial type-I	Preaxial type-II
XV	-	-	-	Postaxial polydactyly	Partially developed extra toe	3.14 C	Postaxial polydactyly type-B	Postaxial polydactyly type-IIB
XVI	Postaxial polydactyly	Postaxial polydactyly	-	-	Fully developed fingers and brachydactyly of feet	3.14 D	EVC syndrome	EVC syndrome
XVII	Postaxial polydactyly	Postaxial polydactyly	-	-	Partially developed fingers	3.14 E	Postaxial polydactyly type-B	Postaxial polydactyly type-B

3.6.2 Anthropometric measurements

Anthropometric measurements of the subjects II, III, IV, V, VI, VIII, I X, X, XI and XII were taken in order to check any other skeletal or developmental abnormality (Table 3.3). All the basic landmarks were normal excluding the involvement of any developmental defect in subjects with polydactyly except for the case of Ellis-van Creveld syndrome (EVC), in subjects XII, anthropometric attributes showed the shortening of limbs and dwarfism.

Table 3.9 Summary of general and anthropometric attributes of sporadic polydactyly cases VII-XVII

Demographic and physical features	**Subjects**									
Case number	**VII**	**VIII**	**IX**	**X**	**XI**	**XIII**	**XIV**	**XV**	**XVI**	**XVII**
Gender	F	F	F	F	F	F	F	F	F	F
Age (years)	22	4	22	4	3	16	5	18	32	9
Growth and anthropometric measurements										
Standing height (cm)	165	91	160	107	79	160	115	150	128*	120
Sitting height (cm)	72	48	76	59	43	74	58	74	79*	62
Arm span (cm)	168	91	173	107	79	152	107	142	117*	114
Head circumference (cm)	55	48	58	48	43	56	48	59	51	50
Neck circumference (cm)	35	23	36	25	30	35	25	38	28	26
Chest circumference (cm)	80	53	86	48	45	76	50	86	67	55

* = retarded development of skeleton, even it was less as compared to the subject VII and IX of similar age (i.e., 22 years).

