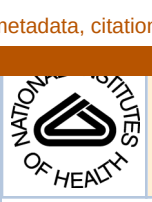

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Hallux Valgus and Lesser Toe Deformities are Highly Heritable in Adult Men and Women: the Framingham Foot Study

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Abstract

Objective—To estimate heritability of three common disorders affecting the forefoot: hallux valgus, lesser toe deformities and plantar forefoot soft tissue atrophy in adult Caucasian men and women.

Methods—Between 2002-2008, a trained examiner used a validated foot exam to document presence of hallux valgus, lesser toe deformities and plantar soft tissue atrophy in 2,446 adults from the Framingham Foot Study. Among these, 1,370 participants with available pedigree structure were included. Heritability (h^2) was estimated using pedigree structures by Sequential Oligogenic Linkage Analysis Routines (SOLAR) package. Results were adjusted for age, sex and BMI.

Results—Mean age of participants was 66 years (range 39 to 99 years) and 57% were female. Prevalence of hallux valgus, lesser toe deformities and plantar soft tissue atrophy was 31%, 29.6% and 28.4%, respectively. Significant h^2 was found for hallux valgus (0.29 ~ 0.89, depending on age and sex) and lesser toe deformity (0.49 ~ 0.90 depending on age and sex). The h^2 for lesser toe deformity in men and women aged 70+ years was 0.65 ($p= 9\times10^{-7}$). Significant h^2 was found for plantar soft tissue atrophy in men and women aged 70+ years ($h^2 = 0.37$; $p=3.8\times10^{-3}$).

Conclusion—To our knowledge, these are the first findings of heritability of foot disorders in humans, and they confirm the widely-held view that hallux valgus and lesser toe deformities are highly heritable in European-descent Caucasian men and women, underscoring the importance of future work to identify genetic determinants of the underlying genetic susceptibility to these common foot disorders.

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No conflicts of interest

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version submitted for publication. Drs. Hannan, Hsu and Cheng had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs. Hannan, Menz, Jordan, Cupples and Hsu were responsible for Study conception and design.

Keywords

hallux valgus; lesser toe deformities; heritability; fat pad atrophy; foot disorders; pedigree

INTRODUCTION

Structural foot disorders affect up to 60% of community-dwelling older adults (1, 2) and are associated with mobility limitations (3, 4) and decreased health-related quality of life (5). Previous studies have identified female sex, older age and higher body mass index as risk factors for foot disorders (5, 6). However, there is little knowledge of the role played by genetic variations. The importance of genetics is commonly suspected in clinical observations that individuals with foot disorders tend to have other affected family members (7-13). These studies estimated that family history of hallux valgus was present in 63% to 90% of patients. To our knowledge, no study has yet estimated the heritability (h^2) of foot disorders. In addition, no linkage, candidate gene association, or genome-wide association studies (GWAS) on foot disorders have been performed.

Hallux valgus is one of the most common foot disorders, affecting approximately 23% of people aged 18 to 65 years and 36% of those aged over 65 years (14). The condition is characterized by the progressive subluxation of the first metatarsophalangeal joint due to lateral deviation of the hallux and medial deviation of the first metatarsal. The etiology of hallux valgus is not well understood. Several factors have been implicated, including ill-fitting footwear, sex, structural factors, biomechanical factors (15) and family history (7-10). Pique-Vidal et al (10) constructed pedigree charts from 350 patients across three generations and found that family history was positive in 90% of cases, with vertical transmission affecting some families across all three generations.

