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Clinical and Phenotypic Study of Two Polydactyly Families Ascertained from Islamabad, Pakistan

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Abstract

Polydactyly is a genetic disorder that is characterized by the presence of an extra toe or finger in the foot or hand respectively. It may be a part of the other syndromes or can occur as a separate anomaly. The aim of this study was to conduct a survey in order to find the clinical and phenotypic variability of polydactyly from Islamabad, Pakistan. Ignite awareness among the people about polydactyly as most people don't even think it is a disorder. They considered it as a miracle from Allah Almighty. In order to achieve this aim, different field visits to the hospitals and other places were arranged. The data taken from the hospitals were screened for the polydactyly and then further study of the affected families was done at their homes. Two recruited families of polydactyly were reported in this study. All the members of both families were screened for any abnormality. They were physically examined for any kind of extra digit, bifurcation, movement of joints, and presence of extra joints. Pedigree of family one consisted of three generations and two males were affected in third generation. Pedigree of family two consisted of three generations and two males were affected in fourth generation. The phenotypic and clinical niceties in these two families were different. Diagnosis, treatment, management, and risk estimation of the family was conducted in this study; further molecular analysis is required to find out the genes mutated in the affected individuals. Genetics counseling is needed to be as common so they could make better decisions for the family through pre-symptomatic testing or prenatal diagnosis.

Keywords: Genetic disorders; Polydactyly; Two families; Islamabad; Pakistan

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. Genetic factors play important role in the etiology of genetic abnormalities or disorders **(Shanti, 2001)**.

Some genetic disorders are congenital and other showed symptoms later. There are approximately 17,000 well-characterized genetic disorders **(OMIM, 2011)**. There are four major classes or types of genetic disorders; single gene disorder,

multifactorial, chromosomal abnormalities, and mitochondrial diseases **(Lewis, 2003)**. 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 because of to mutant gene is present in one parent. The siblingss 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 **(Cumming, 2009)**.

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, 1996)**.

In Pakistan the incidence of congenital malformation has been investigated by different studies. But there is the variation in the prevalence rate of congenital malformation. A study from Liaquat National Hospital Karachi reported a prevalence of 15.8/1,000 of total births **(Shamim *et al.*, 2010)**.

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; these 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)**.

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 other syndromes. Isolated polydactyly has autosomal dominant mode of inheritance; while syndromicpolydactyly 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 digitmedial 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 presented 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 is 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 of 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 mesoaxialpolydactyly. Similarly, the partially developed extra digit is more common as compared to the fully developed extra digit that is originating from wrist **(Elliott *et al.*, 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)**. Preaxialpolydactyly is common and mostly it is sporadic and unilateral **(Kozin, 2003)**. Polydactyly is inherited as an autosomal dominant fashion. Family history is useful in determining the inheritance pattern and risk assessment. **(Case 31. Polydactyly, 2012)**.

Material and Methods

Field Visit

In order to investigate and analyze the families with limb genetic disorders, hospital and medical centers, and educational institutions were visited. The ascertained families belonged to Islamabad, Pakistan. Initially the data were collected from children wards of Pakistan Institute of Medical Sciences (PIMS), Islamabad by monitoring the consecutive live births. The data were refined for genetic defects and refined again for polydactyly cases. 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 two 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.

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 or consent approval all the realistic and unrealistic expectation about the family study was discussed with the elders of the family. Then during next visits, family study was conducted and data were obtained.

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)**.

Clinical and Phonotype 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 understand and note 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 and attachment of the 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 leg lengths were measured to check the length discrepancies. Wrist movement and movement at shoulder joints were observed.

In 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.

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 performa and following parameters were taken: weight, standing height, sitting height, arm span, head circumference, neck circumference and chest circumference.

Diagnosis by Literature Survey and Database Search

With the help of literature survey and search on the standard medical genetics databases, these two families of polydactyly cases were diagnosed and classified.

Following online genetic databases and resources were consulted as shown in table 1:

Table 1: Online Reference Databases for Identification and Classification of Genetic Diseases

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

Family I (with additional digits/thumb in hand)

Field visits and the Family: Family I was studied from a remote town of Rawalpindi. 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 subjects.

Pedigree analysis: The pedigree comprised of three generations (Fig.1). Total number of persons in the family was 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 consangumeous 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 recess1ve 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.