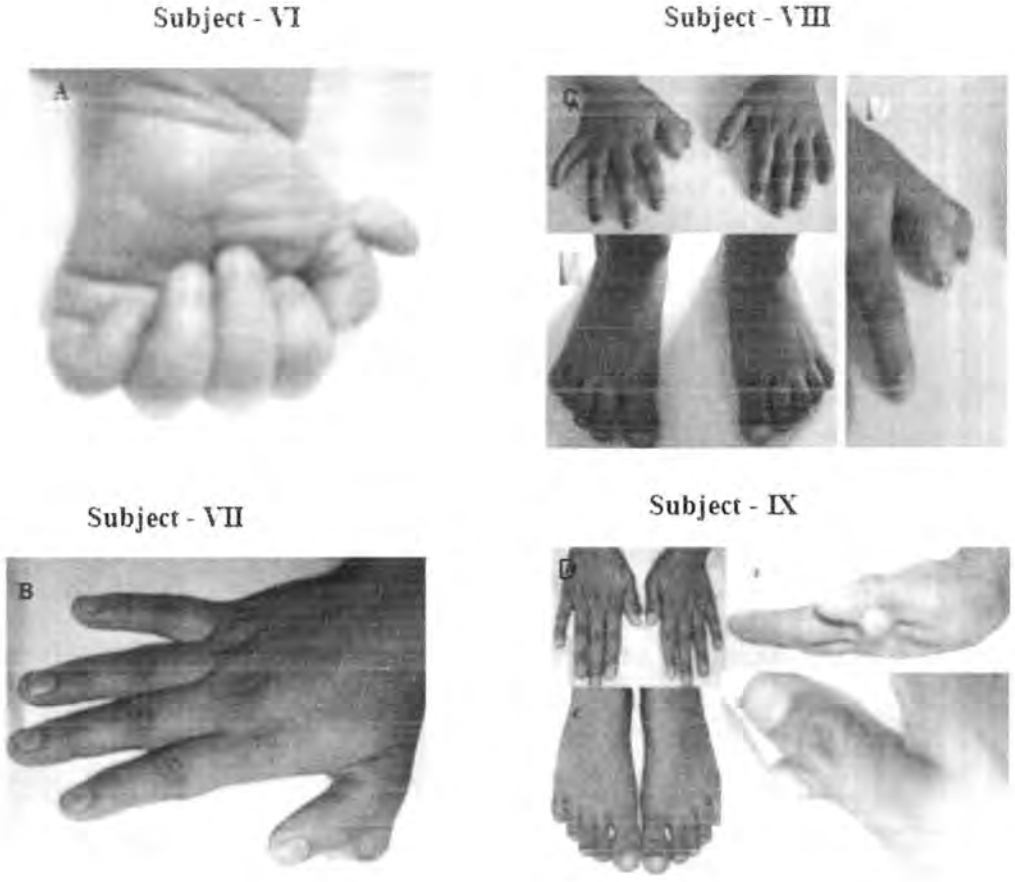

Fig. 3.12 Clinical spectrum of preaxial polydactyly in subjects I-IV

A- A knob like thumb in the right hand is evident that is partially developed and attach to proximal phalangeal joint with the help of cutaneous bridge. It is nonfunctional and hangs as a useless digital structure. **B-** There is partially developed right thumb that bifurcated near the proximal phalangeal joint. It appeared to harbor two digital elements and a distal nail. **C-** Extra thumb in on the right hand that is partially developed. It appear to contain one digit and a nail. **D-** The unilateral pea shaped extra digit bifurcates from distal phalanx of right thumb. In the AP view of the right hand it is not very explicit. It is like an outgrowth near distal phalangeal joint and contained a nail. The feet are normal in this subject.

