Failure of Differentiation Part I: Syndactyly

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KEYWORDS

• Syndactyly • Genetics • Classification • Surgery

Syndactyly is one of the two most common congenital hand anomalies, the other being polydactyly. Both have an incidence of about 1 in 2000 births.[1] Traditionally, syndactyly is considered to be simple when skin alone is involved, complex when there is bone connection, complete when the web involvement includes the nail folds, incomplete or partial when the nail folds are not involved but when the web depth is distal to its normal position, and complicated when there are multiple tissue abnormalities—bones, joints, tendons, muscles and neurovascular bundles (**Fig. 1**). Synpolydactyly and Apert syndrome are two examples of complicated syndactylies.

Syndactyly occurs as an isolated presentation or as part of a syndrome, such as Poland syndrome or one of the acrocephalosyndactyly syndromes, such as Apert syndrome. Tentamy and McKusick[2] have subclassified isolated syndactylies into five groups according to the affected interdigital space or spaces. Syndactyly type I (SD1) is the most common, affecting the long and ring fingers and second and third toes, complete or partial, often but not always bilateral, at times affecting either hands or feet, and occasionally other fingers. It is most commonly of sporadic occurrence, and subsequently autosomal dominant inheritance, but with incomplete penetrance. Syndactyly type II (SD2) is otherwise known as synpolydactyly (SPD), classically with syndactyly between the long and ring fingers and the fourth and fifth toes with duplication within the syndactylous webs. Syndactyly type III (SD3) affects the ring and little fingers in its isolated form, but also occurs at the other end of the spectrum as part of a syndrome, in oculodentodigital syndrome. Syndactyly type IV (SD4) consists of complete syndactyly of all fingers and is rare, as is syndactyly type V (SD5), in which there are metacarpal and metatarsal fusions of commonly the ring and little fingers or the third and fourth toes.

CLASSIFICATION OF CONGENITAL HAND ANOMALIES—WHERE DOES SYNDACTYLY FIT IN?

Under the International Federation of Societies for Surgery of the Hand (IFSSH)/Swanson classification, syndactyly is considered to be a failure of differentiation.[3–5] When skin alone is involved, the failure of separation may reasonably be attributed to a failure in programmed cell death in the particular web. In its complicated forms, however, the process is less clear. Syndactyly accompanies brachydactyly in the condition known as symbrachydactyly, which is classified either as a transverse failure of formation or a hypoplasia. In combination with ipsilateral chest wall anomalies, symbrachydactyly is termed Poland syndrome. The polydactyly of synpolydactyly is classified as a duplication. Central longitudinal deficiency (longitudinal failure of formation) is another condition in which syndactyly occurs regularly and which excites argument in determining the classification group within which it should be included. The elegant clinical and experimental work of Miura,[6] Ogino,[7] and others has demonstrated the association of syndactyly with polydactyly and clefting. The Japanese Society for Surgery of the Hand has suggested the introduction of an additional group within the IFSSH classification, this being abnormal induction of rays, to cater for this association and includes syndactyly within this group.[8]

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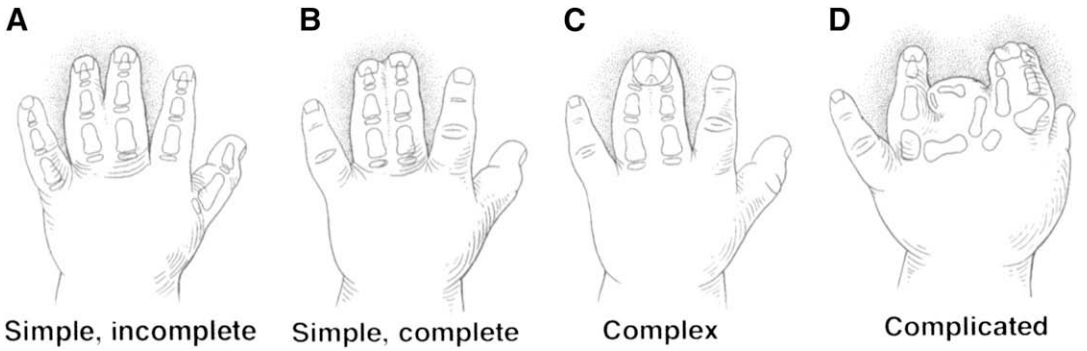

