Pedigree Analysis Of Some Hereditary Diseases in The Successive Five Generations Of A Family Of Punjab With Special Reference To Syndactyly

Dr. (Mrs.) Sushil Gupta
Associate Professor
Dev Samaj College for Women
Firozepur City-152002 (Punjab) India.
(Received December 2014, revised and accepted August 2015)
Hemant Garg
SGRD Dental College and Research Institute, Amritsar, India

ABSTRACT
Syndactyly [from Grek roots ‘Syn’-together+ ‘Dactylus’- [finger ]=fingers together is a condition where tow or more than two digits are fused together. It occurs normally in some mammals, such as siamang but is unusual condition In humans. Syndactyly can be simple, complex or complicated. Syndactyly can be possible out come of a large number of rare inherited and developmental disorders. It can be present over 100 different disorders where they are minor features compared to other characteristics of these disorders. Pedigree Analysis of some hereditary diseases in the successive five generations of a family of Punjab [INDIA] with special reference to Syndactyly was carried out. Some other inheritable characters observed were Greigcephalopolysyndactyly, presence of Flat Feet, Early teeth fall, Early greying of hair, Presence of bow legs, Heart problems, Osteoporosis, Baldness , Asthma, Gout, Ulcerative colitis, Eye defects, upper palate missing and Stammering defect. They may be due to some changes in the same chromosomes which causes Syndactyly or not. This may form basis for further studies.

Keywords: Syndactyly, Greigcephalopolysyndactyly, Osteoporosis and Ulcerative colitis.
INTRODUCTION

Syndactyly (from Greek roots “syn”- (together)+ “dactylos”- (finger) = fingers together) is a condition where two or more than two digits are fused together. It occurs normally in some mammals, such as siamang but is an unusual condition in humans.

Syndactyly can be simple or complex. In simple syndactyly, adjacent fingers and toes are joined by soft tissue. In complete syndactyly, the skin is joined all the way to the tip of the fingers. In incomplete syndactyly the skin is only joined part of the distance to the finger tip. In complex syndactyly, the bones or cartilage of the adjacent digits are fused. The kangaroo exhibits complex syndactyly.

Complicated syndactyly occurs as a part of syndrome (such as apert’s syndrome) and typically involves more digits and with complex syndactyly there may be abnormalities of nerves, vessels and tendons. Syndactyly results from the failure of the programmed cell death that normally occurs between digits, most often this is due to genetic defects. There are several forms of syndactyly, each of these where the genetics is understood, is caused by an autosomal dominant gene. Syndactyly is also possible out come of a large number of rare Inherited and developmental disorders. It can be present over100 different disorders where they are minor features compared to other characteristics of these diseases.

An incidence of occurrence of syndactyly in decreasing order of frequency is as follows:-
- Between the middle and ring fingers (57%)
- Little and ring fingers (27%)
- Middle and index fingers (14%)
- Thumb and index fingers (3%)

Males are affected twice as often females, (http.Syndactyly) complete simple syndactyly of all digits with polysyndactyly involving both hands and feet is rare.[Hosalkar et al,2000]

SUBJECTS AND METHOD

No single individual served as the proband in this kindred since various affected members were brought to our attention during the course of other genetic studies being conducted in the towns of Punjab. The pedigree (fig.1 ) was structured through interviews with nearly 75% of the living members in the last four generations. In the information on the first two generations was supplied by the one of the living member of the family who is considered reliable.

Individuals were examined in their houses for the digital and other defects. Photographs of the most affected members with syndactyly were taken with a camera. X-rays were also done of few available members. Information regarding other defects was collected by asking oral questions from them.

RESULTS

SLIDES A,B,C,D and E showing

The pedigree chart of the family with
A. Slide showing inheritance of Syndactyly, Asthma, Griegcephalo polysyndactyly and distal phalanx inturned.

B. Slide showing inheritance of heart problems, ulcerative colitis, colour Blindness, upper palate missing, stammering and gout.
C. Slide showing inheritance of osteoporosis, Early Teeth Fall, Eye Defects and Baldness.

