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Letter to the editor

Large-scale genome-wide scans do not support petaloid toenail as a Mendelian trait

Petaloid toenail, or accessory nail of the fifth toe, is a physical trait characterized by the presence of an additional tiny toenail on the small toe. Since it can occasionally cause disfigurement and tenderness while wearing tight shoes or walking, standard surgical matricectomy is often carried out to repair the petaloid toenail (Chi and Wang, 2004). Chinese legends recorded petaloid toenails as a trait unique to Han Chinese (Gao, 2010), but population-based studies are largely absent. A recent study of petaloid toenail confirmed its prevalence in Han Chinese (Hao et al., 2005) and proposed a dominant Mendelian mode of inheritance. In this study, we examined the petaloid toenail trait in both Han Chinese and Uyghur populations in China, aiming to 1) obtain a more complete picture of the population prevalence of petaloid toenail; 2) find potential genes associated with petaloid toenail through genome-wide scans, thereby shedding light on the mode of inheritance of this trait.

For this study, we collected 2980 Han Chinese samples and 721 Uyghur samples including 1349 males and 2352 females. The petaloid toenail phenotype was recorded as an ordered categorical variable scored as levels 0 to 2, following a previously established standard (Hao et al., 2005) (Fig. 1A and supplementary data). Apart from the three ordered categorical levels, we further derived two statistics combining the right and left foot statistics: Petaloid_E ("petaloid toenail exist": the presence of a petaloid toenail on at least one foot), and Petaloid_D ("petaloid toenail double": the presence of a petaloid toenail on both feet).

We summarized the frequency of the petaloid toenail trait in Han Chinese and Uyghurs (Tables S1 and S2). The frequency of petaloid toenail in our Han Chinese population in the Jiangsu Province (58.97%) fits well with previous reports (Hao et al., 2005). While we confirmed the presence of the petaloid toenail trait in the Han Chinese population, we also found a substantial prevalence of this trait in Uyghurs (51.15%), suggesting that it is not unique to the Han Chinese. Furthermore, the petaloid toenail trait is not associated with the East Asian ancestral proportion in the Uyghurs ($P = 0.357$). Since the Uyghurs are a quite evenly admixed population with both eastern and western Eurasian ancestries (Xu and Jin, 2008), it is very likely that the frequency of the petaloid toenail in western Eurasian populations is also considerable. Future studies in western Eurasian populations shall provide unequivocal evidence.

We found a significant correlation between the presence of a petaloid toenail on right and left feet in both Han Chinese ($\rho = 0.4684$, $P < 2.2e\text{-}16$) and Uyghurs ($\rho = 0.5024$, $P < 2.2e\text{-}16$). Nonetheless, the distribution of the trait is not symmetric. By comparing the frequency of petaloid toenails between right and left feet and between different populations, we found petaloid toenails to be more common on the right than the left foot. This trend is statistically significant in Uyghurs ($P = 4.9 \times 10^{-3}$, χ^2 test; Fig. 1B) but not in Han Chinese ($P = 0.171$; Fig. 1B). In Han Chinese, on the other hand, there is a greater prevalence of petaloid toenail than in Uyghurs. This finding is statistically significant for the left foot ($P = 1.0 \times 10^{-3}$; Fig. 1C), but not for the right ($P = 0.203$; Fig. 1C).

We applied a linear model to estimate the association between the petaloid toenail phenotype and gender or age. We found that there was generally little gender difference in the presence of a petaloid toenail (in Han Chinese: $P = 0.779$ for Petaloid_E, $P = 0.194$ for Petaloid_D; in Uyghurs: $P = 0.068$ for Petaloid_E, $P = 0.324$ for Petaloid_D). While evaluating gender differences in the presence of a petaloid toenail in right *vs.* left foot, we found a marginal difference for the right foot in Han Chinese ($P = 0.0361$, χ^2 test; Fig. 1D), but no significant difference for the left foot ($P = 0.457$; Fig. S1B). In Uyghurs, neither right ($P = 0.548$; Fig. S1C) nor left ($P = 0.066$; Fig. S1D) foot showed a difference in presence between genders. Furthermore, we found that age was not significantly associated with most of the petaloid toenail phenotypes ($P = 0.069$ for left foot, $P = 0.193$ for Petaloid_E, $P = 0.505$ for Petaloid_D) and it was only marginally associated with the presence of the petaloid toenail on the right foot ($P = 0.036$). The frequency of petaloid toenail of right and left feet, Petaloid_D and Petaloid_E, in different age groups can be seen in Fig. S2.

