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Unraveling the Genetic Landscape of Foot Arch Morphology: A Systematic Review of Single Nucleotide Polymorphisms

Yukun He[1,2] | Marlies Verleyen[1] | Bert Callewaert[3,4] | Arne Burssens[2] | Emmanuel Audenaert[1,2]

[1]Department of Human Structure and Repair, Faculty of Medicine and Health Sciences, Ghent University, Ghent, Belgium | [2]Department of Orthopedic Surgery and Traumatology, Ghent University Hospital, Ghent, Belgium | [3]Department of Biomolecular Medicine, Ghent University, Ghent, Belgium | [4]Center for Medical Genetics, Ghent University Hospital, Ghent, Belgium

Correspondence: Marlies Verleyen (marlies.verleyen@ugent.be)

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ABSTRACT

Variations in foot arch morphology, including flat feet (pes planus) and high arches (pes cavus), range from asymptomatic to debilitating. Limited research exists on the genetics of foot arch geometry. This systematic review aims to identify single nucleotide polymorphisms (SNPs) linked to foot arch morphology. The review protocol was registered in PROSPERO (CRD42024537877). PubMed, The Cochrane Library, Embase, and Web of Science were searched for studies on SNPs related to foot arch morphology published up to December 2023. Nineteen eligible studies (2006–2020) identified 137 SNPs across conditions affecting connective tissue (12 studies, e.g., Marfan Syndrome), nerves (six studies, e.g., Charcot–Marie–Tooth Disease), and muscles (one study, e.g., Distal Arthrogryposis Syndromes). While no studies directly linked SNPs to foot arch morphology, three explored SNPs in genetic diseases associated with foot arch variations. Pes planus was linked to connective tissue disorders, and pes cavus to neuropathies and myopathies. Only two replicated SNPs were found. This review found no direct studies of SNPs influencing foot arch morphology, highlighting a significant research gap. Future research should examine SNPs in larger cohorts to differentiate natural variations from pathology-driven deformities. To enhance reproducibility, standardized methodologies, and a unified genetic database (including phenotypic data on common traits) should be developed.

1 | Introduction

Bipedal walking, a form of terrestrial locomotion on two legs is one of the most critical features distinguishing hominins (humans and their bipedal ancestors) from other primates [1]. This evolutionary trait occurred in human origins and required the complete reconfiguration of the musculoskeletal morphology of the lower limb and the foot complex in particular [1–4].

The foot arch system, also known as the foot core, comprises three subsystems: passive (bones and joints), active (muscles), and neural (sensory). The passive subsystem includes the

Abbreviations: CMT, Charcot Marie Tooth; DA, Distal Arthrogryposis syndromes; EDS, Ehler-Danlos syndrome; GO, gene ontology; GWAS, Genome-Wide Association Study; MAF, Minor Allele Frequency; NGS, next-generation sequencing; PCR-DS, polymerase chain reaction-direct sequencing; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; PTTD, posterior tibial tendon dysfunction; SEMDJL, Spondyloepimetaphyseal Dysplasia with Joint Laxity; SNP, single nucleotide polymorphism; WES, whole exome sequencing.

Yukun He and Marlies Verleyen are contributed equally to this work.

plantar fascia [5], plantar ligaments [6], and the spring ligament [6], which collectively maintain the integrity and shape of the medial longitudinal arch. The active subsystem, crucial for maintaining arch shape and gait stability, involves intrinsic foot muscles (local stabilizers) and larger leg muscles attaching to the foot (global movers) [7]. They work together to control arch deformation during the heel-to-toe roll of the foot during each step. The neural subsystem, a sensory network with receptors in various structures, monitors forces and motion, relaying information to the brain to adjust muscle activation for optimal foot function and stability [7]. This intricate interplay ensures proper foot mechanics.

With recent technological advancements, such as weight-bearing CT scanning, the evaluation of foot geometry becomes more evident and detailed [8–10]. This is particularly due to specific variations in three-dimensional foot arch morphology, which is paramount to assess during the clinical diagnostic process. Variations in foot geometry, such as low-arched feet (pes planus or flat feet), high-arched feet (pes cavus or hollow feet), and metatarsus adductus deformities, are common anatomical variants. Pes planus, or flat feet, is particularly prevalent. Studies have shown that the prevalence of pes planus among children ranges from 58% to 94%, especially among obese children. In adults, the prevalence varies between 2.2% and 59%, with 19% to 37% of adults in random samples exhibiting some degree of pes planus, and about 11% of these being symptomatic and seeking medical attention [11–13].

In addition, the impact of foot type on shock absorption during gait varies across pes planus, pes cavus, and cavovarus [14]. All deformities limit shock absorption that is subsequently translated to increased stress on the forefoot and ankle joints [14]. Cavovarus, a subtype of pes cavus, further complicates gait mechanics due to its pathological malposition often caused by underlying muscular imbalances associated with neurological conditions [15].

There is significant regional and ethnic variation in the prevalence of these foot arch variations. However, there is no existing literature detailing the genetic background of these variations. While the heritability of common flat feet (pes planus) is a topic of ongoing research, specific heritability percentages are not yet explicitly detailed in current literature.

In contrast, variance in foot arch geometry often presents as a typical feature in several well-defined and genetically explored clinical conditions, including disorders of connective tissue and specific neuromuscular manifestations, to rare genetic syndromes [14, 16]. For example, a study involving individuals with hypermobile or classic Ehlers-Danlos Syndrome (EDS) noted a high prevalence of foot deformities: 20% had flat feet, 47% had normal feet, and 33% had high-arched feet. These deformities are associated with high levels of pain, disability, and reduced quality of life [17].

Clinically, differentiating between normal variations and disease-related variants in foot arch morphology remains a challenge [18]. Therefore, this review will focus on syndromes linked to maladaptive foot arches, encompassing a broad spectrum of underlying causes.

With the increasing availability and decreasing cost of genetic testing, identifying and studying relevant genetic markers that might help distinguish between normal and disease-related foot arch variants is becoming more important [19]. Single nucleotide polymorphisms (SNPs) are common genetic variations and account for the majority of polymorphisms responsible for human disease [20]. These variations occurs in both coding and noncoding sequences and reflect a complex relationship influenced by population history, recombination, environmental factors, and selection.

Despite the established impact of foot type on gait mechanics and the available genetic tests, a comprehensive understanding of the genetic underpinnings of foot arch variations is scattered across the literature. We investigate a correlation for different foot-type morphologies by synthesizing existing research on SNPs associated with foot geometry. To our knowledge, such an overview is not present to date. Such knowledge may better differentiate between normal variations and disease-related foot arch problems.

