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Mode of inheritance of syndactyly in selected human families in Bahawalnagar, Pakistan

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Abstract

Syndactyly is joining or merging of web in feet and hands digits. It is inherited by autosomal dominant, autosomal recessive, x-linked, and y-linked manner. Its prevalence is around 1 in 2000 live birth. Non-syndromic syndactyly is classified into nine types. In this study, we find out prevalence, percentage, types, and mode of inheritance of syndactyly in families of district Bahawalnagar. The survey was carried out in hospitals, schools, and villages of district Bahawalnagar to find out the patients with congenital syndactyly. Three families with cousin marriages were selected for pedigrees. These families had 2:1 of foot and hand syndactyly. The percentage of complete and incomplete syndactyly was recorded 50% in all families. Mode of inheritance was autosomal dominant and autosomal recessive pattern because of two types of syndactyly type I (SD1) and syndactyly type I-c. In families Bwn1, Bwn2, and Bwn3 the percentage of family members associated with syndactyly was 16%, 9.7%, and 6.89% respectively. It was further noted that all male members of all families were affected with syndactyly. This study finds out the type I (SD1) and type I-c syndactyly in studied sample population.



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Introduction

Syndactyly, (Greek “syn” join or together and “dactyls” digits) is joining or merging of web in digits of feet and hands. It was discovered in the middle ages by Al-Zahrawi Abulcasis, a popular Andalusian surgeon [1]. Syndactyly is inherited by autosomal dominant, autosomal recessive, x-linked manner [2]. It can also be y-linked as Rayner [3] reported only infected males.

In Syndactyly soft tissues are blend without or with bony intermixing. This is the most common inherited hand disorder and around 1 in 2000 live birth. Its ratio in man is twice compared to female. Toe syndactyly is more common compared to finger syndactyly [4]. It takes place due to delimitation of alongside digits and effect by non-appearance of apoptosis in the interdigital mesenchyme during the seventh and eighth week of gestation [2]. Toe disorder is thirty-five percent and seventeen percent only are affected by webspace of the hand [3]. The incidence rate is 7 in 10000 new born, and many patients use the surgical producer at mature age [5].

The mutation in some gene and factors which cause syndactyly are the zone of polarizing activity (ZPA). This area commands specification and limb structure. When phalanges are format after 44 days of embryonic development the ZPA vanish and then fibroblast growth factor 8 (FGF8) produces on the ridges of the ectoderm and helps in limb growth.

In humans, 39 genes of *HOX* and *HOXD* inflorescence at locus chr2q31 and are involved in many syndactylies. Sonic Hedgehog (SHH) and Indian Hedgehog (IHH) are two hedgehog pathways in which the SHH signalling pathway is important for appropriate limb growth. Pretentious by SHH affect several transcription factors like *HAND2*, *GLI3*, *ALX4*, and many BMP antagonists cause syndactyly. Further, If ZPA is not working properly then it affects the SHH and cannot develop a normal limb [6].

Syndactyly is classified into four types including simple, complex, complete, and incomplete. Simple syndactyly in which only web are involved but on the other hand in complex syndactyly bones are located in different manners. The complete syndactyly, the digits are joined at the end of phalanxes while on the other hand in incomplete syndactyly the digits are not joined at the end [2]. Further it has two major categorize including syndromic and nonsyndromic syndactyly.

Syndromic syndactyly is further classified into seven types. Acrocephalosyndactyly is associated with four

types of the syndrome in which three are autosomal dominant and one is autosomal recessive respectively Apert syndrome (*FGFR2*), carpenter syndrome (*RAB23*), Pfeiffer syndrome (*FGFR1*, *FGFR2*), and saethre-chotzen syndrome (*TWIST1*, *FGFR2*).

Bardet-Biedl syndrome is autosomal recessive it is caused by twenty-plus genes. Greig cephalosyndactyly syndrome is autosomal dominant it is caused by a mutation in the *GLI3*. Pallister-Hall syndrome is autosomal dominant it is caused by a mutation in the *GLI3*. Poland syndrome is autosomal dominant it is genes are not identified. Smith-Lemli-Optitz syndrome is autosomal recessive it is caused by a mutation in the *DHCR7*. Triphalangeal Thumb-polydactyly syndrome is autosomal dominant it is caused by a mutation in the *LIMBR1* [6].