It has been suggested that petaloid toenail is a dominant Mendelian trait (Hao et al., 2005). In order to test this hypothesis, we conducted the first-ever genome-wide scan of the petaloid toenail phenotype. We performed genome-wide scans in Han Chinese and Uyghurs of petaloid toenail on the right and left feet, respectively. However, no genome-wide significant signals were found (threshold $P < 5 \times 10^{-8}$). We further performed a meta-analysis combining the results of Han Chinese and Uyghurs; again, no signal reached the genome-wide significant level (Fig. 1E). We further performed genome-wide scans on the two derived phenotypes (Petaloid_E and Petaloid_D), and did not find any significant signals either (Figs. S3 and S4). Using GCTA (Yang et al., 2011), we found a moderate heritability of the petaloid toenail phenotype (from 34.3% to 57.4%) in Han Chinese. We further tested 16 candidate genes with a known function in nail development for suggestive association with any of the petaloid toenail phenotypes. We found no significant association signals in Han Chinese or Uyghurs, nor in the meta-analysis. The association results for the SNPs on 16 candidate

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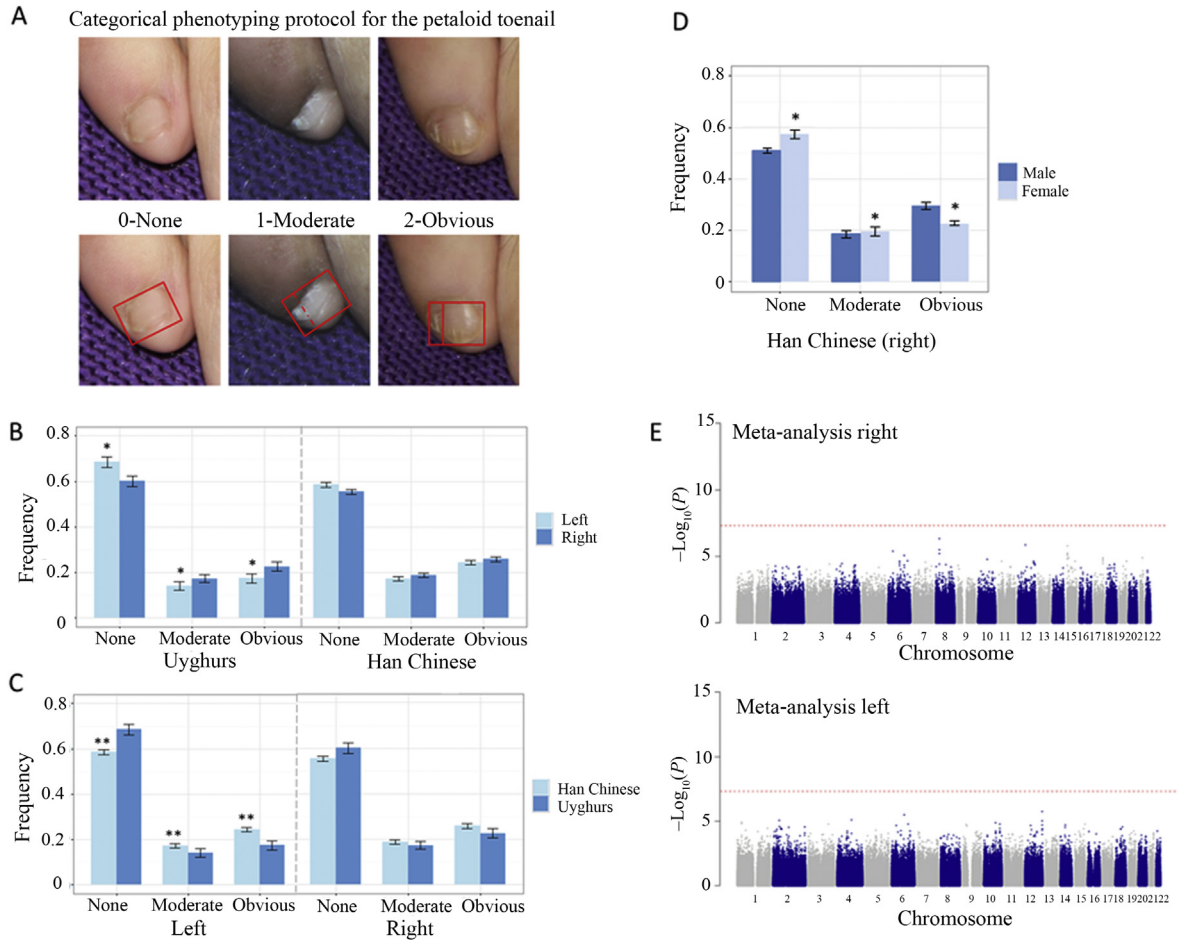