2 | Methods

2.1 | Protocol

Electronic databases DARE, CDSR, and PROSPERO could not identify previously performed reviews investigating SNPs in relation to foot arch morphology. The literature was reviewed according to the Preferred Reporting Project for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. The work was registered in PROSPERO: CRD42024537877.

2.2 | Search Strategy

The databases, including PubMed, Cochrane Library, Embase, and Web of Science, were searched for studies investigating foot arch morphology-associated SNPs before November 2023. Starting with PubMed, the search strategy utilized a combination of free-text and MeSH terms. The search strategy was adapted to the other databases and can be found in Data S1. References were also screened for the identification of additional studies. The study language was limited to English. Data were extracted on December 1, 2023, and alerts were activated for new updates.

2.3 | Study Selection, Inclusion, and Exclusion Criteria

Initially, the search results were evaluated by screening the titles and abstracts of the selected publications. The in- and exclusion criteria of the full texts were assessed independently by two authors (YH and MV) (Table 1). Within this process, SNPs with a minor allele frequency (MAF) $\geq 1\%$ were prioritized. Variants with a MAF $< 1\%$ were excluded for two reasons: (1) they represent rare genetic variation and require large numbers of individuals to demonstrate an association with a specific phenotype; (2) we aim to study genetic variations that are representative of normal population-wide diversity.

TABLE 1 | The inclusion and exclusion criteria.

Inclusion criteria:
The study reported the association between SNPs and adult foot arch changes.
The study reported the association between SNPs and the occurrence or development of genetic diseases causing variations in adult foot arch morphology: 1. The foot arch changes are a common symptom of this disease. 2. Adult patients can have the ability to stand and walk independently.
Exclusion criteria:
Animal research or computational biology research without clinical validation.
Foot arch changes are caused by inflammation, infection, endocrine diseases, autoimmune diseases, trauma, or tumor.
The study only reported an association between SNPs and complications unrelated to foot arch changes.
Variants having a MAF $<1\%$.
Duplicated data or conference abstracts without original data.

2.4 | Data Extraction and Synthesis

Study characteristics and SNPs, including their associated genes and diseases defined by the original authors of the papers, were extracted and collected in a tabular format Excel file. For single nucleotide variants (SNVs) that do not report their rsID in articles, we searched for their rsID in the ClinVar database. In accordance with the impacts on different foot stabilizing structures, we decided to categorize the SNPs into three groups: connective tissue diseases, myopathy, and neuropathy. Additionally, the variant-to-gene mapping used included both functional annotation and the closest gene approach. Functional annotation involves linking genetic variants to genes based on their known or predicted biological functions. The closest gene approach, on the other hand, associates genetic variants with the nearest genes based on physical proximity in the genome. By using both methods, the mapping ensures that it considers both the functional relevance of the variants and their physical locations relative to genes identified in the selected GWAS. The study characteristics and SNPs were recorded and exploratory analyses were conducted in the above-mentioned Excel environment (Microsoft 365; Excel v2406). The results were presented using pie charts. To clarify the findings of previous research, an attempt was made to correlate SNP-associated genes with biological processes potentially involved in foot arch variations. A Gene Ontology (GO) enrichment analysis was conducted using EnrichR (https://maayanlab.cloud/Enrichr), with a specific focus on the GO Biological Process 2021 library. GO enrichment analysis is a well-established method to identify the enrichment of biological processes in an input gene set compared to all genes. The enriched biological processes help to explain the "function" of the input gene set [21]. EnrichR is a widely used web-based tool that facilitates such enrichment analyses by comparing input gene lists to large collections of annotated gene sets [22]. Statistical significance is assessed using Fisher's exact test, which calculates *p*-values, representing the chance that the input genes contributing to a certain biological process could have been randomly selected, to determine whether specific biological processes are associated with the input genes. Since multiple comparisons are performed, the Benjamini–Hochberg correction is applied to adjust *p*-values and control for false discoveries [22]. The most significant biological processes, called enriched terms, with an adjusted *p*-value (*q*-value) <0.05 are considered statistically significant.

2.5 | Quality Assessment

The quality of the genetic association studies tool (Q-Genie) was employed to evaluate the methodological quality of the included studies [23, 24]. With this 11-point scale it was possible to evaluate each article based on various criteria. Each aspect was rated from 1 to 7 (Data S2). According to the Q-Genie guidelines, in studies with a control group, scores ≤ 35 signify poor quality, scores between >35 and ≤ 45 indicate moderate quality, and scores >45 reflect high quality. In studies without a control group, scores ≤ 32 signify poor quality, scores between >32 and ≤ 40 indicate moderate quality, and scores >40 reflect high quality. YH and MV assessed the checklist separately for each study. Differences were resolved by a discussion with the senior author (AE). Due to the small sample sizes in studies on rare genetic diseases, it is often not feasible to perform matching of control and experimental groups, control for confounding factors, and conduct appropriate statistical analyses. Consequently, these studies did not receive scores on these points.

2.6 | Variant Information

The Ensembl genome browser 109 was used to collect variant information located within coding and non-coding sequences and the 5′ and 3′ untranslated regions (UTRs) [25]. The human reference genome used, GRCh38.p13, is a consensus sequence derived from a diverse human population across various geographical locations, reflecting the most common genetic variants observed.

3 | Results

3.1 | Study Selection

A total of 2005 articles were found after conducting the aforementioned search. A total of 368 duplicates were removed, and 1535 articles were excluded after a screening of titles and abstracts. As a result, we retrieved a total of 101 full-text articles. Out of these, 59 articles were excluded because the MAF of SNPs that were reported did not meet the inclusion criteria (MAF < 1%). Four articles were used as pilot studies employing a smaller and repeated dataset from a larger research project, four articles were classified as conference abstracts, and 10 articles described patients with severe conditions that made them unable to walk independently before adulthood, and therefore excluded as well. Six other articles were excluded as they were computational studies lacking clinical data. As a result, 19 studies were included in this review, ranging from 2006 to 2020 (Figure 1). An overview of the included studies can be found in Data S3.

3.2 | Study Characteristics

The key characteristics of the included studies encompass seven case–control studies, five cross-sectional studies, five parents-offspring trios studies, and two case series studies (Data S4, Figure 2).

The studies utilized different methods to detect genetic variations. These methods are categorized into two main groups: targeted variant detection and DNA sequencing. Targeted variant detection methods include low-throughput techniques such as Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) in five studies, and high-throughput methods like TaqMan Genotyping Assays in two studies and SNP chip in three studies. DNA sequencing methods in these studies included low-throughput Polymerase Chain Reaction-Direct Sequencing (PCR-DS) in five studies and Next-Generation Sequencing (NGS) in another five studies. The NGS methods comprised Whole-Genome Sequencing (WGS) in one study and Whole-Exome Sequencing (WES) in four studies.

