Metacarpophalangeal pattern (MCPP) profile analysis in a family with triphalangeal thumb


Abstract

Triphalangeal thumb (TPT) is a rare congenital disorder characterised by a long, finger-like thumb with three phalanges instead of two. It can occur as an isolated defect, in association with other abnormalities of the hands and feet, or as a part of a syndrome. Sporadic cases have been described, but it is usually inherited as an autosomal dominant trait.

In order to examine skeletal morphology in different phenotypic variations of this disorder, we performed metacarpophalangeal pattern profile analysis in one kindred with this disorder. A characteristic profile occurred in all affected people, based on the individual lengthening or shortening of the thumb bones. Comparison of the affected and unaffected people from this family with people with different genetic background suggests that the described profile is specific for TPT and could be used as a helpful diagnostic tool in syndromes which include TPT.

Keywords: triphalangeal thumb (TPT); metacarpophalangeal pattern profile (MCPP); pattern recognition.

Triphalangeal thumb (TPT) is a developmental disorder characterised by a long, sometimes finger-like thumb, with three phalanges instead of two. TPT is rare, and is usually inherited as an autosomal dominant trait, although sporadic cases have been described.1 The underlying genetic defect is probably situated in one of the regulator genes involved in the differentiation of the developing limb. The gene for TPT has recently been localised on chromosome 7q36 by means of linkage analysis in two large Dutch family pedigrees in which TPT was inherited as an autosomal dominant disorder with almost complete penetrance and variable expression.2 Further clinical, molecular genetic, and genealogical study of the original two families showed that they are connected to each other and are both part of a single large kindred. As part of the project examining the aetiology and different phenotypic variations of this disorder, we performed metacarpophalangeal pattern profile analysis in one of the two kindreds in which linkage analysis was performed.

The metacarpophalangeal pattern (MCPP) profile analysis is a method of measuring the length of each of the 19 tubular bones of the hand on radiographs, and comparing this length with a standard of the normal population according to age and sex. This method is used to detect absolute as well as proportional alterations in the length of the hand bones in various birth defects and the pattern profile appears to be specific for several congenital malformation syndromes.3 The osseous configuration of the hands in TPT patients was

Figure 1. Family with TPT. A bar indicates that the person was included in the MCPP analysis. The proband is indicated by an arrow.

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studied. Specific MCPP profiles in this family with TPT are described, in concordance with different clinical phenotypes. For comparison of the affected and unaffected subjects from this family with people with a different genetic background, the population investigated was augmented with two sporadic examples of TPT and 44 subjects randomly selected from the normal population.

**Material and methods**

Clinical data and detailed analysis of the phenotype in the family investigated have been described elsewhere.4 MCPP profile analysis was performed on the radiographs of 16 hands from 13 affected persons, and of 12 hands from 12 unaffected sibs from the same family with TPT (fig 1). When on clinical and x ray examination variation in phenotype between the left and right hands was noticed, metacarpal-phalangeal pattern profiles were determined for both radiographs (n = 3). If the phenotype of the two hands showed no differences between them, MCPP profile of only one hand was used for further analysis. Ages at the time of the radiological investigation ranged from 8 to 74 years. All the affected subjects from this family were proven to be gene carriers by DNA analysis.5 The phenotype in affected subjects varied between non-opposable and opposable TPT. A single case of non-penetrance, in which a carrier of a TPT gene had rudimentary unilateral postaxial polydactyly, is included in the latter group.

We used a type of MCPP analysis called the Q score analysis.6 In a Q plot (graphic illustration of the Q score), the percentage of the pathological lengthening or shortening of the individual bones of the hand can be directly read from the y axis.

