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Evolutionary selection and morphological integration in the foot of modern humans

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Abstract

Objectives: To advance our understanding of the evolution of the hominin foot by quantifying integration and responses to selection in the foot of modern humans.

Materials and Methods: The sample includes 247 female and male adult individuals from Euro-American, Afro-American, European, and Amerindian populations. We collected 190 linear measurements from the 26 skeletal elements that constitute the modern human foot. With these data, we calculated the magnitudes of integration and the ability of the foot to respond to selection demands.

Results: The results revealed that distal phalanges are less integrated, more evolvable, and more flexible than proximal elements (i.e., proximal phalanges and metatarsals). Also, bones from the medial ray (e.g., hallux) show stronger integration and weaker evolvability than their counterparts from the lateral column (e.g., fifth ray), following this trend from medial to lateral positions. Among the tarsals, the talus and calcaneus are the most integrated, least evolvable, and flexible elements from that module.

Discussion: These results suggest that selection for bipedalism would have reorganized the variance/covariance matrix of the foot. The hallux might have been under strong functional selection pressures for bipedal requirements, resulting in a strong integration and low evolvability. Also, differences in the developmental process of each bone seem to have played an essential role in the degree of evolvability, showing those elements that develop earlier have less ability to respond to selection demands.

KEYWORDS
adaptation, constraints, evolvability, feet, flexibility

1 | INTRODUCTION

The foot, like the other autopods, is one of the serially homologous structures of the skeleton (McKenna et al., 2021; Minelli, 2000; Minelli & Fusco, 2013; Wagner, 2014), which at the same time, is formed by meristic elements—repetition of similar parts in the structure of an organism—(Bateson, 1894; Dahn & Fallon, 2000; Held, 2009; Kondo & Miura, 2010; Newman & Frisch, 1979). Most extant tetrapods share a standard number of five digits but with differences in the number of tarsal bones (Zákány et al., 1997). However, there are exceptions to this rule. For example, the Aves and many amphibians commonly show four digits. Also, some mammalian groups present three (Perissodactyla), two (Artiodactyla), or even one digit like horses (Monodactyla) (Klenerman & Wood, 2006). How selection acted to favor this meristic constraint is controversial, as there is fossil evidence of extinct tetrapods with six, seven, and eight digits (Clack, 2006, and references therein). Developmental stability due to pleiotropic effects related to the HoxA13 might have been responsible for selection against polydactyly (more than five digits), as malformations in the hands and limbs first digits are accompanied by abnormalities in the agenito-urinary tract (Zákány et al., 1997). Also, functional selection might have favored the pentadactyl pattern. The fossil record suggests an association between the five digits stabilization with terrestrial locomotion (Clack & Finney, 2005). However, reduction in the number of digits (mainly in fast-running mammals) and morphological variation of the foot bone is common due to functional demands associated with locomotor behaviors (Klenerman & Wood, 2006).