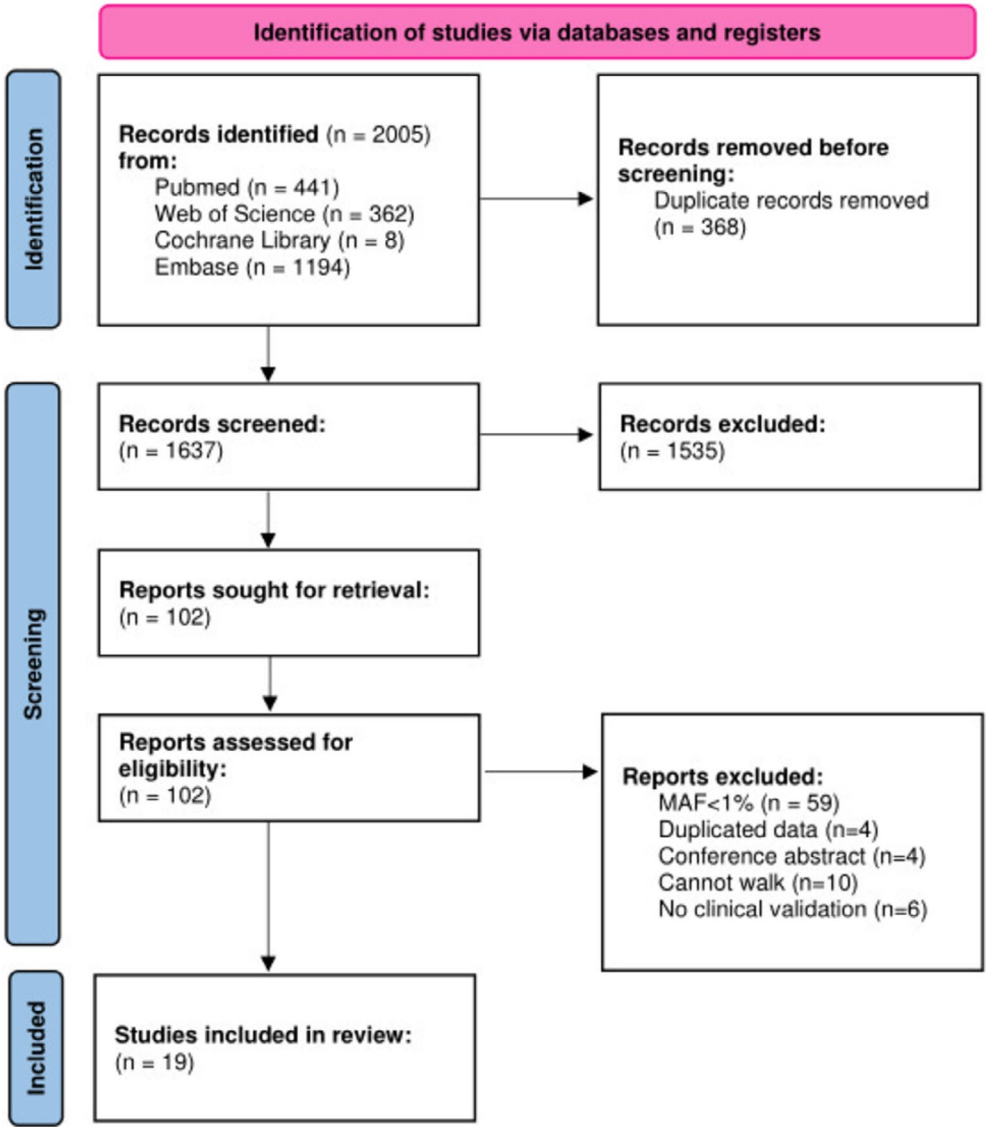

FIGURE 1 | PRISMA flow chart. [Colour figure can be viewed at wileyonlinelibrary.com]

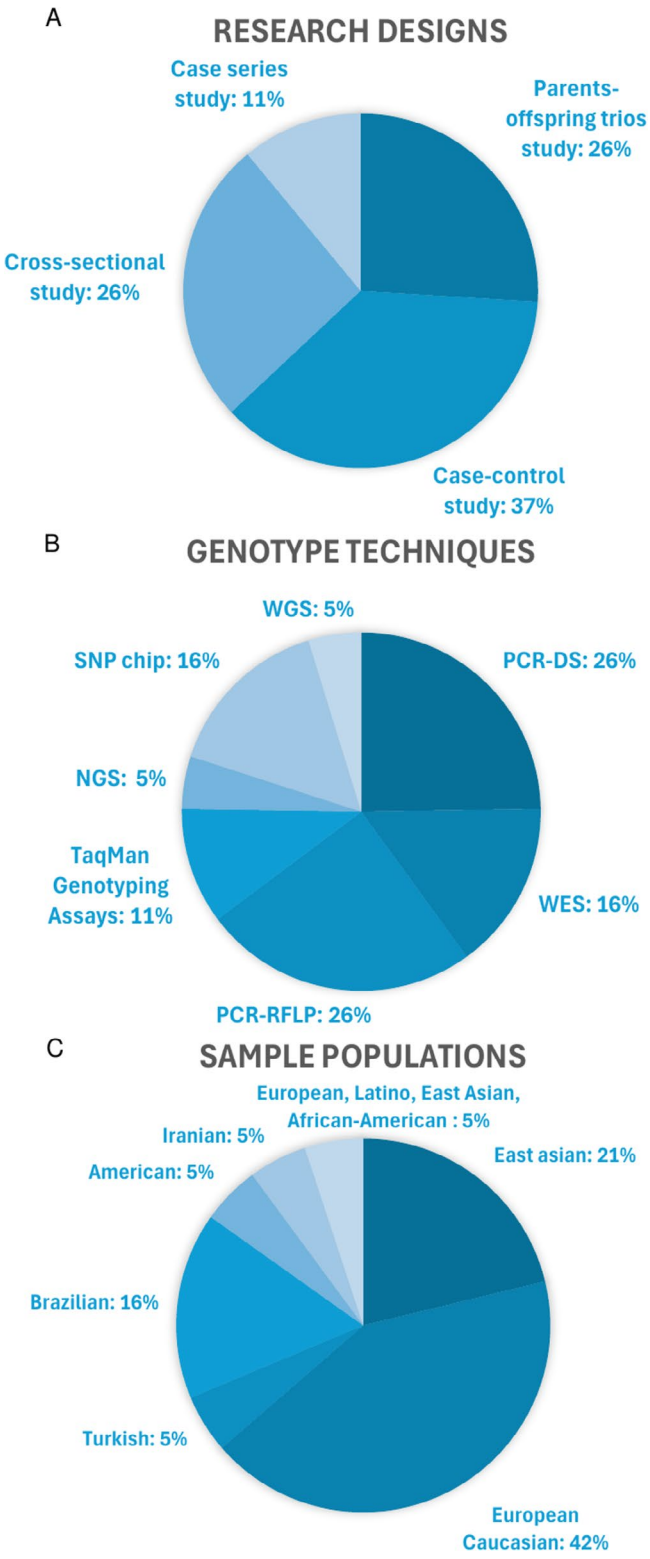

FIGURE 2 | Pie charts representing study characteristics. (A) Research designs, (B) genotype techniques, and (C) sample populations. [Colour figure can be viewed at wileyonlinelibrary.com]