Radiographic measurements were obtained with a digitiser. Length measurements including the epiphysis were used for all the 19 (20 in case of the TPT) metacarpal and phalangeal bones and the Q scores were determined for all the x rays according to the

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**Figure 2** Q scores of the 12 unaffected members of the family. The numbers on the x axis represent the hand bones. They are listed as metacarpal bones 1 to 5 (MC1 to MC5), proximal phalanges 1 to 5 (PPh1 to PPh5), middle phalanges 2 to 5 (MPh2 to MPh5), and distal phalanges 1 to 5 (DPh1 to DPh5). The numbers on the y axis represent the Q scores for each particular bone. The zero line represents the mean of the population. (A) Patients 1 to 6. (B) Patients 7 to 12. The 44 subjects from the general population are not presented as there were no differences between their profiles and those of the 12 unaffected members of the family investigated.
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method described by Dijkstra and Venema.\textsuperscript{5} Measurements of the extra phalanx of the thumb were not included in the plot because of the lack of appropriate reference values. In order to compare the affected subjects with other people with the same disorder but different genetic background, one sporadic patient with TPT and one published TPT radiograph\textsuperscript{6} were included in the analysis. Furthermore, in order to compare the unaffected subjects from the investigated family with people from the population at large, radiographs from 44 people randomly taken from the general population were also measured and analysed. The profiles of the Q scores obtained will be discussed below.

In this study we have applied a new method of normalisation of the bone length measurements resulting in the so-called P scores. These P scores are independent of the absolute scale factor, and therefore the P score describes the shape of a length profile. This method of normalisation has been described elsewhere.\textsuperscript{1} One profile was represented by the score $P_i$, $i = 1, \ldots, 19$, 1 to 19 being the 19 measurements in one hand. Such a vector may be regarded as a point in a 19 dimensional space, each dimension representing one of the hand bones. If it is true that a set of $P_i$ scores is representative of a syndrome, then points representing measurements of patients with the same syndrome will cluster together in this 19 dimensional space. Points corresponding to measurements of patients with different syndromes will lie far apart.

Even though it is difficult to imagine point distributions in spaces with dimensions higher than three, procedures exist to map a set of points in a high dimensional space onto a plane, such that the interpoint distances are preserved as nearly as possible.\textsuperscript{8} Procedure NLMAP in ISPAHAN is such a procedure.\textsuperscript{9} This procedure was used to map the "normal" and "pathological" configurations onto a two dimensional plot. The "normal" class consisted of the unaffected TPT family members ($n = 12$) and the randomly selected subjects from the general population ($n = 44$). The "pathological" class consisted of the affected family members ($n = 13$), one sporadic TPT patient, and one radiographic image of a TPT patient taken from a book.\textsuperscript{6}

Results

The relative lengths of the 19 bones and the profile of the Q plot in the unaffected persons did not differ from the randomly selected people from the general population (fig 2). The Q plots from the affected subjects were divided into three different subgroups according to the severity of the phenotype. The severity of the osseous pathology corresponded with the degree of functional impairment. The most severe phenotype was observed in the group of patients with the so-called "non-opposable" TPT (fig 3). These patients have a rectangular extra phalanx in the thumb which resembles an index finger (“five fingered hand”) and have absent or hypoplastic sesamoid bones, which corresponds with hypoplastic thenar muscles. None of these patients was capable of making a "pinch grip" because they had no normal opposition function. In children with non-opposable TPT, extensive thumb surgery is required at an early age to develop (reasonably) normal hand function.

The mildest phenotype was observed in the group of patients with "opposable TPT" (fig 4). On the x ray the thumb shows a normal configuration with a delta shaped extra phalanx in the interphalangeal joint. The sesamoid bones of the thumb (anchor places of the thenar muscles) were normally developed as were the thenar muscles. These patients have almost normal hand function. One patient from this family showed no clinical or classical radiographical signs of TPT, except for unilateral rudimentary postaxial polydactyly. However,
Finally, the MCPP plots of the patients whose thumbs showed both characteristics of the thumb and the index finger on x-ray examination were classified as "intermediate form of TPT" and are shown in fig 5.

On analysis of the Q plots it appears that all affected persons have a systematic lengthening of the first metacarpal and first proximal phalanx, and a systematic shortening of the distal phalanx of the thumb. The profile of the plots was very consistent in the different phenotypic variations of this disorder and only the relative level of the "peaks" in the thumb measurements correlated with the severity of the disorder.

One sporadic TPT patient and one reproduction of an x-ray of TPT from a book were included in the analysis and both showed the above described profile (figs 6 and 7). This profile appears to be characteristic of TPT in general and not only for this family.