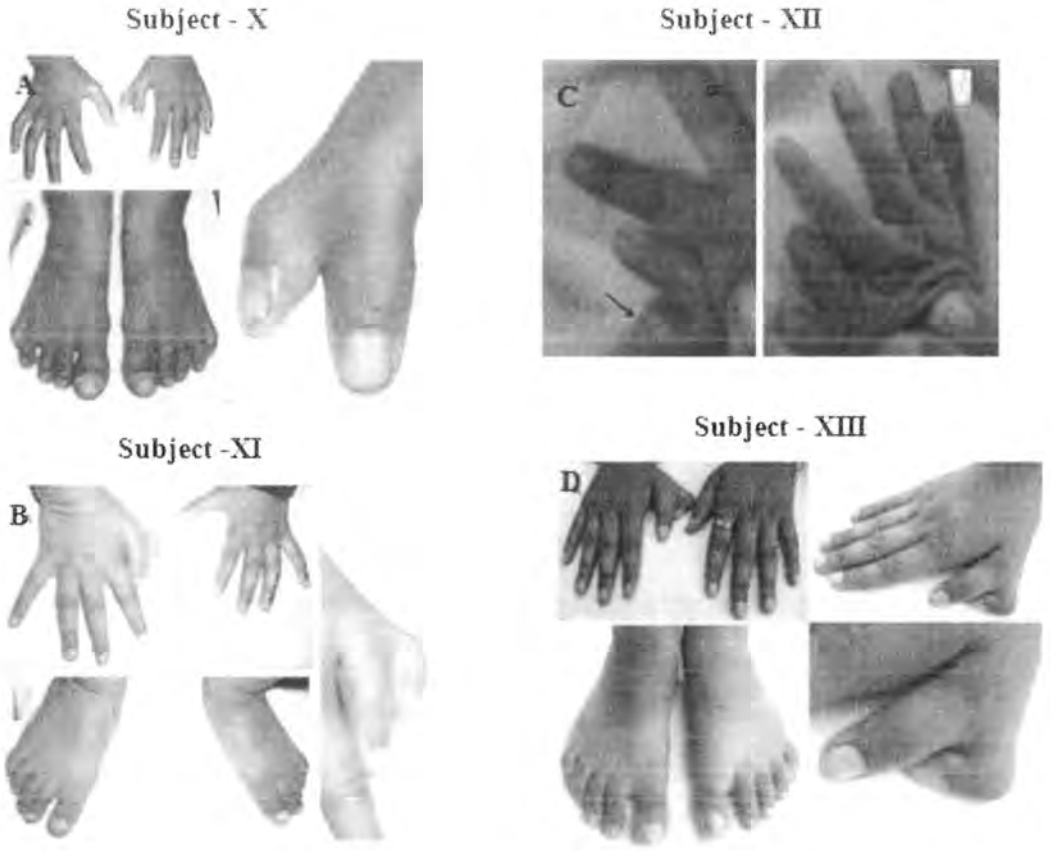

Fig. 3.13 Clinical spectrum of preaxial polydactyly in subjects V-VIII

A- The subject X had an extra thumb in left hand that is partially developed and bifurcated near the proximal phalangeal joint. It contained two digital elements and a dorsal nail. The feet are normal. **B-** Extra thumb in right hand that is not fully developed because it originates from proximal phalangeal joint. The feet are normal. **C-** The subject XII, male have an extra thumb in right hand and that is fully developed and originated from metacarpals. **D-** Extra thumb in right hand that is partially developed. The origin of extra thumb is from proximal phalangeal joint and it appeared hook shaped. Due to contracture extra thumb did not extend fully. Feet are normal.

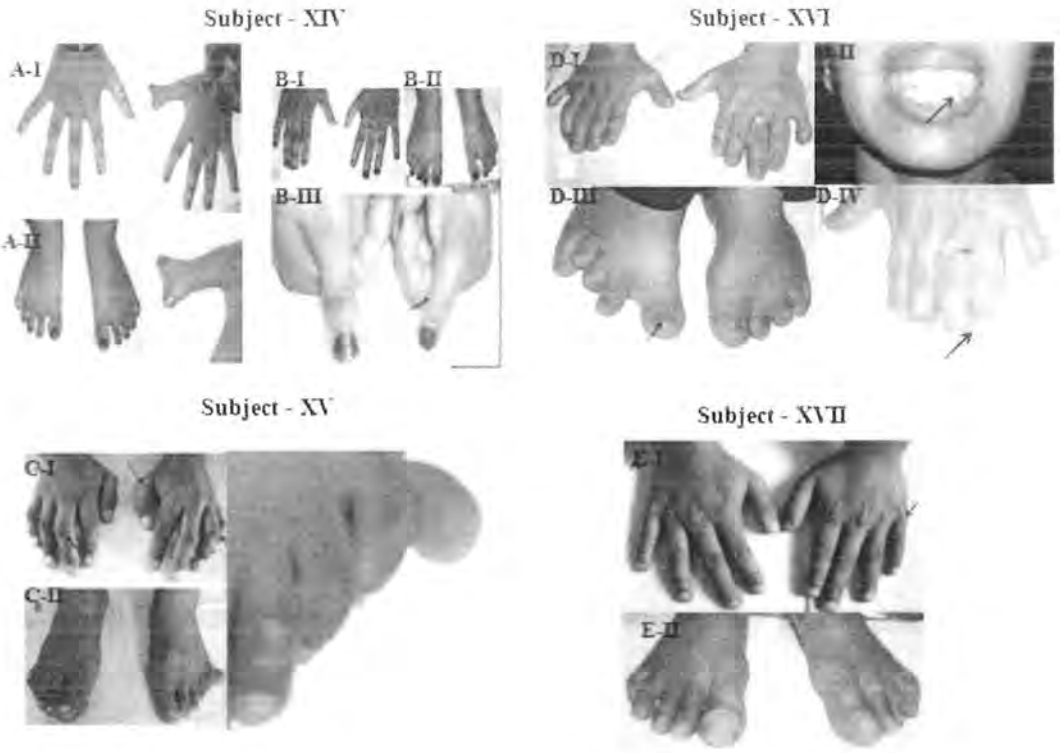

Fig. 3.14 Clinical spectrum of preaxial and postaxial polydactyly in subject IX-XII

A-I- The subject XIV, a female have extra thumb in her left hand that is not fully developed. The affected thumb bifurcates near the distal phalangeal joint. There is the partial duplication of the distal phalanx and additionally it is fused with thumb. **A-II** Feet are normal. **B-I** Associated anomaly in the family is observed that the mother of the subject XIV. She do not have knuckle joint in the thumb of left hand. **B-II-** Feet are normal. **C-I** Contracture at proximal phalangeal joints of digits 3 to 5, that is bilateral. **C-II-** Extra toe in left foot that is partially developed. It attached to the foot with the help of wide peduncle. **D-I** There is extra digit in right and left hand near ulnar side. **D-II** Deformed and discolored teeth. **D-III** Small and disorder fourth toes and there is wide gap between thumb and 2nd toe in right foot. **D-IV** Reduced and deformed nails. **E-I** There were extra digits that were present near ulnar side. The extra digit was not fully developed and was non-functional and it had wide pedicle. It was like a node and did not contain bone but had a nail. Extra digit in left hand was under developed. She had been operated for the extra digits. **E-II-** Feet are normal.