Sample populations also varied. Eight studies included European Caucasians, four studies included East Asians, three studies included Brazilians, two studies included Middle Easterners, and one study included Americans. One study included participants of European, Latino, East-Asian, and African-American descent. All case–control studies and cross-sectional studies ($n = 12$) had sample sizes exceeding 100, while parent-offspring trios studies and case series studies ($n = 7$) had smaller sample sizes. For the studies documenting the average age and the female sex ratio, the mean age was 37.3 years, and the average female sex ratio was 54%.

3.3 | Study Quality Assessment

There are 15 high-quality studies according to the Q-Genie tool, including five cross-sectional studies, six case–control studies, three parents-offspring trios studies, and one case series study. Additionally, there are four medium-quality studies, comprising one case–control study, one case series study, and two parents-offspring trios studies (Data S5).

3.4 | Outcome

3.4.1 | Connective Tissue Disorder-Linked SNPs and Their Potential Impact on Foot Arch Geometry

Connective tissue diseases typically lead to insufficient support for the foot arch, causing the arch to flatten under the influence of body weight pressure and resulting in flatfoot. A total of 91 SNPs, identified across 12 studies, are associated with connective tissue diseases, including Spondyloepimetaphyseal dysplasia with joint laxity (SEMDJL) [26–28], Marfan syndrome [29], EDS [30–33], Posterior Tibial Tendon Dysfunction (PTTD) [34–36], and plantar fascial disorders [37]. Seventy-nine SNPs can be seen as common variations with an MAF greater than 5%, 60 of them have an MAF exceeding 30% (Data S6).

In connection with SEMDJL, 23 SNPs were identified across three studies, with 19 SNPs observed in people of European descent, three in people of Turkish descent, and two in East Asians. These SNPs are associated with genes related to extracellular matrix and connective tissue (*MATN1* and *COL1A2*), cytoskeleton and cell structure (*KRT18*, *KIF22*, and *THSD7B*), cell signaling (*KCNIP4*, *CRIM1*, and *PTPRD*), neuronal function (*SSH2* and *BTBD11*), metabolism (*PECI* and *ATP5G1*), immune response (*MAGEC1*), and epigenetic regulation (*MBD3L3*). Additionally, the functions of some genes, like *LOC100133991*, remain unknown or have not been well characterized. Eight SNPs are related to the *MATN1* gene. Rs2450399, associated with *KIF22*, has been replicated once.

In the context of Marfan syndrome, seven SNPs were identified across one study in the East Asian population. These SNPs are associated with *FBN1*, *FBN2*, and *TGFBR2*.

Four studies have linked SNPs to EDS. One study investigating an Italian population identified three of these genetic variations [33]. The fourth genetic variant rs12722, linked to the *COL3A1* and *COL5A1* collagen genes, has been consistently associated with increased joint range of motion in three studies [30–32]. Notably, this finding was replicated twice in independent studies, with participants of both East Asian and European descent.

PTTD is primarily considered a connective tissue disorder as it involves the gradual degeneration or tearing of the posterior tibial tendon, which is a connective tissue structure responsible for supporting the arch of the foot and stabilizing the ankle during walking. Eight SNPs have been associated with PTTD across three studies involving the Brazilian female population. These SNPs are linked to *MMP1*, *MMP8*, *MMP13*, *ERα*, and *ERβ*.

Forty-nine SNPs have been associated with *WWP2* and *TNFAIP8*, which are implicated in plantar fascial disorders. These disorders include the common plantar fasciitis, causing heel pain, and the rarer plantar fibromatosis, characterized by excessive fibrous hyperproliferation of the deep connective tissue of the foot.

3.4.2 | Myopathy-Linked SNPs and Their Potential Impact on Foot Arch Geometry

Myopathy is a condition that affects muscle function and structure, which can lead to different foot arch variations based on the distribution of muscle lesions. Widespread lesions causing restrictive movement are associated with distal arthrogryposis (DA) syndromes, a group of entities characterized by joint contractures in the distal limbs.

Researchers from one single study on myopathy found 29 different SNPs associated with the condition. All of them have an MAF greater than 5%, and even 25 SNPs have an MAF exceeding 30% (Data S7). Twenty-two were found in the Hispanic-American population, while eight were observed in individuals of European descent [38]. One SNP, rs17690195, was found in both populations. These SNPs are associated with genes related to functioning of the contractile proteins, including Myosin Heavy Chains genes (*MYH1*, *MYH2*, *MYH3*, *MYH4*, *MYH8*, and *MYH13*), Actin genes (*ACTA1*), Myosin Light Chain genes (*MYL1*), Myosin Binding Protein genes (*MYBPH*), Troponin genes (*TNNT3*), and Tropomyosin genes (*TPM1* and *TPM2*).

3.4.3 | Neuropathy-Linked SNPs and Their Potential Impact on Foot Arch Geometry

Charcot–Marie–Tooth Disease (CMT), is a hereditary neuropathy condition that damages nerves and can lead to high arches (pes cavus), and may present with a wide spectrum of foot abnormalities.

Six studies have identified 17 genetic variations linked to CMT, 16 of which are relatively common (MAF > 5%) and four being very prevalent (MAF > 30%) (Data S8) [39–44]. Ancestry also influenced these variations, with some SNPs more frequent in European ($n = 14$), Iranian ($n = 1$), or East Asian ($n = 2$) populations. For CMT1, variations are linked to genes like *LITAF* ($n = 3$), *LINC01346* ($n = 3$), *MIR149* ($n = 2$), and *SIPA1L2* ($n = 4$), while single SNPs were also found for *PMP22*, *LOC124904260*, and *DSCAM*. CMT2 is associated with the *MFN2* gene variation rs2236057. Finally, the SNP rs1025476 is linked to the *SH3TC* gene in CMT4.

3.5 | Variant Information of SNPs

Out of 137 SNPs potentially influencing foot arch morphology, we found that each SNP had a known variant consequence identified in Ensembl. Twenty-three variants were found in coding regions, with 12 being missense and 11 synonymous. Five variants were found in UTRs, and six variants were found in regulatory regions. Lastly, a total of 103 variants were found in other regions, including 82 introns, 13 intergenic regions, one in a transcription factor (TF) binding site, two in splice regions, and five in non-coding regions. An overview of the variants can be found in Data S9.