After the normalisation of the Q scores was carried out as described above, the P scores were used for the non-linear mapping procedure. The "pathological" profiles of the affected subjects grouped in the upper right quadrant of fig 8, whereas the cluster of "normal" subjects remained in the left lower quad-
Discussion

Triphalangeal thumb can be roughly divided, on the basis of the functional impairment, into an opposable, an intermediate, and a non-opposable category. However, the recent linkage study in TPT families\(^2\) shows that different forms of TPT may represent phenotypic variations of a single gene disorder. The underlying defect remains to be discovered, but probably involves disturbance in formation of the anteroposterior axis of the developing limb bud.

Figure 5  (A) X ray and (B) Q plots of the people with “intermediate” TPT.

rant. Four points representing MCPP plots of affected persons came in the vicinity of the “normal” cluster. Two of them belong to the same person. All three persons have the “opposable” form of TPT with a very mild phenotype, one of them being the only case of non-penetrance of the TPT gene in this family. One plot of a normal person came in the vicinity of the “affected” cluster. This probably reflects a coincidental finding that this person had brachyphalangy of the distal phalanx of the thumb.
In MCPP profile analysis, the configuration of the hand can be studied. Normally, the profile remains more or less the same for one person throughout his or her life. Within a syndrome there is usually some variation in the form of a profile. A particular profile is found in a number of congenital malformation syndromes and for most of them there is no consistent profile between individual patients.

MCPP plot analysis of the x-rays of all affected persons from the family with TPT shows a consistent profile. The amount of lengthening or shortening of the metacarpals and phalanges varies with the severity of the phenotype; the patients with non-opposable thumb have a larger percentage of excessive length of the first metacarpal and the first proximal phalanx than the patients with opposable TPT. Similarly, the percentage of shortening of a distal phalanx of the thumb was smaller in the latter group. This can be explained by the presence of a fully developed profile.
mid-phalanx (not included in the plot) in non-opposable TPT. The typical shape of the profile was also present in the only case of non-penetrance where clinical examination and x-ray of the hands failed to show any abnormalities. However, because all the measured values fitted in the range of the normal population, it would have been difficult to recognise if analysed without comparison with other affected family members.

A characteristic profile also emerged in the sporadic patient and in the reproduction of one TPT radiograph from a book. This suggests that the above described profile is specific for TPT and could be used as a helpful diagnostic tool in the syndromes which include TPT. However, more research should be done to investigate the characteristic profiles of the syndromal TPT, such as in Holt-Oram syndrome, Townes-Brocks syndrome, Fanconi pancytopenia syndrome, etc.

An attempt was made to investigate whether MCPP analysis is adequate to discriminate a pattern profile of an affected person from an unaffected relative. Because of the small size of the population investigated, as usually is the case with (familial) congenital malformations, it was decided not to investigate this by means of rigid statistical analysis. Instead, the potential of MCPP analysis as a diagnostic tool in this family was examined by means of exploratory pattern recognition techniques. The applied procedure indicates that profiles of people affected by the TPT syndrome cluster together. This cluster is well separated from the cluster formed by profiles of unaffected family members and normal people. Four patients with non-opposable TPT lie closer to the cluster of normal people, confirming the mild expression of the phenotype in this group.

A characteristic profile that emerges from the MCPP plots of the members of a family with TPT is based on the measurements of abnormal lengths in the thumb bones. Clinical observation of an “index-like” thumb in the patients with non-opposable TPT suggests an underlying differentiation problem between the thumb and index finger during limb morphogenesis. MCPP analysis confirms this by finding up to 50% excessive length in the first metacarpal in patients with non-opposable TPT.

More studies of the patterns that emerge in abnormal phenotypes of human limb malformations will be necessary in the future. During the past few years several genes responsible for congenital limb disorders have been mapped to different chromosomes in the human genome. However, their function, their role in limb development, and especially their interactions remain to be discovered. One of the late events during limb embryogenesis is the morphogenesis of the distal skeleton. Studies of skeletal morphology have the potential, together with molecular genetic studies, to provide new insights into molecular mechanisms controlling developmental “fates” in abnormal genotypes.

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