Primates display a large variety of modes of locomotion, which is also reflected in their foot morphology (Ashton & Oxnard, 1964; Fleagle, 2013; Strasser et al., 2013). Modern humans are the only obligate bipedal extant primate, and the feet have evolved to cope with both body balance and terrestrial propulsion during walking and running accurately (Bramble & Lieberman, 2004; Harcourt-Smith & Aiello, 2004; Lovejoy, 1981; McNutt et al., 2018; Raichlen & Pontzer, 2021; Susman, 1983). The conversion from a prehensile foot to a stiffer propulsion lever commendable for bipedal locomotion was possible thanks to a series of apomorphies in the human feet (DeSilva, 2010; Fernández et al., 2018; Gebo, 1992; Holowka & Lieberman, 2018; Latimer & Lovejoy, 1989; Lewis, 1980; Morton, 1924; Susman, 1983). For example, the medial longitudinal and tarsal transverse arches (Holowka et al., 2017; Morton, 1924; Venkadesan et al., 2020; Zipfel et al., 2009), together with the well-developed plantar aponeurosis and the intrinsic muscles, provide the necessary stiffness against the tarsal break for the exertion during locomotion against the ground (Bojsen-Moller & Flagstad, 1976; DeSilva, 2009, 2010; Farris et al., 2019; Hicks, 1954; Kelly et al., 2012). This characteristic converts the foot into a propulsion lever and allows transmitting the body mass from the proximal to the distal foot through the lateral side (Crompton et al., 2008; Fleagle, 2013). Indeed, during the initial propulsive stage of locomotion, whereas the human feet only dorsiflex at the metatarsophalangeal joints, non-human primates have flat feet that bend in the cuboid-metatarsal joint, resulting in a weaker propulsion strength (DeSilva, 2010; Holowka et al., 2017). The origin of this apomorphy is not clear. However, the fossil record reveals that the foot arches were already present at least at the origin of the genus *Homo* (McNutt et al., 2018), in part as an adaptation for elastic energy savings during running (Bojsen-Møller, 1979; Holowka & Lieberman, 2018).

One of the most remarkable characters in the human foot is the fully adducted and non-opposable hallux (Day & Napier, 1964; Deloison, 1991; Latimer & Lovejoy, 1990a; McHenry & Jones, 2006; Pontzer et al., 2010; Susman, 1983; Tyson, 1699). The human hallux is robust and relatively long compared with great apes to enhance propulsion during the push-off phase (Ankel-Simons, 2010; Fernández et al., 2018; Schultz, 1963). In the early to mid-stance phase of locomotion, human feet bear the body weight in the lateral column of the feet, but then the load is transferred to the medial column in the mid-stance phase to toe-off. The main propulsion in this push-off phase is produced by the first ray, which transmits the force to the ground (Hayafune et al., 1999; Reeser et al., 1983). In contrast, in great apes, during this stance phase, the body weight is distributed more uniformly all over the five rays (Crompton et al., 2008; Tuttle, 1970). This is reflected in the morphology of the rays, especially in that of the hallux, which is opposable, shorter, and more gracile to humans (Harcourt-Smith, 2002; Schultz, 1963). The evolution from an opposable to an adducted, robust modern human-like hallux was not completed until relatively late in human evolution, with the emergence of the genus *Homo* (McNutt et al., 2018; Pontzer et al., 2010). Early extinct hominins who already presented a certain degree of bipedalism, like *Ardipithecus ramidus*, or various species of *Australopithecus*, displayed certain derived features, enhancing them for a certain degree of bipedalism but still retaining some grasping morphologies (Fernández et al., 2017; Lovejoy, Simpson, et al., 2009; Simpson et al., 2019; Ward et al., 2011; Zipfel et al., 2009).

The evolutionary changes associated with a robust and elongated hallux was accompanied by other apomorphies, such as short and straight pedal phalanges, mainly those from the middle foot (Harcourt-Smith, 2002; Lessertisseur & Jouffroy, 1975; Schultz, 1963). The derived hallux has been linked to improved bipedal gait performance, particularly during running, because short toes increase mechanical output of this activity, reduce the metabolic cost, and the risk of injury for overuse (Rolian et al., 2009). Great apes show long and curved phalanges, which are better adapted for grasping than bipedal walking (Fernández et al., 2018; Harcourt-Smith, 2002; Lessertisseur & Jouffroy, 1978; Schultz, 1963; Susman, 1983). Early extinct hominins such as *Ardipithecus Kadabba*, *A. Ramidus*, and *Australopithecus* in general, including Burtele foot, have relatively intermediate curved and long phalanges between African great apes and modern humans, which has been suggested as an indicator of adaptation to bipedal locomotion while retaining climbing abilities (Haile-Selassie et al., 2012; Latimer & Lovejoy, 1990b; Latimer et al., 1982; Lovejoy, Latimer, et al., 2009; Prang, 2019; Rolian et al., 2009; Stern, 2000; Stern & Susman, 1983; White et al., 2009). There are just a few phalanges from early *Homo* species in the fossil record, which includes a single proximal and a first distal phalanges of SKX 16699 and OH 10 respectively, or those of KNM-ER 803 (Day & Leakey, 1974; Day & Napier, 1964; Trinkaus & Patel, 2016), which broadly present intermediate features (i.e., slight curvature) between early hominins and modern humans. Modern human-like intermediate and lateral pedal phalanges were already present in late human species like *Homo antecessor*, Sima de los Huesos fossil remains, or *Homo neanderthalensis* (Arsuaga et al., 2015; Lorenzo et al., 1999; Pablos et al., 2012, 2017; Trinkaus, 2014; Trinkaus & Hilton, 1996). However, these features were not already present in other contemporaneous *Homo* species. For example, *Homo naledi* proximal phalanges are curved, and those of *Homo floresiensis* are relatively long and moderately curved (Harcourt-Smith et al., 2015; Jungers et al., 2009).

