

COMMENTARY ON *J. GENET. CLASSIC*

Brachydactyly A1: New relatives for old families?

(A commentary on H. Drinkwater 1915 *J. Genet.* 4, 323–339;
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Introduction

The early part of the twentieth century saw the birth of many concepts and applications that have shaped modern science, as we understand it today. One was the rediscovery of Gregor Mendel's work on *pisum sativum* or the garden pea by Hugo de Vries, Correns and Eric Tschermak, circa 1900 (D'Vries 1899; Correns 1905; Tschermak 1906). Following this, a number of familial conditions were described in humans including those by Huntington and Osler that were later proven to be dominantly inherited (Huntington 1872; Osler 1892). In 1903, William Farabee, a student of William Ernest Castle (a frontrunner in Mendelian genetics in humans and famously, mice) at Harvard, analysed the heredity of a human hand malformation called brachydactyly in a three generation family, later called 'The Farabee's family' (Farabee 1903).

Brachydactyly is a hereditary disorder of the hand characterised by apparent shortening of digits (figure 1). Brachydactyly type A1 (BDA1) is inherited in an autosomal dominant fashion and was the first recognized dominant Mendelian condition (Bateson 1913). Harry Drinkwater, working independently in England, undertook a comprehensive evaluation of patients with brachydactyly that he described through a series of papers (1908, 1912 and 1915). In his first paper (Drinkwater 1908), Drinkwater describes a family with brachydactyly, earlier referred to as Farabee type of brachydactyly but subsequently classified as BDA1 by Julia Bell (Bell 1951). The second paper (1912) describes another family with BDA1 that Drinkwater called 'minor brachydactyly'.

The third paper by Drinkwater (1915), describes another brachydactylous family (reproduced in pages 99–121 of

this issue) with BDA1. Relatedness among the families described in these papers was unclear at the time of the studies; however, Drinkwater speculated that families from the first paper and the third paper, that happen to reside in the same area of England, might be related. Also he mentioned that both of these families might be related to the Farabee family (Farabee 1903) through an individual named Benjamin Hyde. While relatedness of the two Drinkwater families (1908 and 1915) was resolved only recently by McCready *et al.* (2002), relatedness of these families to the three surviving members of Farabee's brachydactyly family was followed up initially by Haws and McKusick (1963). Even though Farabee's family showed features consistent with Drinkwater's first family, including short stature, no evidence of a possible relatedness between the two families was identified (Haws and McKusick 1963) until recently (McCready *et al.* 2005).

The Farabee type of brachydactyly, later called type A1, is characterised by shortness of middle phalanges of all digits of the hands and feet, shortness of the proximal phalanx of the first digit and occasional fusion of the middle and terminal phalanges (see figure 1). Drinkwater suggested that shortness of phalanges was attributable to a short shaft of the bone, absence of epiphyses, and premature ossification of the cartilage intervening between the shaft of the bone and its epiphysis. Drinkwater also noted that BDA1 individuals tended to be of shorter stature in adulthood but as children showed no evidence, as affected patients were taller than their peers.

In 1951, Julia Bell (1879–1979) classified brachydactyly into seven types based mainly on the shortening of the tubular bones of hands and feet, namely A1, A2, A3, B, C, D and E (Bell J. 1951). In brachydactyly type A1 (figure 1), the hands are broad with shortening of all digits, but middle phalanges and the proximal first phalanx are

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the most severely shortened. Severe shortening can also be accompanied by symphalangism (fusion of the two bones), reported earlier by Harvey Cushing (Cushing 1916). The shortening is confined to the middle phalanx of the index finger in type A2 and to the 5th digit in A3. Later Temtamy and McKusick (1978) added type A4 where middle phalanges of 2nd and 5th digits are short with radial clinodactyly of the 4th finger, and type A5, with absent middle phalanges.

Naomi Fitch (1979) reclassified brachydactyly based on the osteological events. Accordingly, in BDA1 the hands are broad, with proportionate shortening of all digits; all the hand bones may be shorter than those in normal hands, but middle phalanges are the most severely shortened (figure 1). This gave a broad category for BDA1: at one end, the phalanges of 2nd and 5th digits were shortened (McKusick type A4), and at the other end all middle phalanges were missing (McKusick type A5). Therefore, in Fitch's classification, McKusick types A4 and A5 belong to Bell type A1.

In type B, the middle and distal phalanges of fingers and toes are short or absent. Type C is characterised by shortening of the middle and/or proximal phalanges of the 2nd, 3rd and 5th digits associated with hypersegmentation of the proximal phalanges (usually 2nd and 3rd digits). In type D, terminal phalanges of the thumbs and halluces are short and broad. Finally in type E, there is shortening of the metacarpals and/or metatarsals. In addition, other subtypes were also described: A6, hypoplastic or absent middle phalanges of hands and feet associated with ankylosis of the carpal and tarsal bones (Osebold *et al.* 1985) and type A7, a combination of types BDA2 and BDD along with dislocated thumbs (Meiselman *et al.* 1989).