3.6 | Geno Ontology (GO) Analysis for SNP-Associated Genes Involved in Myopathy and Neuropathy

A GO enrichment analysis was performed on the SNP-associated genes found in the myopathies and neuropathies, found through the process of this systematic review. As a result, the analysis revealed several highly significant biological processes linked to genes implicated in myopathies and neuropathies (Figure 3). The most significant terms included actin-myosin filament sliding (GO:0033275) and muscle filament sliding (GO:0030049), both with a p-value of 1.21×10^{-16} and a q-value of 2.33×10^{-14}. Additionally, muscle contraction (GO:0006936) was identified with a p-value of 2.93×10^{-13} and a q-value of 3.74×10^{-11}. Other terms included external encapsulating structure organization (GO: 0045229) with a p-value of 1.37×10^{-9} and a q-value of 1.05×10^{-7}, and extracellular structure organization (GO: 0043062) with a p-value of 1.32×10^{-9} and a q-value of 1.05×10^{-7}.

4 | Discussion

This systematic review identified 137 SNPs across 19 studies that could demonstrate potential links to foot arch morphology in specific disease categories. Connective tissue disorders for which SNPs were associated with flatfoot susceptibility included SEDMJL (23 SNPs), Marfan syndrome (7 SNPs), EDS (4 SNPs), PTTD (8 SNPs), and plantar fascial disorders (49 SNPs). In myopathies, 29 SNPs potentially contributed to a higher foot arch in DA. Additionally, within neuropathic disorders, SNPs that may increase foot arch height were identified for CMT1 (1 SNP), CMT2 (1 SNP), and CMT4 (4 SNPs).

The descent of the foot arch is typically attributed to weakened muscles or connective tissues that support the foot arch. PTTD is considered one of the most important connective tissue-related causes of adult-acquired flat foot deformity (pes planus) [43, 45]. In addition, other connective tissue diseases including SEMDJL, Marfan Syndrome, EDS, and plantar fascial disorders, affect collagen production, resulting in weakened connective tissues and joint hypermobility. SNPs that modify the clinical severity of these conditions may contribute to the collapse of the foot arch [46].

Pes cavus has generally been attributed to a muscle imbalance, primarily caused by neurological disorders. Presently,

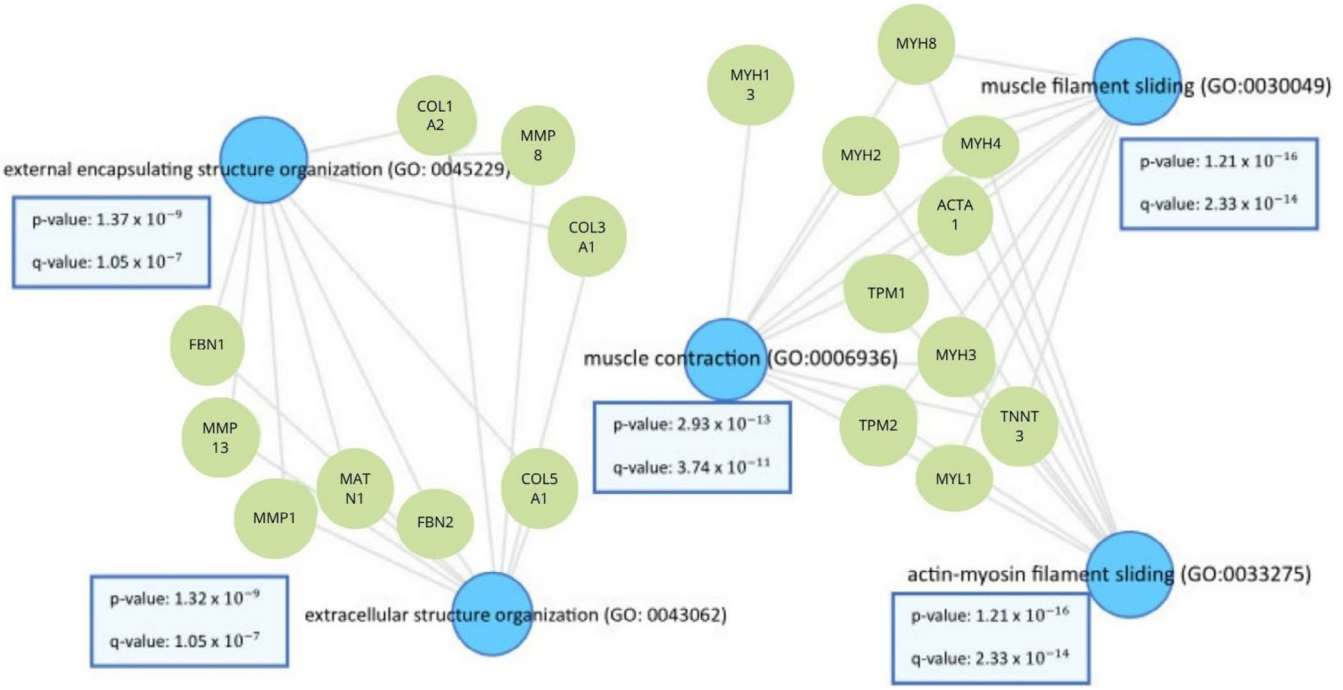

FIGURE 3 | Results of the GO analysis of the SNP-associated genes involved in myopathy (DA) and neuropathy (CMT1, CMT2, CMT4). [Colour figure can be viewed at wileyonlinelibrary.com]

in literature, two primary hypotheses are considered. The first hypothesis, by Piazza et al. posits that the fibularis peroneus longus muscle is more resistant to leg muscle atrophy than the anterior tibial muscle. If the tibialis anterior muscle is weaker compared to the fibularis peroneus longus, this imbalance can result in the plantar flexion of the first metatarsal bone and the formation of pes cavus [47]. The second hypothesis, introduced by authors such as Gallardo et al. implicates intrinsic foot muscle weakness in the development of pes cavus. This deformity is often observed in the early stages of the deformity when there is no evidence of weakness in the leg muscles [48]. Similarly, in our analysis, we observed a significant enrichment of muscle contraction and filament sliding, which underscores the importance of muscle function in the conditions studied. These results align with Piazza's hypothesis, which suggests that an imbalance in muscle strength, particularly a weaker tibialis anterior relative to the fibularis peroneus longus, could contribute to the formation of pes cavus. This suggests that genetic variations affecting these muscle contraction processes may underlie the muscle imbalances observed in pes cavus. However, CMT disease can be caused by more than 100 genetic variations, each leading to distinct phenotypes [49]. These phenotypes present with either pes cavus or pes planus, depending on the specific muscle weakness caused by varying degrees of demyelination and/or axonal loss, rather than a specific foot-related genetic defect [50].