Non syndromic syndactyly is further classified into nine types. In which eight types are autosomal dominant and ninth one is autosomal recessive and the seventh one is both autosomal dominant and autosomal recessive.

Syndactyly I (SD1) also called “zygodactyly” is an autosomal dominant limb disorder it’s maybe the complete or incomplete fusion of soft tissue within the mainly third and fourth fingers or second and third toes may be involved of other digits. The incidence rate is 2-3 in 10000 newborns. In some cases, only hands are affected and, in some cases, only feet are affected. The Location is the first SD I locus at the 2q34-q36 region in a large German family [7, 8].

Syndactyly was also recorded in syndromic condition. For example, long QT syndrome. In long QT syndrome, temporary AV valves blocks. Syndactyly has recorded QT syndrome. Marks, Trippel [9] recorded five patients three are males and two females. All were infected with syndactyly and long QT syndrome in which 4 patients had died in early childhood. Syndactyly is also recorded with Apert syndrome, an acute autosomal recessive disease distinguishes by craiosynostosis (fusion of premature cranial structure). Apert syndrome was linked with bilateral bony syndactyly of hands and feet [10, 11]. Whyte, Deepak Amalnath [12] recorded syndactyly with Sclerosteosis. Many surgical treatments had developed for syndactyly since the time of discovery [13]. Straight cutting is used in 19th century [14]. Numerous ideas, concepts, and theories had been developed and normally taken up. For example, flaps were used for the formation of web and wrapping of fingers for skin grafts. [15]. In recent scenarios, pediatric plastic surgery is used in

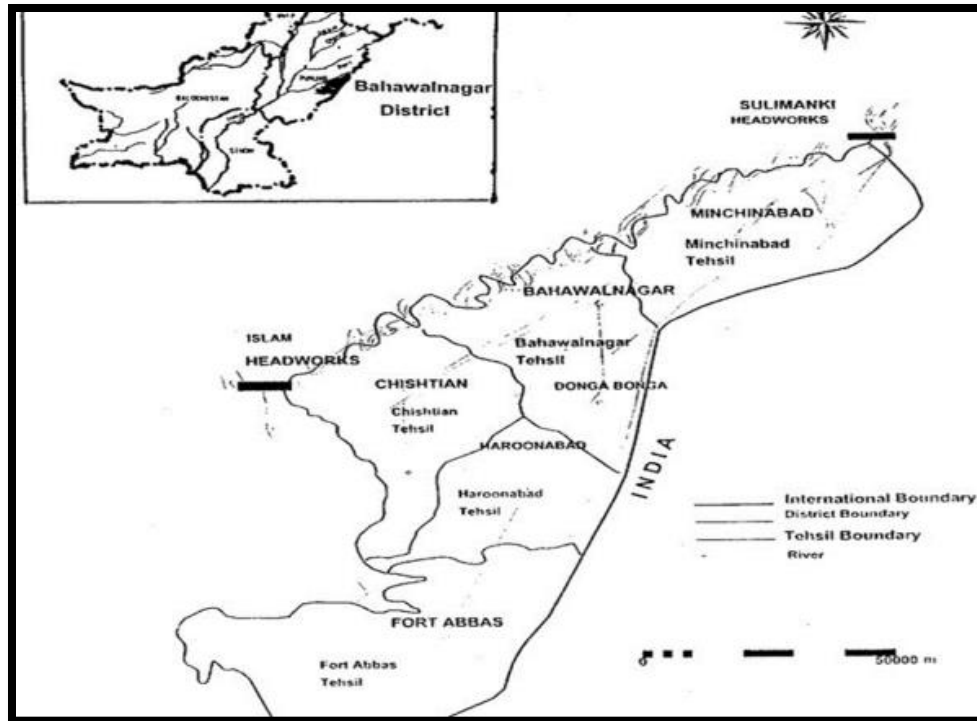


Fig. 1: Map of district Bahawalnagar (Source: https://www.researchgate.net/figure/Map-of-Bahawalnagar-District_254426077)

regeneration techniques instead of utilizing skin grafting [16]. This study was designed to determine the syndactyly in families of district Bahawalnagar.