Deformities of the lesser toes (i.e., potentially all but hallux), affect between 24 and 60% of older people (1, 16-18). There are several different types of lesser toe deformities, which are classified according to the relative alignment of the metatarsophalangeal and interphalangeal joints. A hammer toe is a deformity in which the proximal interphalangeal joint is plantarflexed, and the metatarsophalangeal joint may be hyperextended. A mallet toe is a fixed deformity in which the distal interphalangeal joint is plantarflexed. A claw toe is a deformity in which the metatarsophalangeal joint is hyperextended, and both the proximal and distal interphalangeal joints are plantarflexed (19, 20). The Feet First study of 784 Americans aged over 65 years found that 35% of the sample had hammer toes, 33% had mallet toes, and 9% had claw toes (1). Factors considered to be associated with the development of lesser toe deformities include ill-fitting footwear (19, 21, 22), abnormal foot posture (both pes planus (23) and pes cavus (24)) and excessively long toes (25). Lesser toe deformities are also considered to have a hereditary basis in mutant mouse models (26), which narrowed down to a genomic region near *D5mit387* marker on mouse chr5.

Many individuals with hallux valgus and/or lesser toe deformity also develop atrophy of the plantar soft tissues under the metatarsal heads (27). However, whether this is also a heritable component of each of these conditions is unclear, as degeneration of plantar soft tissues is also associated with aging and conditions such as rheumatoid arthritis, peripheral vascular disease and diabetic neuropathy (28-30). Determining which aspects of these common forefoot disorders are heritable would improve our understanding of their underlying pathophysiology and assist in identifying high-risk individuals for early intervention. Therefore, the aim of this study was to examine the overall heritability (adjusting for age, sex and BMI) as well as age- and sex-adjusted heritability of hallux valgus, lesser toe

deformities and plantar forefoot soft tissue atrophy in adult Caucasian men and women from the Framingham Foot Study families.

METHODS

Study Population

The Framingham Foot Study (n=2446 participants examined in 2002-2008) was designed to examine common foot disorders and functional limitations. A trained examiner used a validated foot exam to assess specific foot disorders in 1076 male and 1370 female participants (31). The structural foot disorders (hallux valgus, lesser toe deformities and plantar forefoot soft tissue atrophy) were assessed in the Framingham participants. Disorders were indicated as present or absent based on an atlas of pictorial depictions of each foot disorder. Presence of hallux valgus (yes/no) was evaluated based upon visual inspection and considered to be present if there was a medial bony enlargement of the first metatarsal head and if the weight bearing angle of the hallux towards the lesser toes was observed to be greater than 15 degrees. For this study, lesser toe deformities included hammer toes, claw toes, and overlapping toes. Hammer toes (yes/no) were considered present if the second, third, fourth or fifth toes appeared contracted at one or both joints while weight-bearing. Claw toes (yes/no) were similarly assessed and present when both joints were contracted or clenched while weight-bearing. Overlapping toes were considered present when any toe was observed to be at least 50 percent on top of an adjacent toe. Plantar forefoot soft tissue atrophy was determined by standardized palpatory clinical examination (with the examiner calibrated to 3 pounds of palpatory pressure against a dolorimeter) of the boney prominence of the metatarsal heads and the surrounding soft tissues. Possible confounders that we used as covariates in our analyses included age, sex, and body mass index (BMI). Age at exam was recorded. Weight in pounds was measured using a standardized balance beam scale and recorded to the nearest ½ pound. Height (without shoes) was measured in inches using a calibrated stadiometer and recorded to the nearest ¼ inch. BMI was calculated as weight in kilograms divided by height in square meters. The study participants have given informed consent for the data collection and this study has undergone institutional review by both the Hebrew SeniorLife IRB and the Boston University Medical Center IRB.

Statistical Analysis

Among examined individuals, 1,370 participants (from 429 families with family size that ranged from 2 examined individuals to 22 examined individuals) with available pedigree structure were included in the statistical analysis for h^2 estimation. Briefly, “pedigree structure” is a family tree that shows the relationship among each family member within a family. The parent-offspring and offspring-offspring (siblings) relations were used in our study to estimate heritability. When the parents’ information of foot disorders was unknown, only offspring-offspring relations were used. All of the relationship pairs in our study had their foot phenotype measured.

