



# Clinical characterization of Post-axial Polydactyly

Review article



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## Abstract

Polydactyly is among the most common congenital limb malformations, presenting at an estimated incidence of 1 in approximately 700–1,000 live births. Clinical manifestation of polydactyly remains poorly understood because of their phenotypic variabilities and genetic diversity. Prenatal ultrasound screening can detect polydactyly and can alert the health care worker and the pregnant woman to proceed with further anomaly screening to exclude possible concomitant anomalies. The aim of this review is to provide an overview of the genetic basis of non-syndromic post axial polydactyly (PAP) and discuss the role of biological pathways in non-syndromic PAP to help clinicians understand and characterize the disease.

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## Public Interest Statement

Current study presented here help clinicians to diagnose and characterize the disease to alert the health care worker and the pregnant woman to proceed with further anomaly screening to exclude possible concomitant anomalies, moreover, help molecular biologist to understand the molecular basis of non-syndromic post axial polydactyly.

## Introduction

Hyperdactyly or polydactyly, is a commonly occurring hereditary limb malformation (1,2), with an incident rate, ranging from 0.37 to 1.2 cases per 1000 live births, its incidence also varies between different racial groups (3, 4). Polydactyly is a malformation characterized by having extra digits on feet/ hands (5). Polydactyly of hands and feet both can have different morphologic phenotypes (6), and the extra or abnormal digits can be either superficial or functional (7). Likewise, many of the effected ones undergo surgical removal of the extra digits (6). This malformation results from a defect occurring during limb development stage, mostly at the stage of anterior-posterior patterning of limb bud development. Polydactyly can occur as a syndromic form or as an isolated form (7).

## Postaxial Polydactyly (PAP)

Two clinical manifestations of postaxial polydactyly are reported that are PAPA and PAPB. In postaxial polydactyly type A (PAPA) an extra digit is well developed and fully formed like a normal digit while in type B, the extra digit is in the form of a skin tag referred to as pedunculated post minimus (8, 9). Sporadic cases of polydactyly are known to occur in normal healthy individuals. Thus there is considerable genetic heterogeneity of the malformation (9). This type of polydactyly is characterized as the duplication of the finger/toe from the ulnar or fibular side of hand or feet, respectively (10). The prevalence of postaxial polydactyly in live birth is 1-2 out of 1000 (11). Postaxial polydactyly type A is characterized as a completely developed extra digit at ulnar or fibular side with dominant inheritance pattern or autosomal recessive inheritance. While postaxial polydactyly type B is characterized with having undeveloped or partially developed fifth digit in the form of skin tag generally appearing as pedunculated postminimus (8, 9, 10). Both PAP-A and PAP-B have variations in the inheritance pattern, penetrance estimates and severity (12).

## Postaxial Polydactyly (PAP) Type A

postaxial polydactyly type-A, the supernumerary digit is fully developed and articulate (<30–180°) with the 5<sup>th</sup> metacarpal or metatarsal, either duplicated metatarsal/metacarpal (8). The extra or duplicated finger may have more than one bony elements and developed clear nail, wrinkles on skin tags on digit. PAP-A is further classified for the disease-causing genes and loci. There are eight different types of postaxial polydactyly (13). Recently, PAPA9 has been reported caused by *FAM92A* gene on 8q21.13-q24.12 (14).

**PAP-A**

Umair et al. (2018)<sup>13</sup> categorized Postaxial polydactyly into eight different types on the basis of phenotypes and the causative genes involved in the inheritance of this type of Polydactyly. Recently, a new type PAPA9 was published (14). The non-syndromic polydactyly types (PAPA1-PAPA9) are caused by mutations in six different genes including *IQCE*, *ZNF141*, *GLI1*, *GLI3*, *PITX1*, *MIPOL1* and *FAM92A* (14). These genes regulate different pathways at embryonic limb developmental stages (15,13). PAP-type 8 without or with Ellis-Van Creveld syndrome (EVC) involve diminished Hh signaling pathway due to truncation in *GLI1* (16).

**Postaxial Polydactyly Type A1 (PAPA1)**

There is a well-developed extra digit on the 5<sup>th</sup> metacarpal that is reported for this type of Polydactyly with autosomal dominant inheritance pattern in non- syndromic cases. Mutation in the causative gene was reported on *GLI3* at 7p14.1 (17, 18).