3.6.3 Diagnosis and classification

Twelve sporadic families/cases recruited had only one member affected. Normally polydactyly has an autosomal dominant mode of inheritance but in these families only one individual was affected. So it was very difficult to predict about the mode of inheritance. It can be a novel mutation.

Preaxial polydactyly is the most general and frequent type of polydactyly in the hand. It is supposed that before eighth week of embryonic life preaxial polydactyly occur due to proliferation of excessive cells and distressed cell necrosis of pre-axial ectodermal and mesodermal tissues (Yasuda, 1975). Radial polydactyly is most frequent innate abnormality. Out of twelve these sporadic cases nine have this anomaly. Mumoli et al. (2008) reported a family in which only one member is affected and had fully duplicated thumb. Affected subject in Family VII had fully developed thumb.

In my cases duplication proximal and distal phalanx and articulation of thumb is variable. According to duplication sizes criteria Wassel (1969), Miura (1976), Wood (1978) further classified the preaxial polydactyly cases as compare to Temtamy and McKusick. In subject VIII, XI and XIII polydactyly classified as preaxial polydactyly type-III and in subject VII, and XVI as preaxial polydactyly type-II. In subject VI and IX classified as preaxial polydactyly type-I. Zuidam et al., (2008) modified the classification given by Wassel, Miura and Wood but these cases are still classified as preaxial polydactyly type-III, II and I respectively.

The degree of bifurcation, size and articulation is supportive in surgical decisions. Literature survey reveals that point mutation in *SHH* regulatory sequence ZRS was responsible for preaxial polydactyly (Farooq et al., 2010). The mutation in the *SHH* (OMIM 600725) regulatory element *ZRS* that present in intron 5 of the *LMBR1* (OMIM 605522) on chromosome 7p because preaxial polydactyly type I can be caused by mutation in this gene. For molecular analysis we can check the mutation in this gene.

In family fifteen and seventeen postaxial polydactyly is present. Kucheria et al. (1981) described a family from India in which twelve affected cases were reported. Both preaxial polydactyly type A and B was present. In my families postaxial type B is observed and these are sporadic cases. Mukherjee et al., (2011) reported a sporadic case in which a female had extra toe in all limbs but in my reported families, in the Family XII, subject III-2 toe in left foot and in Family XIV, subject III-10 had extra fingers in both hand. In both cases it is partially developed.

Family eleven is consistent with the phenotype in Ellis–van Creveld syndrome. Ruiz-Perez and Goodship (2009) reported a case in which a patient was affected with EVC syndrome, but he had congenital heart defect along with deformed nail, dwarfism, nail dysplasia and postaxial polydactyly, all symptoms are present in my case except heart defect. For molecular analysis, the mutations in the *EVC* gene (OMIM 604831) and a non-homologous gene, *EVC2* (OMIM 607261), located close to the EVC need to be investigated.

Discussion

4 Discussion

In the present study, 17 families showing apparently monogenic deformity with variable phenotypic spectrum of polydactyly have been investigated. Sixteen were non-syndromic and one was syndromic (i.e., Ellis-van Creveld syndrome; EVC). In the non-syndromic cases, nine were sporadic preaxial polydactyly type, one familial preaxial polydactyly, two sporadic postaxial type, and four familial postaxial polydactyly cases. In sporadic families preaxial polydactyly was common phenotype. This has been reported to be the most frequent abnormality in other studies (Mumoli et al., 2008).

The distribution of polydactyly phenotypes is different in different populations. Ethnic and genetic factors greatly affect the type of polydactyly in the world populations. Radial polydactyly is very frequent in a variety of Asian populations (Medscape, 2012).

