Response to Potuijt et al.

We thank Potuijt et al. for their attention to our article "A novel ZRS variant causes preaxial polydactyly (PPD) type I by increased sonic hedgehog expression in the developing limb bud"[1] and argument about the type of PPD.[2] We will respond to their argument point by point.

First, we phenotyped the hands of patients II-11, II-7, III-4, III-8, III-11, III-12, and IV-1 as "incomplete duplication of distal phalanx" and PPD type I. The reason is that we referred to the widely accepted classification systems of Temtamy-McKusick[3,4] (geneticists) and Wassel[5] (hand surgeons). According to Temtamy-McKusick and Table 1 in ref. [4], PPD I (MIM17400), duplication of a biphalangeal thumb, corresponds to Wassel types 1 to 6. PPD II (MIM174500), also known as triphalangeal thumb (TPT), isolated opposable triphalangeal thumb, or thumb polydactyly with a triphalangeal component, corresponds to Wassel type 7. Since the radiographs of patients II-11 and IV-1 with obvious PPD phenotype display a Wassel type II radial polydactyly, we believe that the phenotypes of the affected members of this family should be classified as preaxial polydactyly type I (PPD I).

In addition, PPD classification varies among geneticists and hand surgeons. The disagreement regarding the phenotyping of the affected family stems from the fact that Potuijt et al. adopted a different PPD classification system than us. While conflicts in different classification systems usually exist, in fact, there is not a perfect classification mode to include all PPD types, especially according to PPD phenotype. A generic term, "ZRS-associated syndromes," for limb malformations caused by variants of ZRS has been suggested,[6] and our study will assist in developing this new genetic classification system for PPD.

Second, family member III-9 with a heterozygous variant manifests small sesamoids, which are found in normal members II-2, II-5, II-9, II-13, III-2, III-6, III-7, III-10, and III-13. We also know that there are sesamoid bones at the interphalangeal (IP) joint of the thumb in the normal population. We examined X-ray images of both hands of 50 hand trauma patients. The results showed that 9 patients had bilateral sesamoids between the two phalanxes of the thumb. Hence, the phenotype of III-9 with heterozygous variant is a normal phenotype, not PPD. In our paper[1], we definitively stated that "the variant in our PPD family shows incomplete penetrance" (see "Discussion").

Third, we thank Potuijt et al. for agreeing with the observation that the radiograph of patient II-11 resembles a Wassel type II radial polydactyly. We believe they will also agree that the phenotypes of the affected members of this family should be classified as PPD I according to ref. [3] and Table 1 in ref. [4]. The radiographs of patient II-11 were indeed made at an adult age, and we did not get a radiograph of patient II-11 at a younger age. We genuinely appreciate Potuijt et al. providing radiographs of two young patients from their series, which provided more perspective for us to understand PPD.

We are in agreement that PPD type I usually occurs in sporadic patients and unilaterally in 67% of cases. So, we think that the four-generation Chinese family with isolated PPD I is precious and rare, and provided a good chance to clarify its genetic mechanism. However, follow-up sequencing in another seven sporadic PPD I patients from different families did not identify a variant in the ZRS. So, we think that a single genetic substrate may not be the only cause of this phenotype.

Finally, we thank Potuijt et al. for their approval and encouragement of our study. We will try our best to optimize genotype–phenotype correlation within ZRS-associated anomalies and gather more knowledge on long-range regulation in embryonic limb development.

Furthermore, we agree that dedicated clinical geneticists or congenital upper limb surgeons should be involved in (molecular) genetic research. We also advocate a combined effort by experts from multiple fields within genetic research on congenital upper limb anomalies.

DISCLOSURE

The authors declare no conflicts of interest.

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