In sum, what we know now, is that with some variation, most of the revised modern human pedal apomorphies were already present at the origin of the genus *Homo*. In contrast, earlier hominins displayed a mosaic of the human-like foot with primitive features (McNutt et al., 2018 and references therein). These derived morphological pedal adaptations for bipedalism did not appear all at once. The fossil record indicates that early hominins (i.e., *A. ramidus*) first show derived lateral push-off mechanisms for bipedal locomotion (Lovejoy, Latimer, et al., 2009; Zipfel et al., 2009), then with *Australopithecus* the hallux became relatively adducted and the transverse arch appeared, losing to some extent the climbing ability, and utilizing the medial column for bipedal propulsion (Latimer & Lovejoy, 1990a). However, there is debate about the presence of a longitudinal arch in *A. Afarensis*, which would indicate complete, human-like bipedalism (Berillon, 2003; Prang, 2015). Finally, selection for long-distance walking and endurance running in early *Homo* would have favored short and strait pedal phalanges morphologies, losing their last primitive foot grasping abilities (Latimer & Lovejoy, 1990b). Although *A. afarensis* had relatively longer and more curved phalanges than humans, it is suggested that this would have had "little or no effect on flexor output during walking" (Rolian et al., 2009).

Beyond the fossil record, in the last decades, other evolutionary methods have been applied in palaeontological studies to understand the evolution of organisms better. Morphological integration is a frequently applied approach, which refers to the patterns of correlations among traits in a structure (Cheverud, 1982; Olson & Miller, 1958). Integration reflects how variability between traits is organized due to developmental and functional factors, affecting how characters evolve (Alberch, 1982; Goswami et al., 2014; Hallgrímsson et al., 2002). Morphological integration can influence both the rate and the pattern of evolution (Cheverud, 1984; Cheverud et al., 1989; Hallgrímsson et al., 2002; Marroig & Cheverud, 2001; Wagner & Altenberg, 1996). Under a strong magnitude of integration, the rate of evolution can be slowed if a trait is selected in the opposing direction to the fitness of the other traits. On the contrary, the rat of evolutionary change may be increased if correlated traits are selected in the direction of least resistance (Lande, 1979; Schluter, 1996). Broadly, integration is seen as a factor that biases the production of new phenotypes, either by selecting negatively to the fitness or by constraining the variation exposed to selection in a determined direction (Rolian, 2014; Villmoare, 2013). The reduction of the levels of integration can enhance evolvability (Hallgrímsson et al., 2002; Wagner, 1996; Wagner & Altenberg, 1996). This process can occur by decreasing pleiotropic constraints that control functionally unrelated morphological characters, producing modular structures and thus, favoring evolvability (Cheverud, 1996; Cheverud et al., 2004; Ehrich et al., 2003; Wagner et al., 2007). Integration evolves in response to selection demands and, thus, can help to explain and interpret the emergence of novel phenotypes through the fossil record (Parins-Fukuchi, 2020; Young et al., 2010).