D. Slide showing inheritance of Flat Feet and Grey Hairs.
E. Slide showing inheritance of BowLegs.
inheritance of different characters

In the male member of Gen 1 terminal phalangeal bones of all fingers of both hands were inturned (bent fingers). This character appeared only in one member of Gen. 1 and all others were normal. (SLIDE A)

In generation II female no. 3 of the family inherited this character of bent fingers from her father. Some other defective characters e.g. flat feet, early teeth fall, early graying of hair, leg turned in ward, osteoporosis etc. appeared in her. She died due to heart attack. The inheritance pattern of these characters was observed in successive three generations. Syndactyly appeared in Gen.III and inherited in Gen IV & V. (SLIDE A,B,C,D and E)

Syndactyly was observed in the members of Gen. III-1,2,5,7 no. of males(SLIDE A) Gen. IV-7,11,13,19,21(SLIDE A) Gen. V-21,22,34,36(SLIDE A)

The 1,2 individuals of generation III and 22 male of Gen. V died immediately after their birth due to greigcephalopoly syndactyly. (SLIDE A)

5 no male of Gen III showed complete simple syndactyly in between 3 and 4th fingers of left hand.

7 no male of Gen III showed complete Complex syndactyly in between 3 and 4th fingers of left hand (PHOTO FILE 011.jpg) but complete complex syndactyly in 3rd and 4th fingers of right hand (PHOTO FILES 010.jpg, 012.jpg, 013.jpg AND 014.jpg).

Syndactyly of 4th and 5th toes of right foot was also observed. Small toe always remained under 4th toe (photo)

7 number male of Gen IV showed complete simple syndactyly in between fingers of left hand (PHOTO FILES 007.jpg and 009.jpg) but complete complex syndactyly in between 3rd and 4th fingers of right hand. (PHOTO FILES 008.jpg and 009.jpg, X-RAY 4X6d.jpg) Small toe was present under 4th toe.

11 number male of Gen IV showed complete simple syndactyly in between 3 and 4th fingers of left hand. (PHOTO FILES 015.jpg,016.jpg and 017.jpg)

13 number male of Gen IV showed complete simple syndactyly in between fingers of right hand syndactyly was also observed in 4th and 5th toes of right foot. To separate the fingers his hand was successfully operated.

19 number male of Gen IV showed complete Simple syndactyly in between 3 and 4th fingers of Right hand (PHOTO FILE 004.jpg) and Complete Complex Syndactyly in between 3rd and 4th fingers of left hand (PHOTO FILES 001.jpg, 002.jpg and 003.jpg). Right foot also showed syndactyly between 4th and 5th toes.

21 number female of Gen IV showed complete complex syndactyly in between fingers of both hands. She was operated to separate the fingers but operation was not successful.

21 number male of Gen V showed complete simple syndactyly in between 3 and 4th fingers of left hand (PHOTO FILES 018.jpg, 019.jpg and 020.jpg).

34 number female of Gen V showed complete complete syndactyly between 3rd 4th fingers of right hand.

Some other inheritable characters appeared in the female of gen. II are also heritable and observed in the subsequent generations. They may be due to some changes in the same chromosomes which is causing syndactyly or not. This needs further investigations. Observations are given below –

(1) **Flat Feet** – Character appeared in the members of
Gen II-3 (SLIDE D)
Gen III- 4,5,6,7,8,9&10 (SLIDE D)
Gen IV- 5,7,10,11,12,14,18,19,& 20
(SLIDE D)
Gen-V- 33 (SLIDE D)

2) Early teeth fall character was observed in
Gen II-3 (SLIDE C)
Gen III- 3,4,5,6,8,9 & 10 (SLIDE C)

3) Early Graying of hair was observed in the members of
Gen II- 3(SLIDE D)
Gen III- 3,4,5,6,7,8,9 and 10 (SLIDE D)
Gen IV - 1,2,4,5,6,7,12,13,15,18 ,19
and 20 (SLIDE D)
Gen V-31,33 (SLIDE D)