Fig. 1. (*A–D*) Types of syndactyly. (*From* Upton J. Management of disorders of separation—syndactyly. In: Hentz VR, editor. The hand and upper limb (Part 2). In: Mathes SJ, editor. Plastic surgery vol. 8. Philadelphia: Saunders Elsevier; 2006. p. 140; with permission.)

It is apparent that our increasing knowledge of the molecular processes of limb development is modifying our approach to classification of anomalies. The IFSSH/Swanson classification is based on appearance and is unable to satisfactorily incorporate modifications based on the causation of abnormalities at a molecular level. Currently, a descriptive basis for classification probably remains the optimal method to document the anomalies present in any particular limb.[9,10] In the future, classifications based on etiology, site of insult in the developing limb bud, the timing of insult, and abnormalities within molecular pathways may become possible.

EMBRYOLOGY—NORMAL AND ABNORMAL

The limb buds develop as outgrowths in the body wall, the upper limb at 26 to 27 days after fertilization and the lower limb bud at 28 to 30 days. Digits in the upper limb become distinguishable at 41 to 43 days and are fully separated by about 52 to 53 days.[11]

The limb bud consists of a mesenchymal core with overlying ectoderm (**Fig. 2**). The process of growth and differentiation of the limb bud is under complex genetic control. Specialized signal centers control three axes of development.[12] The apical ectodermal ridge (AER) is responsible for controlling proximal-distal outgrowth. Removal of the AER in experimental models truncates growth.[13] Beneath the apical ectodermal ridge lies the progress zone, in which mesodermal cells are programmed to form specific cell types destined for specific tissues and specific positions within the limb. Control of the anteroposterior or radioulnar axis lies within mesodermal cells within the zone of polarizing activity in the postaxial aspect of the developing limb. Thumb growth is suppressed in this region, allowing development of ulnar digits. Transposition of cells from the zone of polarizing activity to the preaxial or radial aspect of the limb suppresses thumb formation. A mirror hand, or ulnar dimelia, results.[14] The third signal center lies within the cells of the dorsal ectoderm, which control the development of the dorsal-volar characteristics of the limb. Transposition of dorsal ectoderm to the volar aspect of the limb bud results in the dual development of dorsal limb structures.[15] These three signal centers interact through the expression of specific morphogens, which act within cascades of molecular pathways that orchestrate limb development. Fibroblastic growth factors (FGFs) play a major role in the apical ectodermal ridge;[12,13,16,17] sonic hedgehog protein (SHH) in the zone of polarizing activity;[8,12,18] and Wnt-7a is involved in an interaction with the morphogens, Engrailed 1 and Lmx-1b, in determining dorsal and ventral patterning.[15,19–22]

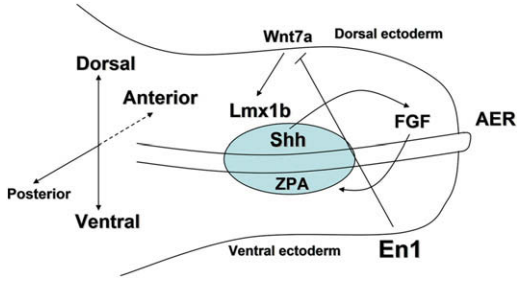

Fig. 2. Diagram of the developing limb bud.

What role do these three axes play in the development of syndactyly? Our knowledge remains imprecise. From day 38, the hand begins to appear in its adult form. Apoptosis is the process of programmed interdigital mesoderm cell death. By 8 weeks, digital separation is almost complete and phalangeal ossification centers are developing.[23] Apoptosis would seem to be mediated by the bone morphogenic protein (BMP) family.[24] These proteins, along with fibroblastic growth factors and members of the homeobox (Hox)