In addition to the concept of morphological integration and investigating the ability of an organism to evolve, other studies also apply an approach to test how a structure responds to selection demands (Arlegi et al., 2020; Goswami et al., 2014; Porto et al., 2009, 2013; Shirai & Marroig, 2010; Villamil, 2018). This approach was initially developed by Hansen and Houle (2008) based on Lande's equation (1979) and calculates different indexes that assess the ability of a population to respond to simulated selection vectors. These indexes evaluate the population under different evolutionary scenarios, like directional and stabilizing selection, also its capacity to respond in the direction of selection or the degree of constraints to evolve (Hansen & Houle, 2008). Here, to better understand the evolution of the human foot, we evaluate the ability of the 26 bones of the modern humans foot to evolve by analyzing both the magnitudes of integration and the index of response to selection. The metatarsals and phalanges, similar to all meristic elements, such as teeth, ribs, or vertebrae, are ideal for investigating serial disparities in anatomical metameric structures. Serially homologous elements share similar genetic and developmental architecture and thus are, at origin, strongly integrated (Hall, 1995; Young & Hallgrímsson, 2005). Posterior reduction in the degree of integration between them might occur due to functional differential selection (Hallgrímsson et al., 2002; Wagner & Altenberg, 1996). Thus, the analysis of integration, and the index of selection at the individual autopod level, can partially explain the differential selection process of each element, which might be mainly due to functional and developmental factors.

Here, we aim to further knowledge of integration and selection in the pedal bones (e.g., Hallgrímsson et al., 2002; Rolian, 2009, 2020; Rolian et al., 2010; Young et al., 2010; Young & Hallgrímsson, 2005) to better understand the evolution of this anatomical structure in humans. These studies mainly focused on the coevolution between homologous structures like the fore and hindlimbs in mammals (Hallgrímsson et al., 2002; Rolian, 2020; Young et al., 2010; Young & Hallgrímsson, 2005) and the autopods of the fore and hindlimbs in primates (Rolian, 2009; Rolian et al., 2010). These studies showed that among primates, hominoids show the lowest covariation between homologous limbs, plausibly due to differential selection due to functional diversification between homologous elements (e.g., hands and feet). However, also reveal that functional specialization of a single element (e.g., the first human toe) is responsible for driving strong internal integration, constraining the ability to be selected and thus, lowering the degree of evolvability (Rolian, 2020). These works principally investigated covariation and selection between homologous elements, using, in the case of the autopods, one single bone (Young et al., 2010) or three rays without including distal phalanges (Rolian, 2009). Thus, in this study, we intend to extend these findings by including the 26 bony elements of the modern human foot (tarsals, metatarsals, proximal, middle, and distal phalanges) and investigating differences in the degree of integration and responses to selection among pedal bones in a species with a unique locomotion behavior and derived foot morphology (Harcourt-Smith, 2007; Holowka & Lieberman, 2018). These results will be discussed and interpreted in the context of hominin evolution.

Three main hypotheses are tested:

1. Functionally selected morphological elements show higher correlation between traits and thus integration (Cheverud, 1996). Those

skeletal pedal elements that support higher peak forces during the different phases of gait will show higher magnitudes of integration and lower evolvability (e.g., hallux) and vice-versa (e.g., fifth toe).

2. More distally located phalanges develop later than more proximal units, concentrating greater variation (e.g., Mariani & Martin, 2003; Wagner, 2005). Thus, they will show lower integration and higher evolvability than proximal elements.
3. If there is a relationship between integration and functionality, and developmental modules evolve adaptively to match functional modules (Cheverud, 1984; Wagner & Altenberg, 1996), we expect a correlation between development and integration.