The focus was on the direct association between genetic variants, specifically SNPs, and foot arch morphology. Nevertheless, diseases such as diabetic foot, rheumatoid arthritis, or tumors, may also affect foot arch morphology [13]. In addition, other environmental influences, such as footwear and activity levels, contribute to foot development [51]. Studies have shown that habitual footwear can alter foot structure, including changes to the arch and hallux angles, and that improper footwear fit can lead to deformities like hallux valgus [52, 53]. However, our investigation focused on genetic diseases known to influence foot arch variations and the associated SNPs. It is important to note that this review only encompasses a fraction of the potential SNPs linked to these diseases, as many genetic disorders are rare and limited by sample size.

Importantly, almost no replicated SNPs were retrieved from the literature, highlighting the lack of understanding of the genetic basis of common foot arch variations in general. While genetic diseases could offer insights into the role of SNPs in foot arch (de)formation, their impact on common foot arch variations remains largely unexplored [54, 55].

In conclusion, following a systematic review, we could not identify any studies directly investigating the correlation between SNPs and foot arch morphology, underscoring the need for further research to unravel the genetic architecture of common foot arch morphology in the general population. However, existing research focuses on genetic diseases associated with foot arch morphology variations, which may provide valuable insights into the specific role of SNPs in foot arch (de)formation.

4.1 | Limitations

This study encountered several limitations within the scope of the systematic review process. Firstly, in common with other systematic reviews, some papers may not have been identified with the search criteria we used. However, additional screening of the references was performed to improve the process.

Secondly, there is a lack of direct research on the relationship between SNPs and foot arch morphology, which may be attributed to the inherent complexity of foot arch morphological variations. Numerous distinct factors can contribute to changes in foot arch morphology, making it challenging to study it as a homogeneous condition.

Lastly, there is the study heterogeneity in methodologies, sample sizes, as well as variations in research quality. This can be attributed to the difficulty in obtaining a sufficient number of cases for some rare genetic conditions. Also, the majority of research has been focused on specific populations, such as Caucasians or East Asians, raising concerns about the generalizability of results to other racial or ethnic groups.

4.2 | Future Research

Studies were not directly investigating the role of SNPs in shaping the foot arch itself. Therefore, future research should conduct ethnically diverse large-scale genome-wide association studies (GWAS) using common SNPs (MAF > 1%), which may help to distinguish between natural foot arch variations (ideally under weight-bearing conditions) and or variations associated with foot-related complaints.

To improve reproducibility, standardized methodologies must be clearly defined. Developing a well-controlled unified database and establishing data-sharing networks that include data on common traits such as foot arch anomalies would enable meta-analyses, increasing the reliability of the associations between genetic variants, foot arch morphology, and foot-related complaints. Additionally, advances in imaging technologies, such as weight-bearing CT scans, would provide more detailed insights into how genetic and environmental factors interact to shape foot morphology. Therefore, close collaboration between geneticists, clinicians, and biomechanical researchers is important for translating genetic findings into meaningful clinical applications.

5 | Conclusion

In conclusion, our analysis of 19 studies identified 137 SNPs associated with genetic disorders, involving foot arch variations. While these studies provide insights, they do not directly address the genetic basis of common foot arch variations in the general population. A better understanding of the genetic basis of foot arch morphology could lead to more precise diagnostic criteria and tools, and pave the way for personalized management strategies to prevent foot-related complaints.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

Peer Review

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/cge.14730.

References

1. D. Schmitt, "Insights Into the Evolution of Human Bipedalism From Experimental Studies of Humans and Other Primates," *Journal of Experimental Biology* 206 (2003): 1437–1448, https://doi.org/10.1242/jeb.00279.

2. E. J. McNutt, B. Zipfel, and J. M. DeSilva, "The Evolution of the Human Foot," *Evolutionary Anthropology* 27 (2018): 197–217, https://doi.org/10.1002/evan.21713.

3. D. Babu and B. Bordoni, *StatPearls* (StatPearls Publishing LLC, 2024).

4. A. S. Gwani, M. A. Asari, and Z. I. Mohd Ismail, "How the Three Arches of the Foot Intercorrelate," *Folia Morphologica* 76 (2017): 682–688, https://doi.org/10.5603/FM.a2017.0049.

5. K. A. McDonald, S. M. Stearne, J. A. Alderson, I. North, N. J. Pires, and J. Rubenson, "The Role of Arch Compression and Metatarsophalangeal Joint Dynamics in Modulating Plantar Fascia Strain in Running," *PLoS One* 11 (2016): e0152602, https://doi.org/10.1371/journal.pone.0152602.

6. C. Cifuentes-De la Portilla, R. Larrainzar-Garijo, and J. Bayod, "Analysis of the Main Passive Soft Tissues Associated With Adult Acquired Flatfoot Deformity Development: A Computational Modeling Approach," *Journal of Biomechanics* 84 (2019): 183–190, https://doi.org/10.1016/j.jbiomech.2018.12.047.

7. P. Caravaggi, T. Pataky, M. Günther, R. Savage, and R. Crompton, "Dynamics of Longitudinal Arch Support in Relation to Walking Speed: Contribution of the Plantar Aponeurosis," *Journal of Anatomy* 217 (2010): 254–261, https://doi.org/10.1111/j.1469-7580.2010.01261.x.

8. F. Lintz, P. Beaudet, G. Richardi, and J. Brilhault, "Weight-Bearing CT in Foot and Ankle Pathology," *Orthopaedics & Traumatology, Surgery & Research* 107 (2021): 102772, https://doi.org/10.1016/j.otsr.2020.102772.

9. A. Barg, T. Bailey, M. Richter, et al., "Weightbearing Computed Tomography of the Foot and Ankle: Emerging Technology Topical Review," *Foot & Ankle International* 39 (2018): 376–386, https://doi.org/10.1177/1071100717740330.

10. J. Li, M. Fang, A. van Oevelen, et al., "Diagnostic Applications and Benefits of Weightbearing CT in the Foot and Ankle: A Systematic Review of Clinical Studies," *Foot and Ankle Surgery* 30 (2024): 7–20, https://doi.org/10.1016/j.fas.2023.09.001.

11. S. K. Ling and T. H. Lui, "Posterior Tibial Tendon Dysfunction: An Overview," *Open Orthopaedics Journal* 11 (2017): 714–723, https://doi.org/10.2174/1874325001711010714.

12. P. O. McKeon, J. Hertel, D. Bramble, and I. Davis, "The Foot Core System: A New Paradigm for Understanding Intrinsic Foot Muscle Function," *British Journal of Sports Medicine* 49 (2015): 290, https://doi.org/10.1136/bjsports-2013-092690.