Several studies have undertaken the search for genes associated with BDA1, including the evaluation of two BDA1 families of Mexican and Scandinavian descent, respectively, for eight candidate genes, including *TGF α* , *HOXD*, *MSX1*, *MSX2*, *FGF1* and *PDGF β* . No evidence of linkage with markers within genes was shown, with LOD scores of less than -2.00 (Mastrobattista *et al.* 1995). It was not until 2000, when Yang *et al.* (2000) localised a gene for BDA1 to a narrow region of chr 2q35–36 flanked by markers D2S2248 and D2S360 with a maximum LOD score of 6.59 in two families. Within this 8.1 cM interval, Gao *et al.* (2001) identified three heterozygous missense mutations (Glu95Lys, Asp100Glu, and Glu131Lys) in the region encoding the amino-terminal signaling domain of the Indian hedgehog gene (*IHH*) (figure 2). Since then, the same or different dominant mutations in the *IHH* gene have been identified in different populations (McCready *et al.* 2002 and 2005, Kirkpatrick *et al.* 2003 and Giordano *et al.* 2003). Essentially, 5 different heterozygous missense mutations affecting just three different amino acids have been identified in 7 families, thus far (figure 2)

A speculation that the families described by Drinkwater were related was resolved by McCready *et al.* (2002) when they identified a novel mutation, a G to A transition causing an amino acid change from aspartic acid to asparagine (Asp100Asn), in *IHH* in the descendants of Drinkwater's first and third families (Drinkwater 1908, 1915). Both families had characteristics consistent with BDA1, including pronounced shortness of the middle phalanges. Although inter and intra-familial phenotypic heterogeneity was seen, a common haplotype was identified in affected individuals of both families between markers D2S2250 and D2S1323 spanning a 5 cM region including the *IHH* gene.

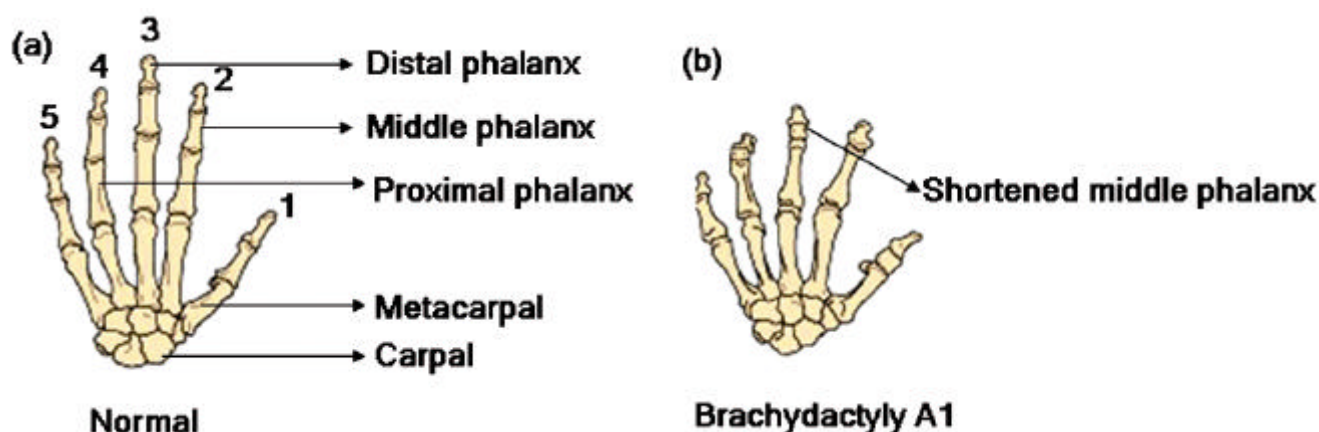


Figure 1. Brachydactyly type A1. (a) Bone morphology of a normal hand is shown. The hand is composed of carpal bones, metacarpals and phalanges. Note that the first finger (thumb) has only two phalanges while others have three. The numbering is from the thumb towards the little finger. (b) The bone morphology of a brachydactylous hand is shown. A hand with brachydactyly A1 has shortened middle phalanges (2nd to 5th digits) or absence of the middle phalanx (5th digit). (Figure modified from *Introduction to Genetic Analysis*, Griffith *et al.* Seventh Edition, Copyright ©2000, W. H. Freeman Co. New York).

As this manuscript was under preparation, Dennis Bulman's group identified a Asp100Asn mutation in the descendants of Farabee's kindred (McCready *et al.* 2005), the same mutation as previously identified in both Drinkwater families (McCready *et al.* 2002). Although a common haplotype between markers was apparent, new recombination events were identified in individuals from the first Drinkwater family (1908) that were not observed in either the third Drinkwater (1915) or the Farabee kindreds (1903). While Drinkwater predicted that Farabee's kindred was related to the first family he described in 1908, haplotype analyses using sixteen markers surrounding the *IHH* gene showed that Farabee's family is more closely related to the family Drinkwater described in 1915 (McCready *et al.* 2005). The same mutation and common haplotypes were also observed in a study from two families from the USA and New Zealand, respectively (DE Bulman, personal communication). These data suggest that this disorder may likely have arisen from a common founder or this mutation is an ancestral allele that may be a major cause of BDA1 across populations (McCready *et al.* 2005).