2 | MATERIALS AND METHODS

2.1 | Sample and data

To investigate magnitudes of integration and responses to selection in the 26 skeletal elements that constitute the modern human foot, we collected between six and 13 linear measurements on each bone using a digital caliper, following the Martin system from previously published standard measurements (Tables S1–S11 and Figures S1–S9; Bräuer, 1988; but see Pablos et al., 2017; Trinkaus, 1975). The sample comprises 247 adult male and female individuals who belonged to Euro-American, Afro-American, European and Amerindian populations (Table 1), producing more than 50,500 measurements. The variables were selected trying to capture the morphology of each skeletal element. Preferentially, we collected data from the right foot. However, in the case of missing skeletal elements, the left foot was used if better represented. Pathological individuals and damaged or incomplete bones were not included in the sample. We estimated missing values using the package MICE v. 3.13.0 (van Buuren & Groothuis-Oudshoorn, 2011) for R software v. 4.0.5 (Core Team, 2021). The total amount of estimated values was <2.6% of the entire database. The individuals that form the sample were housed at the Hamann–Todd osteological collection (Cleveland Museum of Natural History, United States), the University of Burgos (Spain), and the collections of the Department of Anthropology, Kent State University (Ohio, United States).

One of the issues in phenotypic integration studies is that these approaches need large sample sizes to obtain accurate results. Before performing any analysis, we tested the reliability of our sample size by applying a statistical approach that calculates both the necessary sample size and the estimated accuracy of the results from our raw datasets. This approach estimates the minimum sample size and the degree of inaccuracy for a dataset using the coefficient of determination (r^2) and the number of traits (Grabowski & Porto, 2017). The results obtained from these tests revealed that our sample size for every dataset is sufficiently large and accurate for these analyses (accuracy <0.05 at 95% of confidence).

TABLE 1 Sample included in this study organized by population, sex, and period.

	Male	Female	Period	N
Afro-American	44	42	Modern	86
Euro-American	39	37	Modern	76
Amerindian	Indet.	Indet.	Modern	40
European	22	23	Middle-Age	46
Total	105	102	Period	247

2.2 | Variance/covariance matrices

Analyses of integration and responses to selection were performed using the population's variance/covariance (V/CV) matrix. These approaches are based on the distribution of variation of a population in the matrix and require that sources of variation are removed. Thus, previous to constructing the V/CV matrices for each pedal element, we performed an analysis of variance (ANOVA) to detect significant sources of variation in the raw datasets. The potential additional sources of variation tested included sexual dimorphism, population, and the measurer (three researchers collected data). Then, to adjust the datasets for those significant sources of variation, a permutational multivariate ANOVA was conducted, and the residuals were used to construct each V/CV matrix. Finally, to avoid differences due to size, the V/CV matrices were normalized by the mean of each trait (Hansen & Houle, 2008).

2.3 | Morphological integration and responses to selection

We calculated the magnitudes of integration of each skeletal element V/CV matrix using the integration coefficient of variation of the eigenvalues (ICV; Shirai & Marroig, 2010). This index is adapted from Wagner's correlation coefficient (Wagner, 1984) and divides the SD of the eigenvalues (λ) by the average of the eigenvalues (λ) and thus, is scale-independent. We generated 1000 random vectors by resampling the supplied data and from which we calculated the mean and the SE of ICV values.