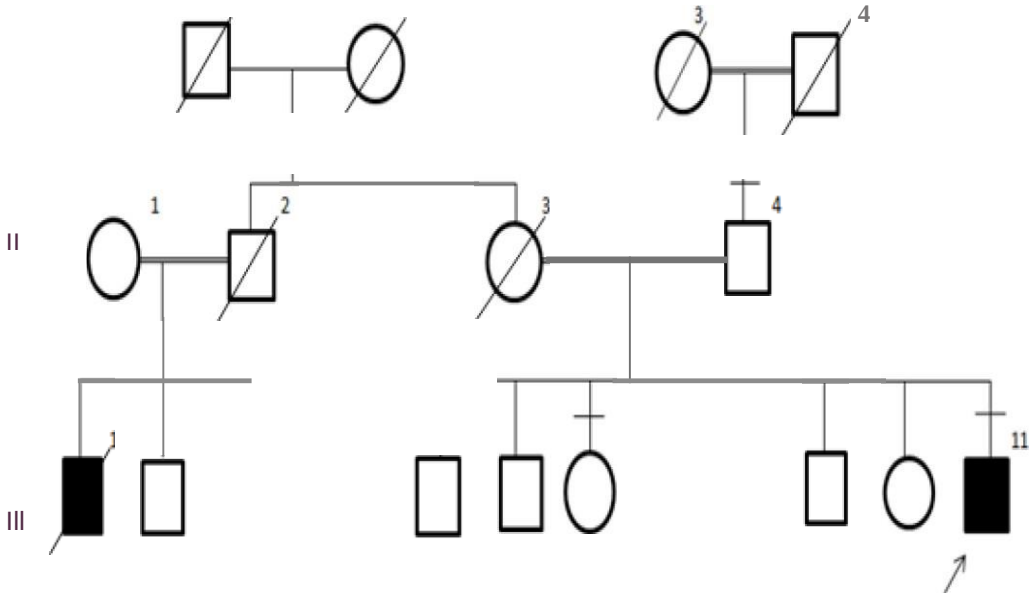

Figure 1. Pedigree ofFamily I

Clinical and Phenotypic Description: The subject III-11, a male of thirty three years. 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.2). 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 other joints were 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 are presented in Table. 2.

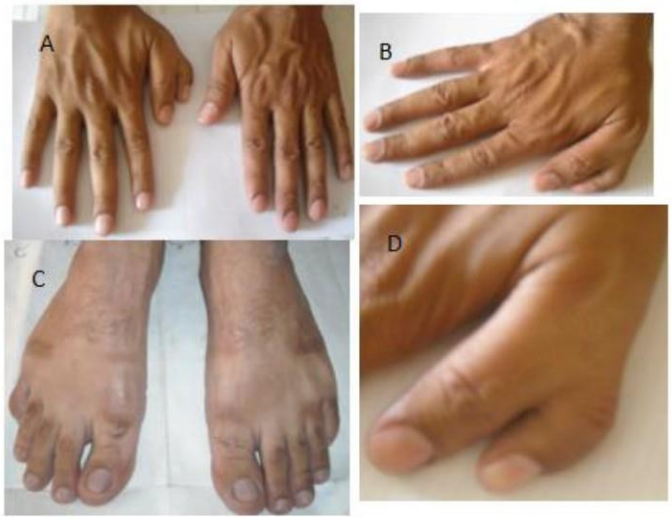

Figure 2. Photographs of hand and feet of Subject III-11 (A, B & D-Extra thumb bifurcating from proximal phalangeal joint in the right hand, C- Feet were normal)

Table 2. Clinical and Phenotypic Spectrum in Family I

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

Diagnosis and Classification: The literature survey and review of reported cases in the OMIM data base showed that clinical symptoms are 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 in (1969)**, **Miura in (1976)**, **Wood in (1978)** and **Zuidam *et al* in (2007)** 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. Polydactyly normally had autosomal dominant mode of inheritance but this family showed the autosomal recessive mode of inheritance.

Mumoli *et al.* (2007) reported a sporadic family in which a female was affected and her extra thumb was bifurcated from metacarpal while the subject of this 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.

Family II (with Additional Digit and Thumb in Hands)

Field Visits and the Family: Family IV was the resident of a small town of Rawalpindi. 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 individuals and all the available normal persons were physically observed. 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.

Pedigree Analysis: Pedigree comprised of four generations (Fig. 3). Total number of individuals in the pedigree was 23 (10 males, 11 females), of which only two males III-5 and III-12 were affected. There were five marriages in the pedigree and 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 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 but there was only one consanguineous marriage we could not justify it as autosomal dominant mode of inheritance.

Clinical and Phenotypic Descriptions: The subject III-12, male of 21 years of age, was neurologically abnormal, he was found to have extra thumb in right hand (Fig. 4). On close examination it was observed that extra thumb was partially developed and bifurcated near proximal phalangeal joint. It contained nail, bone and joint also but its movement 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 is presented in Table. 3.