Mumoli et al., 2008 reported a case of radial polydactyly, in which subject had extra thumb. The additional thumb had duplicated proximal phalanx. The extra digit commonly not fully developed, and like an abnormal fork in an existing digit, or it may rarely arise at the wrist like normal digit. In my nine preaxial sporadic reported cases only one subject XII had extra digit aroused from wrist. In subject VI, VII, VIII, X, XI it come up from proximal phalangeal joint and in subject IX, XIV it originated from distal phalangeal joint. In subject XIV there was the complete duplication of the distal phalanx and additionally it was fuse with thumb. The subject XIII had extra thumb that was originate from metacarpals and hook shaped. Due to contracture extra thumb did not extend fully.

Polydactyly of the foot is a comparatively common congenital abnormality but it is less common than polydactyly of the hand. It is most often postaxial. Galois et al. (2002) reported three cases of polydactyly of foot. In the present case I, there was the bilateral and partial duplication of fifth toe. In case two there was widen mid foot due to widen metatarsals. In case three fully developed extra toe was reported. While in my reported case (subject XV) had postaxial polydactyly of foot but it was partially developed. It did not contain bone and attached to foot with wide peduncle. But the subject III-6 of family one had similar phenotype as case one reported by Galois et al., (2002).

EVC phenotype is erratic and affects multiple organs. It is a prenatal deformity and may be revealed or exposed before time, after the 18th week of gestation; the phenotype involves contracted thorax, polydactyly of hands and feet, discernible reduction of the long bones and cardiac defect (Baujat and Merrer, 2007). On the other hand after birth, the prime features are small height, polydactyly affecting hands, shortening of the middle and distal phalanges, ectodermal dysplasia mainly affecting nails and teeth innate heart malformations (Eswar, 2001).

In my represented case subject XVI had deformed nail. Nails were either absent or reduced. Extra digit also had reduced or deformed nail. She had extra digits in both hands near fifth finger. On close examination it was observed that extra digits contained bone joint and its nail is also deformed. Extra digits were fully developed and it was independently moveable. In feet the lengths of third and fourth toes were small and equal to the fifth toe. Extension of joints of arms was not normal. Limbs were short, and due to limb reduction her stature was short. Teeth were abnormal in shape and deformed. Skin and hairs were normal. The case presented in my study, I

found all main feature of this syndrome; additionally the brachydactyly of foot was observed and there was no heart defect was found in my subject.

Aggarwal et al. (2009) reported a postaxial polydactyly in which a subject had seven fingers in right hand and six fingers in left hand. There was also the additional toe in right foot. Extra digits were well formed. Their subject also had cleft lip. But in my family two, subject V-2 had six, six digit in both hand and left foot. In right hand and left foot it was not well formed and operated. While the extra finger in left hand was fully developed.

During a screening study of postaxial polydactyly, Watson et al. (1997) reported twenty one subjects that had postaxial polydactyly type B. one case was similar phenotype to my subject III-5 of family IV. Both subject had an extra non functional pedunculated digit near little finger that was attached to the hand with the help of small pedicle. In my reported subject it was present in the left hand while in Watson et al reported subject it was present in the right hand. But one deviation was that in another subject III-12 of family IV had preaxial polydactyly.

Feng et al. (2007) reported a familial family of postaxial polydactyly from China in which nineteen members were affected in four generations. All affected subjects had bilateral duplication of fifth digit in hands and feet. The mode of inheritance was autosomal dominant. In my reported families the subject IV-1 of family V had extra fifth digit in both hands and feet. But another subject IV-3 had preaxial polydactyly. In my family one and two, had trait of postaxial polydactyly, but there were the phenotypic variability among the affected subjects. All subjects did not have bilateral postaxial polydactyly of hands and feet.

Subjects with polydactyly may experienced difficulty in the normal routine work. It also depends on the degree of development of extra digit some time it is under developed and immobile as in many of my preaxial polydactyly sporadic cases and one familial family number one. Sometimes it is fully developed and mobile as in the extra digits of subject IV and subject III-1 of Family V. The opposable thumb and underdeveloped finger cause serious problem in daily routine tasks. If there is good clinical study of affected subjects it leads to fine decision making in clinical management and surgery.

The main treatment of polydactyly is surgery or operation. Surgery is to be done to confiscate the extra parts. Sometimes the surgery is somewhat complex because it may be required variations in all of the structures of the digit. The treatment or surgery is planed and tailored for every patient by the evaluation of clinical and phenotypic details. The appraisal and treatment preparation is based on the conclusion that what is the medical and social history, psychological and social disturbances. Co-operative studies between psychiatrists and surgeons provide various valuable guiding principles in the evaluation and assortment of patients for remedial surgery (Mumoli et al., 2008).