Then we investigated the ability of the foot skeletal elements to respond to selection demands. We applied an approach that calculates a series of indexes that measure the evolutionary responses of the V/CV matrices to selection (Hansen & Houle, 2008; Marroig et al., 2009). This approach is based on Lande's equation ($\Delta Z = G\beta$) (1979), where ΔZ is the evolutionary response to selection, G is the genetic covariance matrix, and β is the directional selection vector. In this equation, we substituted the genetic covariance matrix (G) for the phenotypic matrix (P) because they are similarly structured (Cheverud, 1988, 1996). Then 1000 normal distribution random selection vectors (β) with a unit norm were generated using the rnorm function of R (R Core Team, 2021). The V/CV matrices were subjected to these vectors to estimate the responses to selection, and the average distribution was calculated to estimate the following indexes of responses to selection: (1) Mean evolvability, which represents the magnitude of response under directional selection; (2) Mean conditional evolvability is the magnitude of response in a situation of stabilizing selection; and (3) Mean flexibility measures the ability to track the direction of selection without considering the magnitude of evolutionary response (Hansen & Houle, 2008; Marroig et al., 2009; Porto et al., 2013). Last, we also compute Mean constraints, a property of the V/CV matrix, to limit the ability to evolve. Hereafter, evolvability, conditional evolvability, flexibility, and constraints. Then, we compared differences in the obtained magnitudes of integration and the indexes of selection, first between the skeletal elements within the same anatomical module (e.g., between the seven tarsal bones), and second between digits (e.g., between second and third digits, each including the metatarsal and the phalanges values). To do so, we performed non-parametric pairwise Mann–Whitney *U* tests using the 1000 distributions previously generated. To avoid type II errors, the significance was corrected using the Benjamini–Hochberg (B–H) procedure (Benjamini & Hochberg, 1995).

Finally, we performed two correlation analyses. First, we correlated integration with the indexes of response to selection to test its ability to constrain selection. Second, to test the influence of the development of the human pedal bones on integration and the indexes of response to selection, we correlated the chronologic sequence of chondrification of the pedal bones in the embryo with those values. We used the 14 stages of chondrification (Kelikian & Sarrafian, 2011) as a proxy for foot development, which is based on data from Senior (1929) and O'Rahilly et al. (1957). Thus, we assigned a number from 1 (earlier development) to 14 (later development) to each pedal bone (see Table 2). From the three stages of skeletal development (mesenchymal, cartilaginous, and osseous), we took the cartilaginous stage (weeks 6–8 approx.) as the 26 foot skeletal elements clearly appear as individual entities (Kelikian & Sarrafian, 2011).

TABLE 2 Values of integration and indexes of selection from each pedal bone.