13. T. J. Seaman and T. A. Ball, *StatPearls* (StatPearls Publishing LLC, 2024).

14. A. K. Buldt, S. Forghany, K. B. Landorf, P. Levinger, G. S. Murley, and H. B. Menz, "Foot Posture Is Associated With Plantar Pressure During Gait: A Comparison of Normal, Planus and Cavus Feet," *Gait & Posture* 62 (2018): 235–240, https://doi.org/10.1016/j.gaitpost.2018.03.005.

15. K. M. Kruger, A. Graf, A. Flanagan, et al., "Segmental Foot and Ankle Kinematic Differences Between Rectus, Planus, and Cavus Foot Types," *Journal of Biomechanics* 94 (2019): 180–186, https://doi.org/10.1016/j.jbiomech.2019.07.032.

16. H. J. Hillstrom, J. Song, A. P. Kraszewski, et al., "Foot Type Biomechanics Part 1: Structure and Function of the Asymptomatic Foot," *Gait & Posture* 37 (2013): 445–451, https://doi.org/10.1016/j.gaitpost.2012.09.007.

17. I. C. Palomo-Toucedo, C. Vázquez-Bautista, P. V. Munuera-Martínez, G. Domínguez-Maldonado, J. M. Castillo-López, and M. Reina-Bueno, "Podiatry Alterations in Ehlers-Danlos Syndrome," *Medicina Clínica (Barcelona)* 154 (2020): 94–97, https://doi.org/10.1016/j.medcli.2019.05.006.

18. D. I. Swedler, J. J. Knapik, T. Grier, and B. H. Jones, "Validity of Plantar Surface Visual Assessment as an Estimate of Foot Arch Height," *Medicine and Science in Sports and Exercise* 42 (2010): 375–380, https://doi.org/10.1249/MSS.0b013e3181b571cc.

19. J. I. Bell, "Single Nucleotide Polymorphisms and Disease Gene Mapping," *Arthritis Research* 4, no. S3 (2002): S273–S278, https://doi.org/10.1186/ar555.

20. G. T. Marth, I. Korf, M. D. Yandell, et al., "A General Approach to Single-Nucleotide Polymorphism Discovery," *Nature Genetics* 23 (1999): 452–456, https://doi.org/10.1038/70570.

21. M. V. Kuleshov, M. R. Jones, A. D. Rouillard, et al., "Enrichr: A Comprehensive Gene Set Enrichment Analysis Web Server 2016 Update," *Nucleic Acids Research* 44 (2016): W90–W97, https://doi.org/10.1093/nar/gkw377.

22. Z. Xie, A. Bailey, M. V. Kuleshov, et al., "Gene Set Knowledge Discovery With Enrichr," *Current Protocols* 1 (2021): e90, https://doi.org/10.1002/cpz1.90.

23. E. Aromataris, C. Stern, C. Lockwood, et al., "JBI Series Paper 2: Tailored Evidence Synthesis Approaches Are Required to Answer Diverse Questions: A Pragmatic Evidence Synthesis Toolkit From JBI," *Journal of Clinical Epidemiology* 150 (2022): 196–202.

24. Z. N. Sohani, S. Sarma, A. Alyass, et al., "Empirical Evaluation of the Q-Genie Tool: A Protocol for Assessment of Effectiveness," *BMJ Open* 6 (2016): e010403, https://doi.org/10.1136/bmjopen-2015-010403.

25. F. J. Martin, M. R. Amode, A. Aneja, et al., "Ensembl 2023," *Nucleic Acids Research* 51 (2023): D933–d941, https://doi.org/10.1093/nar/gkac958.

26. E. R. Chimusa, P. Beighton, J. Kumuthini, and R. S. Ramesar, "Detecting Genetic Modifiers of Spondyloepimetaphyseal Dysplasia With Joint Laxity in the Caucasian Afrikaner Community," *Human Molecular Genetics* 28 (2019): 1053–1063, https://doi.org/10.1093/hmg/ddy373.

27. M. Grosch, B. Grüner, S. Spranger, et al., "Identification of a Ninein (NIN) Mutation in a Family With Spondyloepimetaphyseal Dysplasia With Joint Laxity (Leptodactylic Type)-Like Phenotype," *Matrix Biology* 32 (2013): 387–392, https://doi.org/10.1016/j.matbio.2013.05.001.

28. B. J. Min, N. Kim, T. Chung, et al., "Whole-Exome Sequencing Identifies Mutations of KIF22 in Spondyloepimetaphyseal Dysplasia With Joint Laxity, Leptodactylic Type," *American Journal of Human Genetics* 89 (2011): 760–766, https://doi.org/10.1016/j.ajhg.2011.10.015.

29. H. Sakai, R. Visser, S. Ikegawa, et al., "Comprehensive Genetic Analysis of Relevant Four Genes in 49 Patients With Marfan Syndrome or Marfan-Related Phenotypes," *American Journal of Medical Genetics. Part A* 140 (2006): 1719–1725, https://doi.org/10.1002/ajmg.a.31353.

30. J. C. Brown, C. J. Miller, M. P. Schwellnus, and M. Collins, "Range of Motion Measurements Diverge With Increasing Age for COL5A1 Genotypes," *Scandinavian Journal of Medicine & Science in Sports* 21 (2011): e266-272, https://doi.org/10.1111/j.1600-0838.2010.01271.x.

31. S. T. Lim, C. S. Kim, W. N. Kim, and S. K. Min, "The COL5A1 Genotype Is Associated With Range of Motion," *Journal of Exercise Nutrition and Biochemistry* 19 (2015): 49–53, https://doi.org/10.5717/jenb.2015.15052701.

32. M. Collins, G. G. Mokone, A. V. September, L. van der Merwe, and M. P. Schwellnus, "The COL5A1 Genotype Is Associated With Range of Motion Measurements," *Scandinavian Journal of Medicine & Science in Sports* 19 (2009): 803–810, https://doi.org/10.1111/j.1600-0838.2009.00915.x.

33. B. Drera, G. Tadini, S. Barlati, and M. Colombi, "Identification of a Novel TGFBR1 Mutation in a Loeys-Dietz Syndrome Type II Patient With Vascular Ehlers-Danlos Syndrome Phenotype," *Clinical Genetics* 73 (2008): 290–293, https://doi.org/10.1111/j.1399-0004.2007.00942.x.

34. F. B. de Araujo Munhoz, J. E. Baroneza, A. Godoy-Santos, et al., "Posterior Tibial Tendinopathy Associated With Matrix Metalloproteinase 13 Promoter Genotype and Haplotype," *Journal of Gene Medicine* 18 (2016): 325–330, https://doi.org/10.1002/jgm.2934.

