A new locus for brachydactyly type A2 maps to chromosome 20p

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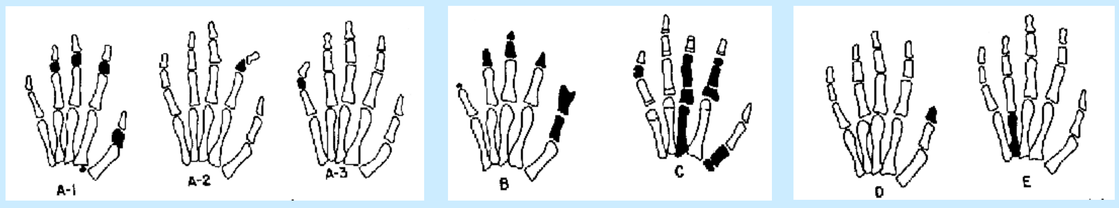
Introduction:

Brachydactyly, or shortening of the digits, is due to the anomalous development of the phalanges or metacarpals. As an isolated feature, the different types of brachydactyly have been classified on an anatomical and genetic basis into five groups, A-E, including three subgroups (A1-A3) by Julia Bell [1951].

Bell´s classification of brachydactyly:

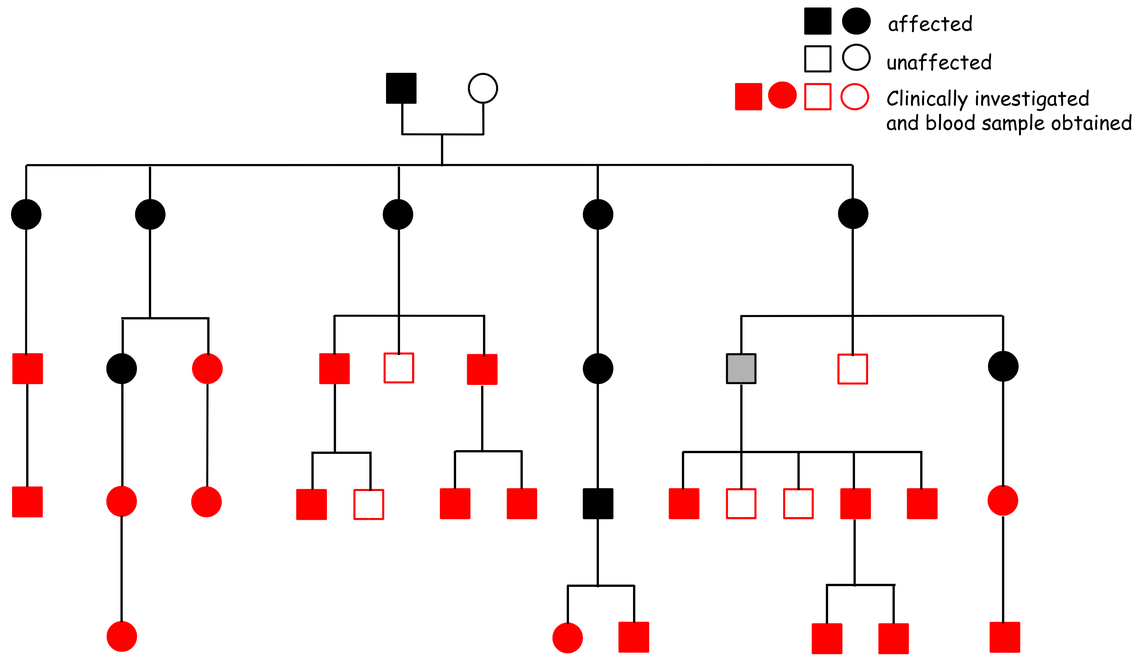


Brachydactyly A2, an autosomal dominant hand malformation, is characterized by short and laterally deviated second and fifth fingers. Also, the first and second toes can be affected in a similar way. The other fingers and toes are for the most part of normal form (see exemplary cases).

Recently, heterozygous missense mutations in the gene coding for bone morphogenetic protein receptor 1b (BMPR1B) were shown to cause brachydactyly A2 in some families by acting in a dominant negative manner (Lehmann et al, PNAS, 2003)[1].