			ICV		Evolvability		C. Evolvability		Flexibility		Constraints	
	n	CS	Value	SE	Value	SE	Value	SE	Value	SE	Value	SE
Calcaneus	246	3	1.2901	0.002	0.0064	<0.001	0.0016	<0.001	0.6634	0.002	0.5928	0.008
Talus	247	3	1.5054	0.003	0.0043	<0.001	0.0017	<0.001	0.6470	0.004	0.7776	0.009
Navicular	195	6	1.2101	0.002	0.0121	<0.001	0.0035	<0.001	0.6865	0.004	0.6516	0.008
Cuboid	194	2	1.4608	0.002	0.0143	<0.001	0.0051	<0.001	0.6587	0.003	0.8125	0.009
Medial Cuneif.	195	4	1.0885	0.003	0.0060	<0.001	0.0028	<0.001	0.7919	0.003	0.6747	0.009
Interm. Cuneif.	195	4	0.8692	0.003	0.0066	<0.001	0.0047	<0.001	0.8463	0.003	0.6974	0.009
Lateral Cuneif.	195	3	1.1834	0.002	0.0061	<0.001	0.0031	<0.001	0.7336	0.003	0.7079	0.009
Mt. I	226	5	1.5885	0.002	0.0048	<0.001	0.0009	<0.001	0.6356	0.004	0.7711	0.008
Mt. II	227	1	1.3571	0.002	0.0068	<0.001	0.0012	<0.001	0.6868	0.004	0.7468	0.009
Mt. III	225	1	1.3645	0.003	0.0058	<0.001	0.0021	<0.001	0.6785	0.003	0.7396	0.009
Mt. IV	223	1	1.3680	0.002	0.0067	<0.001	0.0013	<0.001	0.6906	0.003	0.7234	0.009
Mt. V	224	2	1.1866	0.003	0.0090	<0.001	0.0031	<0.001	0.7300	0.003	0.6764	0.008
Ph.P. I	244	9	1.7827	0.002	0.0070	<0.001	0.0024	<0.001	0.6042	0.004	0.8475	0.008
Ph.P. II	234	7	1.6751	0.002	0.0076	<0.001	0.0027	<0.001	0.6182	0.004	0.8221	0.008
Ph.P. III	235	7	1.6522	0.002	0.0074	<0.001	0.0024	<0.001	0.6231	0.005	0.8000	0.008
Ph.P. IV	235	7	1.5932	0.003	0.0082	<0.001	0.0025	<0.001	0.6245	0.005	0.7768	0.008
Ph.P. V	237	8	1.3533	0.002	0.0094	<0.001	0.0036	<0.001	0.6736	0.004	0.7244	0.008
Ph.M. II	218	10	1.4795	0.002	0.0135	<0.001	0.0032	<0.001	0.6039	0.004	0.6940	0.008
Ph.M. III	203	10	1.4744	0.002	0.0196	<0.001	0.0042	<0.001	0.6154	0.003	0.7120	0.008
Ph.M. IV	187	11	1.4903	0.002	0.0176	<0.001	0.0040	<0.001	0.6023	0.004	0.6787	0.008
Ph.M. V	166	12	1.2549	0.002	0.0139	<0.001	0.0055	<0.001	0.6820	0.003	0.6262	0.009
Ph.D. I	235	13	1.3488	0.002	0.0104	<0.001	0.0048	<0.001	0.7006	0.003	0.7508	0.009
Ph.D. II	185	13	1.2951	0.002	0.0159	<0.001	0.0072	<0.001	0.7059	0.003	0.7237	0.008
Ph.D. III	186	13	1.4188	0.003	0.0165	<0.001	0.0070	<0.001	0.6744	0.003	0.7376	0.009
Ph.D. IV	167	13	1.3078	0.003	0.0162	<0.001	0.0076	<0.001	0.7012	0.003	0.7256	0.009
Ph.D. V	156	13	1.2792	0.002	0.0207	<0.001	0.0091	<0.001	0.7026	0.003	0.7095	0.009

Abbreviations: CS, chondrification stage; ICV, integration coefficient of variation; Mt., metatarsal; Ph.D., phalanx distal; Ph.M., phalanx medial; Ph.P., phalanx proximal; SE, standard error.

3 | RESULTS

3.1 | Magnitudes of integration

The results of the magnitudes of integration of each skeletal element are reported in Table 2 and Figure 1. Among anatomical modules (i.e., tarsal, metatarsal, proximal phalanx, middle phalanx, and distal phalanx), all the modules differ significantly in their degree of integration (Table S10). On average, the tarsal bones display the lowest integration values (mean ICV = 1.230), and the proximal phalanx the highest values (mean ICV = 1.611; Table 3). Among phalanx modules, the magnitudes of integration decrease from proximal to a distal position (Figure 1). The least integrated bones from the metatarsal and phalanx modules are those from the fifth digit. On the contrary, the most integrated are those from the hallux in the metatarsal and proximal phalanx modules and the fourth and third elements in the middle and distal phalanx modules, respectively. Among the tarsals, on the one hand, the three cuneiforms display the lowest degree of integration, which are also the lowest values from the entire foot. On the other hand, the talus is the most integrated tarsal bone. Among digits, all the rays display significant differences among them except between the second and fourth. Broadly speaking, we can observe two main trends in the distribution of the degree of integration in the foot. On the one hand, there is a pattern in which the degree in the