It is interesting to note that mutations in Asp100 and Glu95 were also reported by Gao *et al.* but leading to different amino acid substitutions. It seems that this region might be a 'hot spot' for mutation. Also, recurrent mutation in the same codon in unrelated families of different ethnic backgrounds suggests functional importance of these residues in the *IHH* protein. It is hypothesised that these residues are involved in binding to the patched receptor (PTC) based on its functional homology in sonic

hedgehog (Stone *et al.* 1996; Marigo *et al.* 1996; Carpenter *et al.* 1998). Therefore, the *IHH* mutations are also likely to disrupt binding of the *IHH* protein to PTC. If the missense mutations cause complete loss of binding, then BDA1 would be caused by haploinsufficiency of the wild type protein. These mutations may also lead to partial loss or altered binding, the latter predicted to result in a gain of function or dominant negative effect. The *IHH* mutations identified in brachydactyly so far are represented schematically (figure 2).

While mutations in *IHH* have been shown to cause BDA1 in unrelated families, not all BDA1 is linked to *IHH*. Armour *et al.* (2002) identified a second locus mapping to 5p13.3–p13.2 with a LOD score of 6.91 in a large BDA1 family. Further, Kirkpatrick *et al.* (2003) predicted the existence of a third locus in the same Scandinavian brachydactylous family reported by Mastrobatista (1995), as no evidence of linkage to previously identified loci was found. These indicate the genetic and locus heterogeneity of BDA1.

Various methodologies have been adapted to identify BDA1 using the century-old radiological evaluation, notable of which is the metacarpophalangeal pattern profile (MCP). The MCP is a plot of age related standard deviations of the length of each hand bone. However, metacarpophalangeal profile allows a more quantitative and objective means of diagnosis and has been used in the diagnosis of several dysplasia syndromes including Holt-Oram and hand foot-genital syndrome (Poznanski *et al.* 1972). Metacarpophalangeal profile was done on a family evaluated by Armour *et al.* (2000) who showed mild

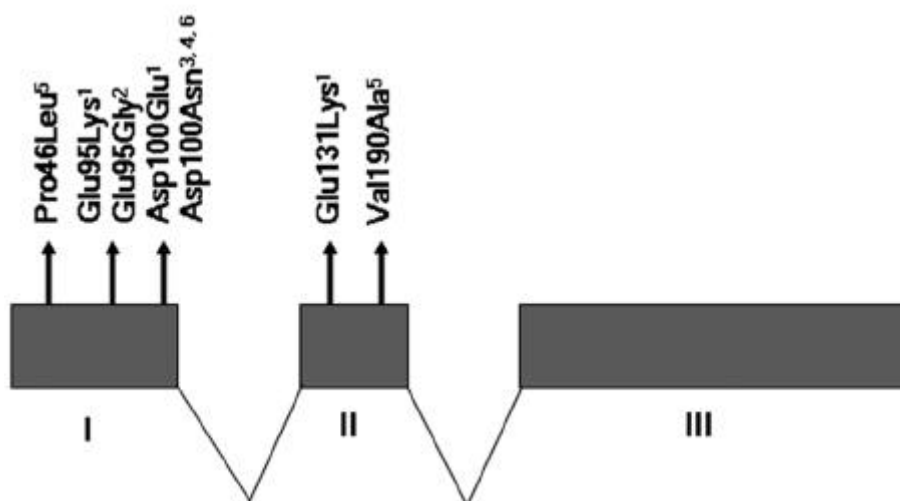


Figure 2. *IHH* mutations in brachydactyly type A1. The genomic structure of the *IHH* gene is shown. Exons 1–3 are indicated by black boxes. Mutations identified to date in BDA1 patients are shown. The amino acid residue numbers are based on GenBank sequence ABO18076. Key to the figure: 1. Gao *et al.* (2001); 2. Kirkpatrick *et al.* (2003); 3. Giordana *et al.* (2003); 4. McCready *et al.* (2002); 5. Hellemans *et al.* (2003); 6. McCready *et al.* (2005).

features of BDA1 with shortness of the 2nd–5th middle phalanges, 1st proximal and distal phalanges, and of the 4th and 5th metacarpals, with early fusion and cone shaped deformities of the affected epiphyses. No absence of the middle phalanx or fusion of phalanges was observed, although clinodactyly in the form of ulnar deviation of the right 2nd to 4th proximal interphalangeal joints and radial deviation of the left 4th proximal interphalangeal joints were apparent.

The identification of *IHH* as the gene for BDA1 has led to speculations of other possible modifier genes or genes that might act downstream of the *IHH* signaling pathway (Mastrobattista *et al.* 1995). Hellemans *et al.* (2003) identified homozygous mutations in the signaling domain of *IHH* in two Belgian families with acrocapitofemoral dysplasia that is characterized by short stature with short limbs, BDA1, and cone-shaped epiphyses in hands and hips. It will be interesting to see if the genes in the other loci discovered recently interact with *IHH* and contribute to the heterogeneity of BDA1. Proper identification and (molecular) evaluation of brachydactylous families will be useful.

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