**Postaxial Polydactyly Type A2 (PAPA2)**

In this type of polydactyly, the clinical features or phenotypes are same like that of PAPA1 and show autosomal dominant inheritance pattern but this is mapped at chromosomal locus 13q21-q32 instead of *GLI3*. The exact gene is still not identified (19).

**Postaxial Polydactyly type A3 (PAPA3)**

There is a well-developed extra digit in hands and feet in this type of polydactyly. Variable phenotypes with unilateral or bilateral digits are found. No syndactyly is observed for PAPA3 (MIM 607324). This type of polydactyly shows incomplete autosomal dominant inheritance penetrance. This type was linked to chromosome 19 at locus 19p13.1-13.2 (20). But still the gene involved is not recognized.

**Postaxial Polydactyly type A4 (PAPA4)**

Partial cutaneous syndactyly along with postaxial polydactyly is present in this type of polydactyly (MIM 608562) inherited in an autosomal dominant manner (21).

**Postaxial Polydactyly type A5 (PAPA5)**

Postaxial polydactyly of this type shows autosomal recessive mode of inheritance. Clinical features of PAPA5 (MIM 263450) include the presence of a sixth digit both in hands and feet, the hallux vallux deformity and fifth metatarsals of feet in partial duplicated fork shaped form. Through genome mapping it is linked on chromosome 13q13.3-q21.2. The candidate gene in this locus is not identified (10).

**Postaxial Polydactyly type A6 (PAPA6)**

PAPA6 have wide bilateral, well-formed duplicated fifth digit that is deviated to either ulnar or radial side. The inheritance of this type of polydactyly is autosomal recessive. Missense mutation in zinc finger gene *ZNF141* located on chromosome 4p16.3 was reported for this type of Polydactyly (10).

**Postaxial Polydactyly type A7 (PAPA7)**

PAPA7 (MIM617642) was characterized with well-developed nails to lower limbs. The inheritance pattern of this type is autosomal recessive. A homozygous splice site variant was reported in *IQCE* which alters the Hedgehog *Hh* signaling pathway as this gene "*IQCE*" is the positive mediator of this pathway (22).

**Postaxial Polydactyly type A8 (PAP-A without or with EVC Phenotype)**

PAPA associated with EVC having phenotypes of atrial septal defects, mild nail dysplasia, short stature or genu valgum are some syndromic feature associated with the EVC along with Polydactyly. *GLI1* gene causing PAPA-EVC have been reported by (16). The mutational position and the *GLI1* dosage effect might be associated with the phenotype spectrum of type A Postaxial Polydactyly without or with EVC syndrome (16).

**Postaxial Polydactyly type A9**

A newly identified *FAM92A* gene at chromosome 8q21.13-q24.12 with nonsense mutation for the phenotypic expression of polydactyly, recently reported and conformed the Homozygosity in non-syndromic polydactyly with autosomal recessive inheritance pattern (14).

**Postaxial Polydactyly type B**

Postaxial polydactyly type B is the most common one among all types of Polydactyly. The extra digit may appear as a skin tag from the ulnar side of the fifth finger and not fully developed and variably articulated along the nubbin. The estimated penetrance is 43% while the limbs and left hand is more affected (23, 24). Both PAP types A and B due to their different segregation patterns and independent occurrences have been suggested two separate and genetically heterogeneous groups (23, 8). However, the contributory gene for both types (PAPA1 and PAPB) is *GLI3* located on chromosome 7p14.1 (25, 26).

**Conclusion**

The skeleton contains more than two hundred skeletal elements, which are composed of bones and cartilage. Development of the limb is regulated by several proteins members of signaling pathways. Sequence variations in genes encoding these proteins involved result in various types of human skeletal deformities. This included hereditary polydactyly, which is

caused by abnormal patterning of the limb. Polydactyly occurs in syndromic or non-syndromic form. For Post-axial polydactyly (PAP), four non-syndromic autosomal dominant and similar numbers of autosomal recessive loci have been reported. For these eight loci, six genes including *GLI3* (7p13), *ZNF141* (4p16.3), *IQCE* (7p22), *GLI1* (12q13.3), *FAM92A* (8q22.13), and *KIAA0825* (5q15) have been identified. Proper genotype-phenotype associations might assist in upcoming genetic testing, control medical impairments, develop our acquaintance about newly identified diseases and their associated genes thus providing substantial knowledge about large number of variants recognized through NGS technologies, which in recent years might be used for screening and molecular diagnosis in the near future.

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#### **Authorship and Level of Contribution**

The authors equally contributed in the research, writing and revision of the paper.

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