Materials and Methods

Study population

This study was based on hereditary disorder syndactyly, mode of inheritance, and prevalence in the families. To visit the families, permission letters from the University of Okara Department of zoology was obtained, and visits the Hospitals, schools, and villages of the District of Bahawalnagar. Consent was also taken from the participants. This Consent form was signed by the affected families to assure that the information and data were taken with their complete willingness and harmony without any pressure (**Data provided to journal**).

Study area

Hospitals in district Bahawalnagar were visited for data collection and families' selection. THQ Minchanabad, DHQ Bahawalnagar, National Hospital Bahawalnagar, Arif hospital Bahawalnagar and Atif clinic Bahawalnagar were visited (**Fig. 1**).

All participants were interviewed to find out the Genetic disorder particularly syndactyly and to construct the pedigrees to find out the origin of mutation among each family. Both public and private sector schools were also visited for tracing the affected families.

Villages

Different villages like Mulligarh, Chack hootiana, Rojhan vali, Toba qalandar shah, Basti dhudian, Santeaaka, Takhat mahal in district Bahawalnagar were also visited for tracing the syndactyly affected families. The majority of the inhabitants of these villages were unknown to genetic disorders and their causes, therefore, presentations were given at different sites in the village, and people were convinced to share their family history. After detailed visits, three families were selected for study and to construct the pedigree. The pictures of affected individuals were also taken with the consent of each family.

Pedigree analysis

Three families were selected for pedigree analysis. Each family was detailed interviewed, and a pedigree was constructed on the spot. The prevalence of the

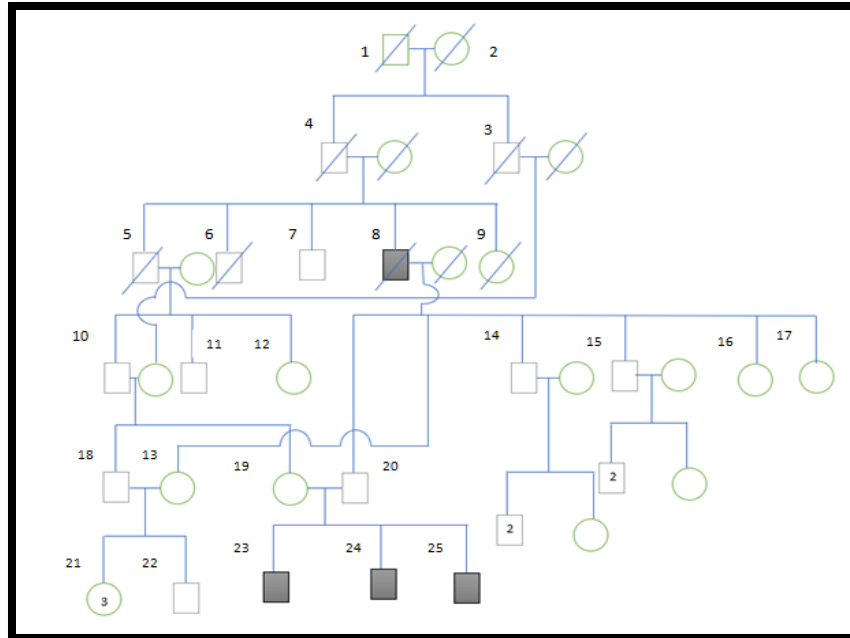


Fig. 2: Pedigree of family Bwn1 showing six generations with four affected males



Fig. 3: (A) Family member 24 with incomplete syndactyly in one foot, (B) Family member 23 affected with complete syndactyly in both feet, (C) Family member 25 affected with complete syndactyly in right feet and incomplete in left feet and (D) Three brothers with syndactyly.

syndactyly among each family and origin of mutation was recorded through pedigree analysis.