Heritability is the proportion of total variation between individuals in pedigrees in a given population attributable to genetic variation (32). This narrow-sense heritability (h^2) is defined as a ratio of variances, the proportion of total variance in a population for a particular measurement (phenotype) that is attributable to variation in additive genetic or total genetic effects. H^2 can range from 0 (no genetic contribution; the phenotype is not heritable) to 1 (all differences on a trait reflect genetic variation; the phenotype is highly heritable). As benchmarks for h^2 in adult human population, one may consider adult height which ranges from 0.68 to 0.93 depending on sex, age, geographic locations and populations (33). The h^2 of BMI in a Caucasian population is estimated at 0.44, (34) whereas the h^2 was estimated at 0.26 for type 2 diabetes in Caucasian populations (35). Our estimates of h^2 were

obtained from a standard quantitative genetic variance-components model implemented in the Sequential Oligogenic Linkage Analysis Routines (SOLAR) package. A liability threshold model was applied for dichotomous traits in the current study (36). Briefly, in order to estimate the variance of a dichotomous trait (all-or-none disease status) that is due to additive genetic effects, one assumes an underlying normally-distributed liability phenotype, which is the sum of the independent normally-distributed genetic and environmental components. The assumption indicates that the liability to disease is multi-factorial and the contributions from each genetic risk factor are small. When the score on the scale of the liability distribution exceeds a specific threshold then the individual has a disease value of 1 and otherwise it is 0. The proportion that exceeds the threshold of the underlying liability distribution is equal to the disease incidence.

Due to the small sample size in each of the age- and sex-specific stratum, for statistical analyses, we pooled individuals of ages ≤ 60 years old together and we also grouped individuals of ages > 70 years old, so that we have similar sample size across three age groups. We estimated overall, sex-specific and age-specific (<60, 61-70 and >70 years old) h^2 values for hallux valgus, lesser toe deformities, and plantar forefoot soft tissue atrophy. Overall h^2 estimates were adjusted for age, sex and BMI.

RESULTS

The mean age of the participants was 66 years (range 39 to 99 years). Among participants, 57% were female. The prevalence of hallux valgus, lesser toe deformities and plantar soft tissue atrophy was 31%, 29.6% and 28.4%, respectively. Table 1 reports the age- and sex-specific prevalence of hallux valgus, lesser toe deformity and plantar soft tissue atrophy. The prevalence of hallux valgus and plantar soft tissue atrophy was higher in women compared to the prevalence in men across the age groups. However, compared to men, the prevalence of lesser toe deformities was higher only in women aged 70+ years. Increased prevalence of these three foot disorders was found in older age groups for both men and women. Almost half of the women aged 70+ years had hallux valgus, lesser toe deformity and/or plantar soft tissue atrophy.

Due to the small sample size in each of the age- and sex-specific stratum seen in Table 1, we pooled individuals of ages ≤ 60 years old together and we also pooled individuals with ages > 70 years old, so that we had similar sample size across three age groups. The number of parent-offspring pairs, same-sex sibling pairs and same-sex half-sibling pairs among our study participants within each sex-and age-specific stratum used in analyses are shown in Table 2. There were 248 parent-offspring pairs, 296 same-sex sibling pairs and 5 same-sex half-sibling pairs. All three types of informative family relations (parent-offspring, siblings, half-siblings) were used to estimate the h^2. The total numbers of informative family relationship pairs were 134, 72 and 35 pairs for men in ≤ 60, 61-70 and ≥ 71 years old groups, respectively; and 154, 84, 70 pairs for women in ≤ 60, 61-70 and ≥ 71 years old groups, respectively. The number of these informative family relation pairs, especially parent-offspring pairs, decreased in the older age groups, which affected the statistical power of the h^2 estimation.

Table 3 reports the h^2, SE of h^2 and p-values of hallux valgus, lesser toe deformity and plantar soft tissue atrophy using the 1370 study participants in the heritability analyses. The overall age-, sex- and BMI-adjusted h^2 of hallux valgus was 0.29 with p-value of 3.9×10^{-3} (h^2=0.39 for women and 0.36 for men). The highest h^2 was observed in women aged less than 60 years (h^2=0.89; $p=3.2\times10^{-3}$). Due to smaller sample size, we could not estimate h^2 of hallux valgus for men in the age group 71-100 years due to lack of informative family

relations. In addition, the h^2 value for hallux valgus in men did not reach statistical significance.