4) Legs turned in wards(Bow Legs) appeared in the members of
Gen II-3 (SLIDE E)
Gen III- 3,4,5,6,7,8,9 &10 (SLIDE E)
Gen IV- 1,2,3,4,5,6,7,9,10,11,12,13, 14, 16,18,19 &20. (SLIDE E)
Gen V-11,12,32,33,34.(SLIDE E)

5) Heart problem was observed in the members of
Gen II- 3 no female died to heart attack.
(SLIDE B)
Gen III-4,5,6 No males died due to heart attack 8,9, no male and 10th no female are suffering from heart problem.
(SLIDE B)

6) Osteoporosis appeared in the members of
Gen II- 3 number female (SLIDE C)
Gen III 3,4,5,6,8,9,& 10 (SLIDE C)

7) Baldness character appeared in member of
Gen IV-11.(SLIDE C)

8) Asthma was observed in
Gen II 3 number female.(SLIDE A)
Gen III-4,6,10 (SLIDE A)
Gen IV-5,9(SLIDE A)

9) Ulcerative colitis appeared in
Gen IV-4, 14. (SLIDE B)

10) Gout was observed in
GenIV-10 (SLIDE B)

11) Eye defects were observed in
Gen IV- 2, 3,7,14,15,16,17 (SLIDE C)
Gen V- 15,17,33,34(SLIDE C)

12) Upper plate missing in one member of
Gen- V-17 (SLIDE B)

13) Stammering defect in one member of
Gen IV-18 (SLIDE B)

**DISCUSSION**

On the basis of study of 63 pedigree Bell proposed a classification of syndactyly based primarily on the localization of the webbing. [Bell,1953]

**Type A1** - Webbing occurs between the second and third toes with no involvement of the hands.

**Type A2** - Webbing between the third and fourth fingers

**Type B1** - Webbing between the fourth & fifth toes.

**Type C** - Webbing occurs between three or more digits in one or more extremities.

In some pedigrees, however multiple digital anomalies were present and these were considered combinations of the above types such as A1 with A2 or A2 with B1.

After reviewing the literature and studying additional families five types of syndactyly was concluded.[Temtamy,1966]

**Type 1** - Syndactyly of the third and fourth fingers and the second and third toes.
**Type II** - Syndactyly between third & fourth fingers and fourth and fifth toes.

**Type III** - Syndactyly involves the fourth and fifth fingers only.

**Type IV** - Complete syndactyly of all fingers.

**Type V** - Syndactyly is associated with metacarpal and metatarsal synostosis.

Each of these types is inherited as an autosomal dominant malformation with variable expressivity and incomplete penetrance. [Cross et al, 1967]

Syndactyly with metacarpal 4-5 fusion with X linked recessive inheritance was also reported. [Orel, 1928; Holmes et al, 1972]

Inheritable syndactylism is associated with genetic defects involving particular candidate regions on the second chromosome. [Kozin, 2001]

Five type of syndactyly have been identified in humans. [Flatt, 2005] The corresponding loci associated with these types and their common phenotypical expression are as follow-

**Type I** - 2q34-2q36, Webbing occurs between middle and ring fingers and/or second and third toes. [Bosse et al, 2000]

**Type II** – 2q31, Involves long and ring fingers but has a sixth finger merged in between. [Sarfarazi et al, 1995]

**Type III** – 6q21-23, Small finger is merged into the ring finger. [Sarfarazi et al, 1995]

**Type IV** – 7q36, involves all fingers and toes. [Sato et al, 2007]

**Type V** – 2q31-q32, similar to type I but the metacarpals and metatarsals may also be fused. [Sato et al, 2007]

Synpolydactyly and HOXD13 polyalanine repeat were reported and it was found that addition of 2 alanine residues is without clinical consequences. [Malik et al, 2007] Type II syndactyly is characterized by webbing between 3/4 fingers and 4/5 toes with partial or complete digit duplication with in the dactylus web Three loci have been identified at chromosomes 2q31, 22q 13.31 and 14q 11.2 q12 and have been designated as SPD1, SPD2, SPD3 respectively. [Apert, 1956 and Akarsu et al, 1956] Unique expansion mutations in a polyalanine repeat (PolAR) of HOXD 13 have been implicated in SPD1 families.