Results

Family Bwn1

Family Bwn1 belongs to district Bahawalnagar, province of Punjab, Pakistan. Affected members

were present in three-generation. One male was affected in some generation. The autosomal recessive mode of inheritance pattern was recorded among the family members.

Clinical examination of affected members showed the syndactyly type I in feet because physically 2nd and 3rd toe finger in feet was webbed. The pedigree sketch (**Fig. 2**) showed six generations consisting of 27 family members with one affected member in the

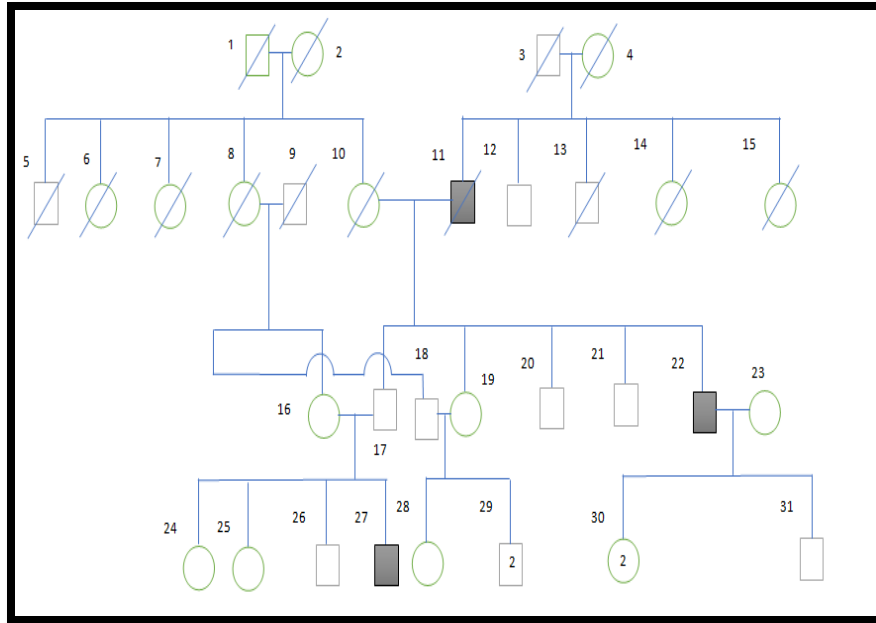


Fig. 4: Pedigree of family Bwn2 showing all affected males



Fig. 5: (A) Family Bwn2, member 22 with incomplete syndactyly and (B) Family Bwn2, member 27 with incomplete syndactyly

third generation and three in the sixth generation. The family was suffering from non-syndromic type syndactyly type I and also known as zygodactyly. In this family, three members in sixth-generation had a different manner of webbing of digits in three brothers. Family member number 23 had webbing their feet fingers 2nd and 3rd and present in both feet

with complete syndactyly (**Fig. 3B**). Family member number 24 had webbing their feet fingers 2nd and 3rd but webbing of 2nd and 3rd finger was present only in left feet with incomplete syndactyly (**Fig. 3A**). Family member 25 had webbing their feet fingers 2nd and 3rd but webbing of complete syndactyly was

present in 2nd and 3rd finger in right feet but in left feet the syndactyly was incomplete (**Fig. 3C**).

Family Bwn2

Family Bwn2 are living in in district Bahawalnagar, province of Punjab, Pakistan. The affected members were present in three generations with at least one male in each generation. The mode of inheritance was an autosomal dominant pattern.

Clinical examination of affected members showed the syndactyly type I in feet because physically 2nd and 3rd toe finger in feet were partially webbed. The pedigree sketch (**Fig. 4**) shows four generations consisting of 31 family members with one affected male in the 2nd, 3rd and 4th generations. It was also a non-syndromic type. In this family, numbers 22 and 27 were affected with syndactyly type I in which 2nd and 3rd fingers was incomplete webbings with no bones intermixing (**Fig. 5A&B**).