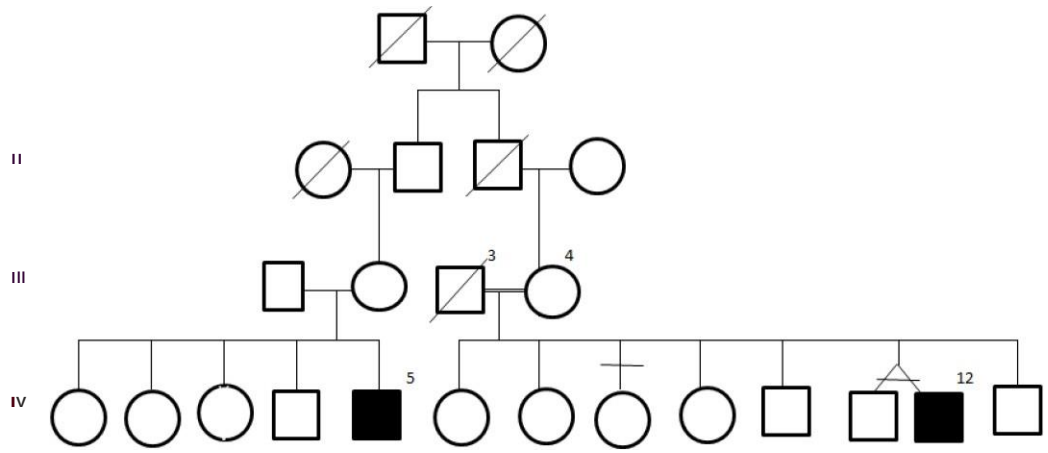

Figure 3. Pedigree of Family II
*=horizontal line over the symbols, denotes the subjects who were physically examined.

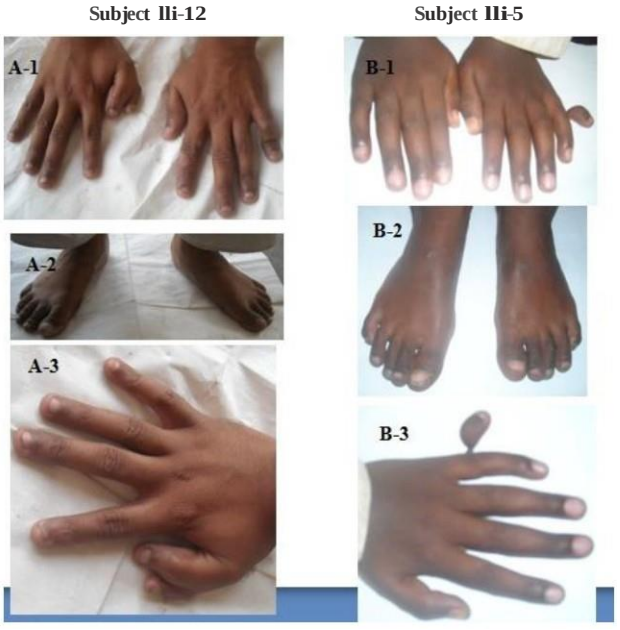

Figure **4.** Clinical spectrum of polydactyly in Family II (A1-3- An extra partially grown thumb right hand, A2- Normal feet, B1-3 An extra non functional pedunculated digit in the left hand near small finger in the left hand that was attaches to the hand with the help of small pedicle, B2- Feet are unaffected)

Table 3. 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-1
III-4	N	-	-	-	-	-	-	-

Diagnosis and classification: The literature survey and review of reported cases in the OMIM data base showed that clinical symptoms in subject III-12 were consistent with preaxial polydactyly type I **(OMIM 174400)**. According to **Temtamy and McKusick (1969)** classification it was classified as preaxialpolydactyly type-I.

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

Wassel (1969) categorized it as preaxialpolydactyly type-III. **Miura (1976)**, **wood (1978)** classified it similarly although they gave extension to the Wassel scheme. **Zuidam *et al,* (2007)** reported a similar case and classified it as preaxialpolydactyly 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)** 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.

Nicolai and Hamel (1988) described a large family in which multiple members exhibited a spectrum of preaxial and postaxial anomalies of the limbs inherited as an autosomal dominant.

Vander Meer *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.

Discussion

In the present study, 2 families showing apparently monogenic deformity with variable phenotypic spectrum of polydactyly have been investigated. Both families were non-syndromic. 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* in 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.

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.

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 subject III-5 of family IV. Both subjects 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 preaxialpolydactyly.

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 has isolated or syndromic polydactyly. Isolated polydactyly does not have any bad effect on the health and can be treated **(yahoo health, 2012)**.

Subjects with polydactyly may experience 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 preaxialpolydactyly sporadic cases and one familial family number one. The core 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.

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 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)**.

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)**.

Conclusion

All the cases reported in this study 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.

Conflict of Interests

The authors declared that there is no conflict of interest in this paper.

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