Fig. 1. Characterization and analysis results of petaloid toenail. **A:** Categorical phenotyping protocol of petaloid toenail. Level 0: the toenail is complete, and has no petaloid. Level 1: moderate petaloid. Level 2: obvious petaloid. **B:** Frequency of petaloid toenail from different sides of foot in Han Chinese and Uyghur populations. The light blue bar shows the frequency of petaloid toenail on left foot. The dark blue bar shows the frequency on the right. *, $P < 0.05$. **C:** Frequency of petaloid toenail from different populations on both sides of foot. The light blue bar shows the frequency of petaloid toenail in Han Chinese. The dark blue bar shows the frequency in Uyghurs. **, $P < 0.01$. **D:** Frequency of petaloid toenail on right foot in Han Chinese between two genders. The frequency of petaloid toenail in males is marginally more than in females. The light blue bar shows the frequency of petaloid toenail in females. The dark blue bar shows the frequency in males. *, $P < 0.05$. **E:** Manhattan plot showing the result of meta-analysis of petaloid toenail of the Han Chinese and Uyghurs. Manhattan plots illustrate the results of the genome-wide scan adjusted for gender, age and top four ancestral PCs (principal components) on meta-analysis. The top PCs calculated from the genotype data reflect population structure among the sample individuals. The red line indicates the threshold for genome-wide statistical significance ($P < 5 \times 10^{-8}$).

genes related to nail development are summarized in Table S3 (see supplementary data for the choice of genes and inclusion of SNPs). We further performed the association analysis of the derived petaloid toenail phenotypes Petaloid_E and Petaloid_D, but did not find any significant signals either (Table S4).

The results of our genome-wide scans indicate that petaloid toenail is a heritable trait. However, instead of following a Mendelian pattern of inheritance, as previously suggested, petaloid toenail is likely to be a complex trait affected by multiple genes with minor genetic effects. Future studies involving a larger sample size might be able to pinpoint the genes underlying the petaloid toenail phenotype.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jgg.2016.10.003.

References

Chi, C.C., Wang, S.H., 2004. Inherited accessory nail of the fifth toe cured by surgical matricectomy. Dermatol. Surg. 30, 1177–1179.
Gao, J., 2010. The Last One of Xiongnu. Beijing October Literary Press. Beijing Publishing Group, Beijing.

Hao, W., Bian, J., Zhu, P., 2005. Petaloid toenails: its types, distribution and hereditary mode-a survey of a village in Zhouzhi county, Shaanxi Province, China. Acta Anthropol. Sin. 24, 319–327.
Xu, S., Jin, L., 2008. A genome-wide analysis of admixture in Uyghurs and a high-density admixture map for disease-gene discovery. Am. J. Hum. Genet. 83, 322–336.
Yang, J.A., Lee, S.H., Goddard, M.E., Visscher, P.M., 2011. GCTA: a tool for genome-wide complex trait analysis. Am. J. Hum. Genet. 88, 76–82.

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