Family Bwn3

Affected members were present in two generations. Fourth-generation was not affected but both children male and female affected with thalassemia. This family mode of inheritance was also autosomal dominant.

Clinical examination of affected members showed the difference from the other two families. In this family, members were affected with syndactyly type I-c with 3rd and 4th webbed fingers. The pedigree (**Fig 6**) showed four generations consisting of 29 family members in which two males were infected with syndactyly type I-c in the second and third generation and one male and one female were infected with thalassemia. This syndactyly was also non-syndromic type.

Family members 17 and 24 had joined soft tissues third and fourth digits with complete syndactyly (**Fig. 7A&B**). Overall, in three families in district Bahawalnagar were affected with syndactyly, the ratio of foot and hand syndactyly was 2:1.

In three families the numbers of affected members were nine. However, exact data with picture and clinical examination were seven and two members had been died. Three members were affected with complete and three with incomplete syndactyly. One member was affected with one foot with complete syndactyly and another foot with incomplete syndactyly.

Family Bwn1 was consisting of twenty-five members of which four members were affected with

syndactyly (16%). Family Bwn2 was consisting of thirty-one members of which three were with syndactyly (9.7%). Family Bwn3 consisted of twenty-nine members of which two members were with syndactyly (6.89%) (**Fig. 8**).

Discussion

Syndactyly is joining or merging of web in digits of feet and hands. It is inherited by autosomal dominant, autosomal recessive, x-linked [2], or y-linked as reported by Rayner [3] through pedigree in which only males were infected. Ghadami, Majidzadeh [17] described the Iranian family affected with the complete and incomplete syndactyly type I. Syndactyly in the asymmetric form are less common compared to symmetric form. Mostly all patients had ectodermic webbing of soft skin between 3 and 4 fingers in hand or 2 and 3 fingers in toe. Patients of foot syndactyly are widening of distal phalanges as compared to normal toe fingers. Our findings were similar to Ghadami, Majidzadeh [17] as in our study, the families are affected with complete and incomplete syndactyly type I, and all affected individuals were also infected with symmetric syndactyly. Toledo and Ger [18] had a family pedigree and determined the ratio of simple, incomplete, and complete-complex that was 32%, 31%, and 37% respectively. They found that syndactyly mostly occurs in the middle and ring fingers of hands, the thumb and index finger are webbed at minimum range. The mode of inheritance in the family was an autosomal dominant pattern. Our results were replicated to Toledo and Ger [18]. As in our study, the ratio of complete and incomplete syndactyly was 50% and our family Bwn3 has also webbed middle and ring fingers. The mode of inheritance in all three families was autosomal dominant.

Rayner [3] described that females are less affected than males. 48% were affected with the bilateral syndactyly and 35% with toe syndactyly. The fourth webspace of hand was only 17%. This was also similar to our findings as all the males were affected and bilateral syndactyly present in the toe and unilateral syndactyly in hand.

Li and Li [19] studied limb defects in a fetus with homozygous α -thalassemia. The fetus showed limb reduction defect with no clinical feature of syndactyly. The results of our study contradicted from Li and Li [19] as we found a family Bwn3 affected with syndactyly type I-c, in which the individuals of two generations were affected with