Syndactyly between the third and fourth fingers and between the fourth and fifth toes, with partial or complete digit duplication in the synpolydactyly web In most cases this condition is caused by mutations in the HOXD 13 gene which is located on chromosome 2q31. [Akarsu et al, 1996; Muragaki et al, 1996 and Goodman et al, 1997] Classical SPD has been shown to be due to different sized expansions of an imperfect trinucleotide repeat sequence encoding a 15 residue-N terminal polyalanine tract in HOXD-13. An atypical form of SPD, associated with a novel foot phenotype is related with two differing intragenic deletions in HOXD 13. [Goodman et al, 1998] A distinct form of SPD which is not accompanied by an expansion of the HOXD 13 polyalanine tract was also reported and it seems to co-segregate in the family with an apparently balanced translocation t (12:22) (p11.2, q13.3). A Chinese pedigree with congenital synpolydactyly showing partial or complete webbing between 3&4 fingers was analysed and syndactyly type I,II and III were mapped to 2q34-36, 2q31-q32 and 6q21-23.2 respectively. This condition is inherited as an autosomal dominant trait with reduced penetrance. [Deebere et al, 1996; 1998 and 2000]

Syndactyly type II is named synpolydactyly
(SPD). Expansion of polyalanine tract in HOXD 13 gene is known to cause synpolydactyly. HOXD 13 gene locates in the HOXD complex. Nine homologous genes (HOXD1-D3-D4-D8-D9-D11-D12-D13) of HOXD complex locate on chromosome 2 in order of HOXD 1 to HOXD 13, among which HOXD13 is closest to the centromere. Deletions and duplications in HOXD complex or its upstream regulator factors have been identified to cause hand heteroplasia and consequently lead to the abnormalities of finger number or abnormalities of configuration. Synpolydactyly (SPD) locus in the Chinese han population is in the region of chromosome 2q31-q32 but a different casual gene can be involved.[Qin et al,2003] A pedigree of Belgian family, a father and his two daughters all have a complex type of SPD associated with metacarpal and metatarsal synostoses. These individuals also have an abnormal karyotype t(12.22),(p11.2,q13.3). In these members of Belgian family which cosegregate with t(12.22),(p11.2, q13.3) chromosomal translocation.[Desmet,1996] 12 break point of this translocation maps to 12p11.2 between markersD12S1034 and D12S1596 were prepared for the chromosome which showed that mutation in the HOXD 13 gene is not responsible for the phenotype and presented a physical map of the region around the 12p11.2 break point. A search for expressed sequences with the contig have so far revealed one CpG island, Seven anonymous ESTs and three previously characterized genes, DAD,R KRA and HTZ, all of which were found not to be directly disrupted by the translocation. The gene represented by EST R72964 was found to be disrupted by translocation20.

Greigcephalopolysyndactyly syndrome [Biesecker,2008] is caused by the loss of function mutation in the GL 13 transcription factor genes and is inherited in an autosomal dominant pattern. The disorder is allelic to the Pallister Hall Syndrome and one form of Acrocollasal Syndrome.[Williams et al,1997] More than 75% of patients with clinically recognizable GCPS who have been evaluated in NIH study have been found to have mutations in GL13.[Johnston et al,2003] Mutations shown to cause GCPs include nonsense, missense and spilicing mutations and translocations, deletions and insertions.[BIESECKER,2008; and Johnston et al,2003]

ACKNOWLEDGEMENTS:

It is my great privilege to acknowledge Miss. Sonia (Prof. in Computer Sciences) of Dev Samaj College who rendered her services for the preparation of manuscript and Pedigree chart.

BIBLIOGRAPHY


THE SCIENTIFIC TEMPER
ISSN 0976 8653

VOL -VII, No. 1&2, January-2016