The age, sex and BMI adjusted h^2 of lesser toe deformities was 0.56 with p-value of 4×10^{-7} (h^2=0.85 for women and 0.61 for men). The highest h^2 of lesser toe deformities was observed in 70+ age group (when examined by sex, this h^2 was 0.90, $p=4.5\times10^{-3}$ for men; h^2=0.80, $p=1.4\times10^{-4}$ for women). The age, sex and BMI adjusted h^2 of plantar soft tissue atrophy was 0.09 with non-significant p-value of 2.5×10^{-1}. Significant h^2 was found for plantar soft tissue atrophy only in men and women aged 70+ years (h^2 = 0.37; $p=3.8\times10^{-3}$ 0.0038).

DISCUSSION

We found in the Framingham Foot Study samples of European ancestry that hallux valgus and lesser toe deformities are heritable. To our knowledge, these are the first findings of heritability of these foot disorders in humans. We observed moderate to high heritability for hallux valgus (h^2=0.29 ~ 0.89, depending on age and sex) and lesser toe deformity (h^2=0.49 ~ 0.90 depending on age and sex), suggesting that there are genetic variants, common and/or rare, affecting hallux valgus and lesser toe deformity, two of the most common structural foot disorders affecting up to half of older adults in the U.S. and European countries. In contrast, plantar soft tissue atrophy did not demonstrate significant heritability in the same study population. This study reveals new findings in an area that has received little attention, yet is critically important to general populations.

Despite having data from (thus far) the largest study of these foot disorders with family data, we were unable to estimate the distribution of heritability within the specified age groups and we had to pool several age strata for h^2 estimation. In addition, we observed several higher h^2 estimations, particularly in the younger age group, that were not statistically significant. This may be due to lack of statistical power in some age- and sex-specific strata. The original study sampling was not designed for age- and sex-specific h^2 estimation. Even though we attempted to pool samples across age strata, the number of informative family relation pairs in the older age group is far less than the number of informative family relation pairs for the age groups of middle-aged participants (Table 2), especially for the parent-offspring pairs, since far fewer parents of the elderly participants were available (alive) for us to ascertain their foot phenotypes. When we compared our sample size to a previous simulation for statistical power of h^2, we did not have adequate power (70%) when the number of informative family relation pairs was less than 50 pairs (37). In addition to the small numbers of informative family relation pairs, statistical power was also affected by the number of affected participants with foot disorders within each sex-and age-stratum, affecting our ability to obtain a robust estimation of h^2. This is especially true for those age- and sex-strata with very high h^2 that did not achieve statistical significance. Therefore, additional samples are needed to obtain the robust age-specific h^2 of several subsets of the foot disorders considered in our study.

Given that congenital hallux valgus is extremely rare (38), our finding that hallux valgus is heritable in adults raises questions as to which anatomical or functional characteristics are inherited that may predispose to the development of the condition in later life. Anatomical factors such as a large first-second inter-metatarsal angle, an excessively long first metatarsal and a round first metatarsal head have recently been shown to be associated with increased hallux valgus severity in older people, and it has been speculated that these foot structures may be more susceptible to lateral deviation of the hallux and subsequent hallux valgus deformity as a result of footwear compression (39). It is also possible that anomalous muscle insertions may predispose to hallux valgus. An analysis of cadaver feet by Gunal et

al (40) revealed that an abnormal tendinous expansion of the tibialis posterior tendon onto the oblique head of adductor hallucis was present in all feet with hallux valgus and none without. Theoretically, this anatomical variation would provide a mechanical advantage of adductor hallucis over abductor hallucis, thereby pulling the hallux laterally. Similarly, Al-Saggaf (41) reported that cadaver feet with hallux valgus were more likely to have accessory tendinous insertions of extensor hallucis longus into the dorsal and medial aspects of the proximal phalanx, which would also promote lateral displacement of the hallux when the first metatarsophalangeal joint dorsiflexes.