It is very important to recognize or identify if the surgery is required or not. The series of multistage interventions and timing of surgery play a most important role in functioning of the hand. Satisfactory power grip and accuracy in handling both these things may not achieve in all cases. Normal appearance cannot be achieved in many cases. In order to achieve possible function of the existing anatomical parts

approaches that are applied in traumatic injuries can be used in scheduling therapy for innate malformations of the hand (Netscher, 1998).

The goals of surgery are: to improve the appearance of the hand; to improve the physical appearance and psychosocial consequences; to put off the progressive abnormality from developing as the child grows, and to use their hand in a natural and unselfconscious way. One group of scientist shared the surgical experiences of that radial polydactyly. It can be surgically reconstructed pleasingly in adulthood. Many patients got the surgery due to cosmetic aspect and social stigmata of congenital anomalies. Apart from age of the patients, surgery should not be deferred after diagnosis (Cetik et al., 2005).

Genetic counseling is the advantage of excellent genetic study. Mode of segregation and recurrence risks can be obtained from genetic study. During field visits information about the subjects and family was gathered and pedigree was drawn. Pedigree information depicts the complete picture of family members and their relationship in this way risk estimation is calculated and genetic counseling can be provided to family and subjects.

In this study a genetic limb defect were explored from the Islamabad and Rawalpindi district and polydactyly is the most common type of limb defect investigated. Preaxial polydactyly was the most common type of polydactyly that observed. Bellovits, (2003) described an epidemiological study on polydactyly in Hungary. According to his observation the preaxial polydactyly was the most common type observed, and it was common in boys. But in the cases it was common in females.

My finding was also concordant with him that the polydactyly was the most common type of limb anomalies observed. I performed clinical study and scrutinized that what was the segregation pattern of this limb anomaly. A general doctor was unable to classify the genetic diseases. There is little awareness among the people about the genetic disorders. They consider many of the genetic disorders as miracle and mythology. In primeval times a baby who was born with polydactyly was selected to be a King in early stages. Even today people considered that those born with six fingers are more successful in life. I also heard similar tales during my field visits.

In my reported Family IV parents of subject III-5 and parents of subject XIV believed that the extra finger of their child is good omen for their family. Even though the subject IV-5 of Family IV has postaxial polydactyly type B and his extra finger attached with small pedicle that can be removed by binding the horse thread at the time of birth. They did not operate or treat it because they considered it as a miracle of Allah.

This is due to the lack of awareness and education. Special awareness programs are required about the genetic disorders. Related to polydactyly, they can be communicated that what is the importance of the surgery to the patients. And what is the role of consanguineous marriages in causing the genetic disorders.

4.1 Future perspective

Genetic research is different from other areas of applied medical research as it does not offer the immediate cure and benefits but it produces genetic information that is implicated on the whole family even though the study conducted on individuals (Cohen and Wolpert, 1998).

All the cases reported in this thesis have similar trait i.e. polydactyly but different phenotypic and clinical niceties. Polydactyly is a monogenic trait. Different molecular analyses are required to identify the underlying genetic defects in the families. Different mutations are known but it can be confirmed for these families.

Once the underlying gene and loci have been worked out by sophisticated molecular analysis then accurate diagnosis, treatment, management, and risk estimation for family and further generations would be probable or valuable. Congenital anomalies mean that the abnormality appears at developmental stages. Hence through genetic study pre-symptomatic testing or prenatal diagnosis would be possible for better decision making for the family.

In Pakistan the high prevalence of genetic disorder has been reported. Genetic disorders are the cause of psychosomatic anxiety, sadness and regret in the subject. Treatment and rehabilitation of the subjects affected with genetic defect is expensive and it is not completely curable. Special attention and immediate measures are required to minimize or to prevent recurrence of genetic disorder.

- Special awareness programs should be started about the hereditary disorders and highlighting their association with consanguineous marriages.
- Promote the research and development in genetic study for congenital anomalies.
- Prenatal diagnosis and screening should be common.
- Gene therapy for the prevention of genetic disorder should be common and accessible to all, at national level.

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