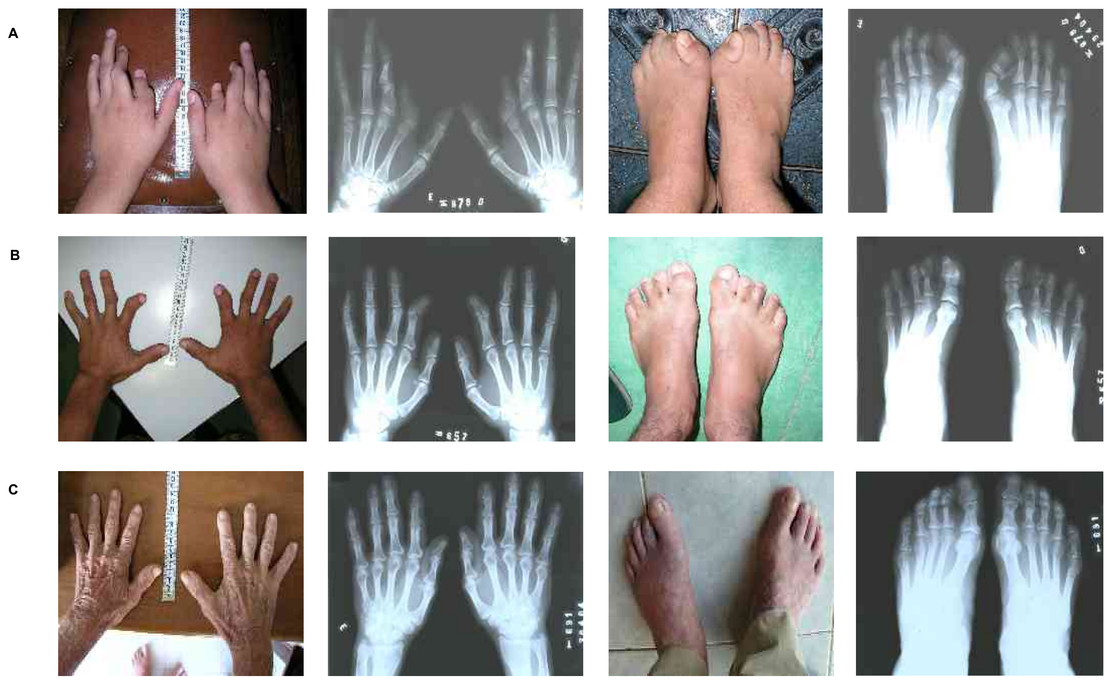
Besides our recent report, families with brachydactyly type A_2 have been published only a few times in the literature. In 1919 Mohr and Wriedt[2] first described this form of brachydactyly in a large Norwegian family. In this pedigree, a possible homozygote affected child as a result of an consanguineous marriage of two affected parents with an isolated brachydactyly, was mentioned to have a very severe skeletal phenotype.

Another description of a large Brazilian family of German origin with 117 family members affected by isolated brachydactyly A2 was published by Freire-Maia et al, 1980[3]. In addition, his clinical report indicated a higher fertility in affected women than in unaffected individuals.
We had the chance to perform a linkage study in 26 family members of this brazilian pedigree presenting with brachydactyly type A2 (see pedigree).

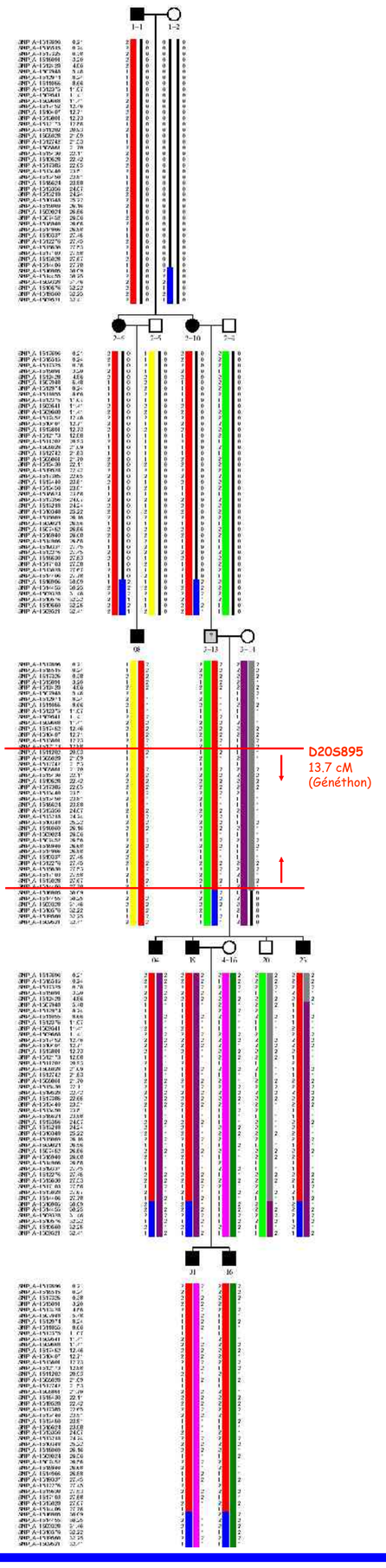


Literature:
1 Lehmann K, Seemann P, Stricker S, Sammar M, Meyer B, Sühring K, Majewski F, Tinschert S, Grzeschik, K-H, Müller D, Knaus P, Nürnberg P, Mundlos S. Mutations in bone morphogenetic protein receptor 1B cause brachydactyly type A2. PNAS 100: 12277-12282.
2 Mohr, OL and Wriedt C. A new type of hereditary brachdactyly in man. Washington: Carnegie Institution 5 - 64 (1919).
3 Freire-Maia N, Maia NA, Pacheco CAN. Mohr-Wriedt (A2) brachydactyly: Analysis of a large brazilian kindred. Human Heredity 30: 225-231 (1980).

The clinical spectrum of limb malformations observed:
A. Most severe; B. Less severe; C. Mildest



SNP-Chip-Data on chromosome 20p, only a part of the pedigree is shown.
The disease haplotype is displayed in red bars. The confining region between microsatellite marker D20S895 and SNP_A-1516905 is located between the red arrows.



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Methods: DNA was extracted from blood samples by standard methods. We performed a genome wide linkage analysis using a SNP-GeneChip (Human Mapping 10K Array) from Affymetrix. Additional polymorphic micro-satellite markers were used for the fine mapping to narrow the defined region.

Results: Using this approach, we mapped a new locus for brachydactyly to a ~17 cM region on chromosome 20p12-p13 between the marker D20S895 and SNP_A-1516905 (see figure of haplotypes on the right).

As a candidate gene within this new locus we first sequenced the coding region of BMP2, known to play an important role in the induction of cartilage and bone development, but no mutation was found. Several other candidate genes located within the disease locus will be sequenced next.