The underlying anatomical or functional mechanism responsible for the high heritability of lesser toe defomities is similarly speculative, although it has been suggested that individuals with excessively long toes may be predisposed to subsequent toe deformity due to footwear compression (25). Alternatively, it is possible that abnormal foot posture (either pes planus (23) or pes cavus (24)) is also heritable, and that the muscular adaptations that occur over time in these foot types may lead to the development of toe deformity.

Plantar soft tissue atrophy was not significantly heritable in our sample, with the exception of those aged 71 to 100 years (h^2=0.37). This result was expected, as although degeneration of plantar soft tissues is frequently observed in people with toe deformities, it is most commonly associated with other systemic conditions such as rheumatoid arthritis, peripheral vascular disease and diabetic neuropathy (28-30). The significant (but modest and age-specific) heritability we observed could simply represent heritability of these comorbidities rather than the association with toe deformities. In addition, plantar soft tissue atrophy was documented from a simple clinical assessment rather than diagnostic ultrasound or magnetic resonance imaging. Therefore, it is likely that some degree of misclassification occurred, particularly in those with retracted toes where the plantar soft tissues are commonly displaced anteriorly.

To our knowledge, the current study is thus far the largest study to estimate the heritability of three common foot disorders in an adult population. Nevertheless, there are limitations that must be acknowledged. As noted above, with our sample size, after stratifying by sex and age, particularly for the younger age groups, we had limited statistical power to estimate heritability either due to small sample size or the lack of available informative families. In addition, the heritability was estimated in a European-descent Caucasian population, and the heritability estimation may not be generalizable to other ethnic groups. It would be interesting to know the heritability of these foot disorders in African populations, since the prevalence of hallux valgus and lesser toe deformity are thought to be high in African-Americans and their ancestral genetic background is different from the ancestral genetic background of Caucasian populations. Also we evaluated hallux valgus visually as present or absent. Other methods allow quantification of hallux valgus and its severity, such as foot radiographs or the non-invasive Manchester Scale for hallux valgus(42-44). Another limitation is that we used the age at examination (prevalence) as we did not have information on age at onset of the foot condition (incidence). While using prevalence data is done in many studies, we may have under-estimated heritability in younger age groups since many study participants certainly already had these foot disorders years before our foot examination. In addition, our narrow-sense heritability estimation only captures the portion of the variance due to additive (allelic) genetic effects, but did not consider potential epistatic (multi-genic interactions) effects, which may also under-estimate heritability. The heterogeneity of anatomical and mechanical factors of these foot disorders may also affect heritability estimations. Heritability estimates reflect the amount of variation in genotypic effects compared to variation in environmental effects. A better assessment of other environmental risk factors relevant to these foot disorders would also improve the accuracy of heritability estimation.

In conclusion, we observed that hallux valgus and lesser toe deformities, two types of common structural foot disorders in older adults, were highly heritable in a Caucasian adult population, suggesting genetic predisposition to the risk of developing hallux valgus and lesser toe deformities. Identifying these genetic determinants can further our understanding of the etiology and biological mechanisms underlying hallux valgus and lesser toe deformities, with an eye toward early prevention.

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Significance and Innovation

- To our knowledge, no study has yet estimated the heritability (h^2) of foot disorders. Thus, these are the first findings of heritability of foot disorders in humans.
- Hallux valgus and lesser toe deformities, two types of common structural foot disorders in older adults, were highly heritable in a Caucasian adult population (n=1370), suggesting genetic predisposition.
- This study reveals new findings in an area that has received little attention, yet is critically important to general populations. Identifying those genetic determinants linked to the risk of developing hallux valgus and lesser toe deformities can further our understanding of the etiology and biological mechanisms underlying these foot disorders, with an eye toward early prevention.