35. P. A. Pontin, P. R. B. Nogara, F. C. P. Fonseca, et al., "ERα PvuII and XbaI Polymorphisms in Postmenopausal Women With Posterior Tibial Tendon Dysfunction: A Case Control Study," *Journal of Orthopaedic Surgery and Research* 13 (2018): 316, https://doi.org/10.1186/s13018-018-1020-x.

36. P. R. B. Nogara, A. L. Godoy-Santos, F. C. P. Fonseca, et al., "Association of Estrogen Receptor β Polymorphisms With Posterior Tibial Tendon Dysfunction," *Molecular and Cellular Biochemistry* 471 (2020): 63–69, https://doi.org/10.1007/s11010-020-03765-z.

37. S. K. Kim, J. P. Ioannidis, M. A. Ahmed, et al., "Two Genetic Variants Associated With Plantar Fascial Disorders," *International Journal of Sports Medicine* 39 (2018): 314–321, https://doi.org/10.1055/s-0044-100280.

38. K. S. Weymouth, S. H. Blanton, M. J. Bamshad, et al., "Variants in Genes That Encode Muscle Contractile Proteins Influence Risk for Isolated Clubfoot," *American Journal of Medical Genetics. Part A* 155a (2011): 2170–2179, https://doi.org/10.1002/ajmg.a.34167.

39. P. Latour, P. M. Gonnaud, E. Ollagnon, et al., "SIMPLE Mutation Analysis in Dominant Demyelinating Charcot-Marie-Tooth Disease: Three Novel Mutations," *Journal of the Peripheral Nervous System* 11 (2006): 148–155, https://doi.org/10.1111/j.1085-9489.2006.00080.x.

40. R. S. Moosavi, J. Sooltani, and M. Houshmand, "Investigation of Mutations in Exon 14 of SH3TC2 Gene and Exon 7 of NDRG1 Gene in Iranian Charcot-Marie-Tooth Disease Type 4 (CMT4D) Patients," *Iranian Journal of Child Neurology* 14 (2020): 93–100.

41. S. H. Nam, S. Kanwal, M. H. Lee, et al., "Association of miR-149 Polymorphism With Onset Age and Severity in Charcot-Marie-Tooth Disease Type 1A," *Neuromuscular Disorders* 28 (2018): 502–507, https://doi.org/10.1016/j.nmd.2018.04.002.

42. J. Neupauerová, D. Grečmalová, P. Seeman, and P. Laššuthová, "Massively Parallel Sequencing Detected a Mutation in the MFN2 Gene Missed by Sanger Sequencing due to a Primer Mismatch on an SNP Site," *Annals of Human Genetics* 80 (2016): 182–186, https://doi.org/10.1111/ahg.12151.

43. F. Tao, G. W. Beecham, A. P. Rebelo, et al., "Variation in SIPA1L2 Is Correlated With Phenotype Modification in Charcot- Marie- Tooth Disease Type 1A," *Annals of Neurology* 85 (2019): 316–330, https://doi.org/10.1002/ana.25426.

44. F. Tao, G. W. Beecham, A. P. Rebelo, et al., "Modifier Gene Candidates in Charcot-Marie-Tooth Disease Type 1A: A Case-Only Genome-Wide Association Study," *Journal of Neuromuscular Diseases* 6 (2019): 201–211, https://doi.org/10.3233/jnd-190377.

45. C. de Cesar Netto, G. H. Saito, A. Roney, et al., "Combined Weight-bearing CT and MRI Assessment of Flexible Progressive Collapsing Foot Deformity," *Foot and Ankle Surgery* 27 (2021): 884–891, https://doi.org/10.1016/j.fas.2020.12.003.

46. M. Pau, M. Galli, C. Celletti, et al., "Plantar Pressure Patterns in Women Affected by Ehlers-Danlos Syndrome While Standing and Walking," *Research in Developmental Disabilities* 34 (2013): 3720–3726, https://doi.org/10.1016/j.ridd.2013.07.040.

47. S. Piazza, G. Ricci, E. Caldarazzo Ienco, et al., "Pes Cavus and Hereditary Neuropathies: When a Relationship Should Be Suspected," *Journal of Orthopaedics and Traumatology* 11 (2010): 195–201, https://doi.org/10.1007/s10195-010-0114-y.

48. E. Gallardo, A. García, O. Combarros, and J. Berciano, "Charcot-Marie-Tooth Disease Type 1A Duplication: Spectrum of Clinical and Magnetic Resonance Imaging Features in Leg and Foot Muscles," *Brain* 129 (2006): 426–437, https://doi.org/10.1093/brain/awh693.

49. M. Stavrou, I. Sargiannidou, T. Christofi, and K. A. Kleopa, "Genetic Mechanisms of Peripheral Nerve Disease," *Neuroscience Letters* 742 (2021): 135357, https://doi.org/10.1016/j.neulet.2020.135357.

50. J. R. Miller and J. E. McAlister, "Charcot-Marie-Tooth Type 1A With a Pes Planovalgus Foot Type: A Case Report," *Journal of Foot and Ankle Surgery* 48 (2009): 208–214, https://doi.org/10.1053/j.jfas.2008.11.005.

51. K. Hollander, J. E. de Villiers, S. Sehner, et al., "Growing-Up (Habitually) Barefoot Influences the Development of Foot and Arch Morphology in Children and Adolescents," *Scientific Reports* 7 (2017): 8079, https://doi.org/10.1038/s41598-017-07868-4.

52. L. Martín-Casado, A. Aldana-Caballero, C. Barquín, J. J. Criado-Álvarez, B. Polonio-López, and F. Marcos-Tejedor, "Foot Morphology as a Predictor of Hallux Valgus Development in Children," *Scientific Reports* 13 (2023): 9351, https://doi.org/10.1038/s41598-023-36301-2.

53. E. Puszczalowska-Lizis, A. Lukasiewicz, S. Lizis, and J. Omorczyk, "The Impact of Functional Excess of Footwear on the Foot Shape of 7-Year-Old Girls and Boys," *PeerJ* 9 (2021): e11277, https://doi.org/10.7717/peerj.11277.

54. J. E. Dunn, C. L. Link, D. T. Felson, M. G. Crincoli, J. J. Keysor, and J. McKinlay, "Prevalence of Foot and Ankle Conditions in a Multiethnic Community Sample of Older Adults," *American Journal of Epidemiology* 159 (2004): 491–498, https://doi.org/10.1093/aje/kwh071.

55. V. M. Salinas-Torres, R. A. Salinas-Torres, L. E. Carranza-García, J. Herrera-Orozco, and J. L. Tristán-Rodríguez, "Prevalence and Clinical Factors Associated With Pes Planus Among Children and Adults: A Population-Based Synthesis and Systematic Review," *Journal of Foot and Ankle Surgery* 62 (2023): 899–903, https://doi.org/10.1053/j.jfas.2023.05.007.

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