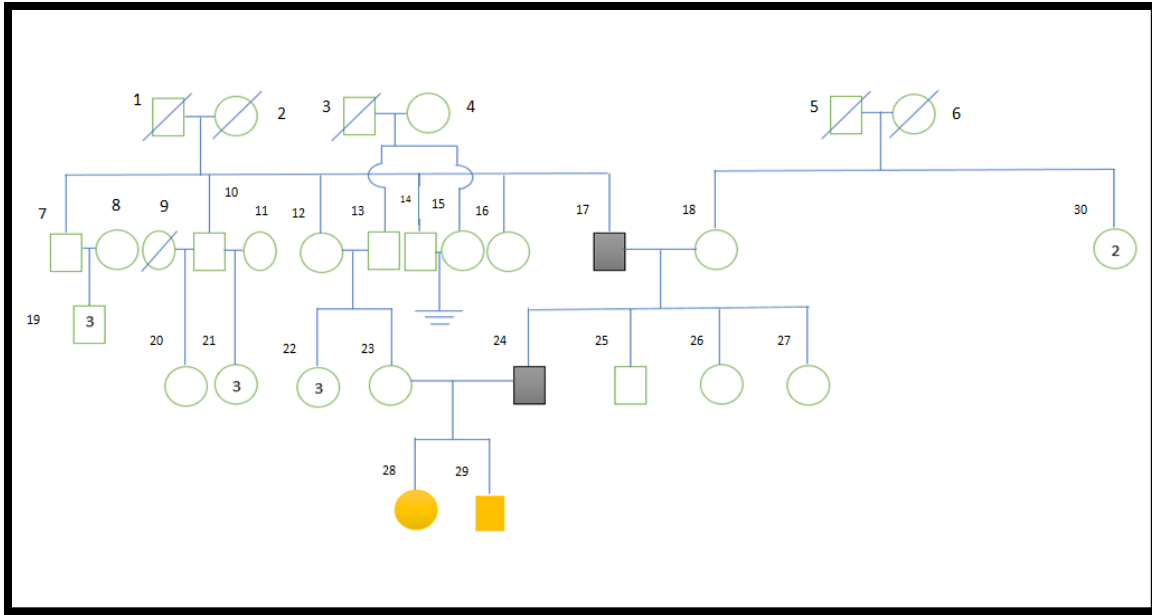


Fig. 6: Pedigree of family Bwn3, two males with hand syndactyly



Fig. 7: (A) Family member 17 which affected with hand syndactyly and (B) Family member 24 with hand syndactyly

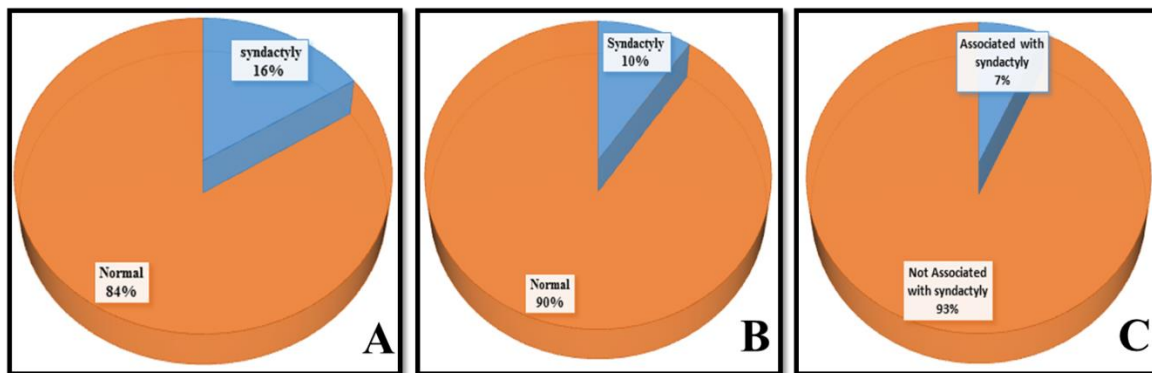


Fig. 8: (A) Percentage of Syndactyly in family Bwn1, (B) family Bwn2 and (C) family Bwn3

Table 1: Percentage of family members who are associated and not associated with syndactyly

Sr #	Family	Total Families	Syndactyly associated	%age
1	Bwn1	25	4	16
2	Bwn2	31	3	9.7
3	Bwn3	29	2	6.89

syndactyly type I-c and the two individuals (1 male & 1 female) of third-generation were affected with thalassemia. Clinical features of syndactyly were absent in the individuals of the third generation affected with thalassemia.

Conclusion

The present study concluded that all male members of all families were affected with syndactyly. The disorder was type I (SD1) and type I-c syndactyly in studied sample population. The studied population was suggested to avoid the cousin marriages.

Conflict of interest

The authors declare no conflict of interest.

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