Table 1

Prevalence of hallux valgus, lesser toe deformity and plantar soft tissue atrophy by age and sex in Framingham Foot Study participants

Age (yrs)	39-50	51-60	61-70	71-80	81-90	91-100
Men	N=43	N=248	N=414	N=234	N=124	N=13
Hallux valgus	7 (16)	45 (18)	75 (18)	51 (22)	29 (23)	5 (38)
Lesser toe deformity	6 (14)	39 (16)	121 (29)	71 (30)	66 (53)	6 (46)
Plantar soft tissue atrophy	0 (0)	11 (4)	70 (17)	95 (41)	65 (52)	9 (69)
Women	N=46	N=354	N=444	N=291	N=205	N=30
Hallux valgus	14 (30)	113 (32)	162 (36)	127 (44)	120 (59)	16 (53)
Lesser toe deformity	7 (15)	55 (16)	116 (26)	128 (44)	118 (58)	20 (67)
Plantar soft tissue atrophy	0 (0)	21 (6)	101 (23)	145 (50)	132 (64)	16 (53)

Numbers in cells are N (%), unless otherwise noted

Arthritis Care Res (Hoboken). Author manuscript; available in PMC 2014 September 01.

Table 2

Number of informative family relation pairs in Framingham Foot Study participants

	Men			Women			Total
Age (yrs)	**39-60**	**61-70**	**71-100**	**39-60**	**61-70**	**71-100**	
Parent-offspring	77	36	3	88	42	2	248
Same sex siblings	54	36	32	66	41	67	296
Same sex half-siblings	3	0	0	0	1	1	5
All	134	72	35	154	84	70	549

Table 3

Heritability (h^2) of hallux valgus, lesser toe deformity and plantar soft tissue atrophy overall and stratified by age and sex in Framingham Foot Study participants

	Men and Women				Men				Women			
	All	**39-60**	**61-70**	**71-100**	**All**	**39-60**	**61-70**	**71-100**	**All**	**39-60**	**61-70**	**71-100**
Hallux valgus												
h^2	0.29	0.45	0.15	0.38	0.36	0.84	0.28	N/A	0.39	0.89	0.31	0.39
SE	0.248	0.195	0.279	0.345	0.252	0.750	0.417	N/A	0.122	0.202	0.253	0.231
P-value	3.9×10^{-3}	3.7×10^{-3}	2.1×10^{-1}	8.0×10^{-3}	1.2×10^{-1}	2.0×10^{-1}	2.9×10^{-1}	N/A	9.0×10^{-3}	3.2×10^{-4}	1.6×10^{-1}	4.0×10^{-2}
Lesser toe deformity												
h^2	0.56	0.56	0.49	0.65	0.61	0.66	0.64	0.90	0.85	0.60	0.69	0.80
SE	0.107	0.027	0.292	0.116	1.167	0.481	0.361	0.328	0.207	1.180	1.107	0.199
P-value	4.0×10^{-7}	5.2×10^{-3}	4.5×10^{-3}	9.0×10^{-7}	6.8×10^{-3}	$6.0 \times 10^{-}$	4.0×10^{-2}	4.5×10^{-3}	2.3×10^{-5}	8.0×10^{-2}	1.0×10^{-3}	1.4×10^{-4}
Plantar soft tissue atrophy												
h^2	0.09	0.73	0.19	0.37	0.24	0.55	0.62	0.64	0.21	0.90	0.11	0.43
SE	0.148	0.329	0.161	0.302	0.321	1.850	0.395	0.205	0.229	0.478	0.58	0.381
P-value	2.5×10^{-1}	6.0×10^{-2}	2.0×10^{-1}	3.8×10^{-3}	2.2×10^{-1}	$4.2 \times 10^{-}$	1.0×10^{-1}	1.8×10^{-2}	1.7×10^{-1}	4.6×10^{-2}	4.2×10^{-1}	2.8×10^{-2}

Note: Overall h^2 estimates were adjusted by age, sex, and BMI. N/A indicates insufficient informative families available to estimate h^2