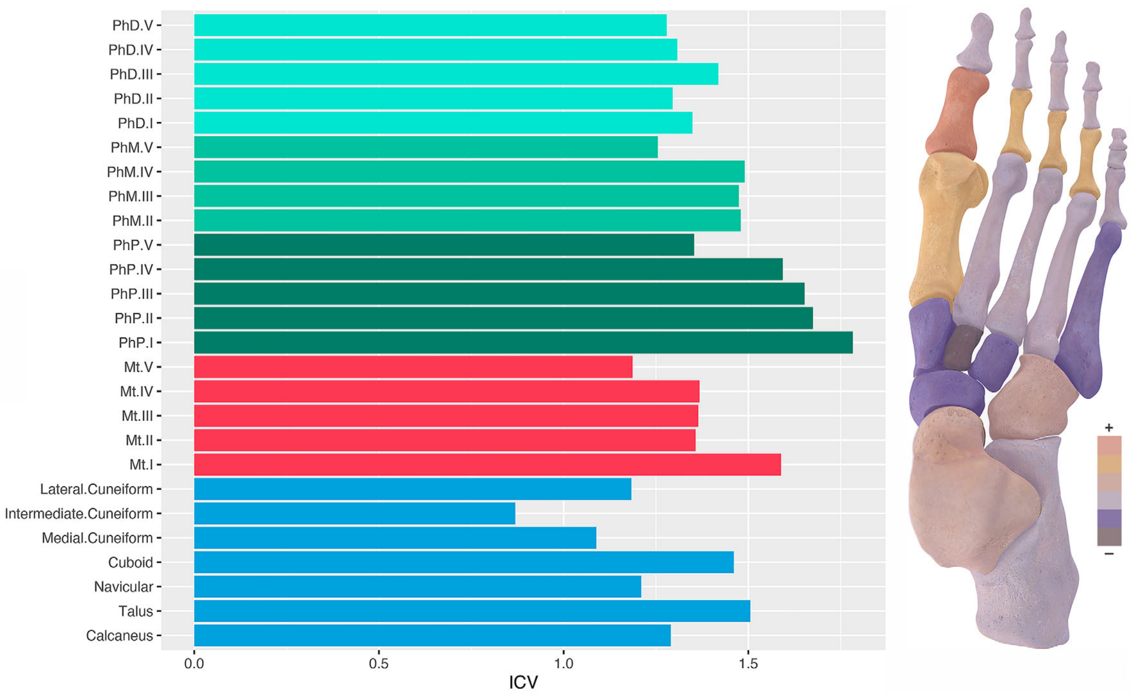

FIGURE 1 Magnitudes of integration in the modern human foot. The diagram on the left represents the integration scores obtained from each pedal bone. Acronyms consistent with key in Table 2: Mt, metatarsal; PhP, proximal phalanx; PhM, middle phalanx; and PhD, distal phalanx. Each color represents an anatomical module, tarsals (blue), metatarsal (red), and proximal, middle, and distal phalanges in different shades of green. The foot on the right represents a heat map of the integration coefficient of variation (ICV) values in all pedal elements. Orange color indicates maximum values of integration and dark-brown the minimum values. The first proximal phalanx shows the strongest integration and the intermediate cuneiform the lowest.

TABLE 3 Mean values by anatomical modules and digits.

	ICV	Evolvability	Cond. evol.	Flexibility	Constraints
Tarsals	1.230	0.008	0.003	0.713	0.702
Metatarsals	1.373	0.007	0.002	0.684	0.732
Phal. Prox.	1.611	0.008	0.003	0.629	0.794
Phal. Med.	1.425	0.016	0.004	0.626	0.678
Phal. Distal	1.330	0.016	0.007	0.697	0.729
First digit	1.573	0.007	0.003	0.647	0.790
Second digit	1.452	0.011	0.004	0.654	0.747
Third digit	1.477	0.012	0.004	0.648	0.747
Fourth digit	1.440	0.012	0.004	0.655	0.726
Fifth digit	1.269	0.012	0.005	0.697	0.684

Abbreviation: ICV, integration coefficient of variation.

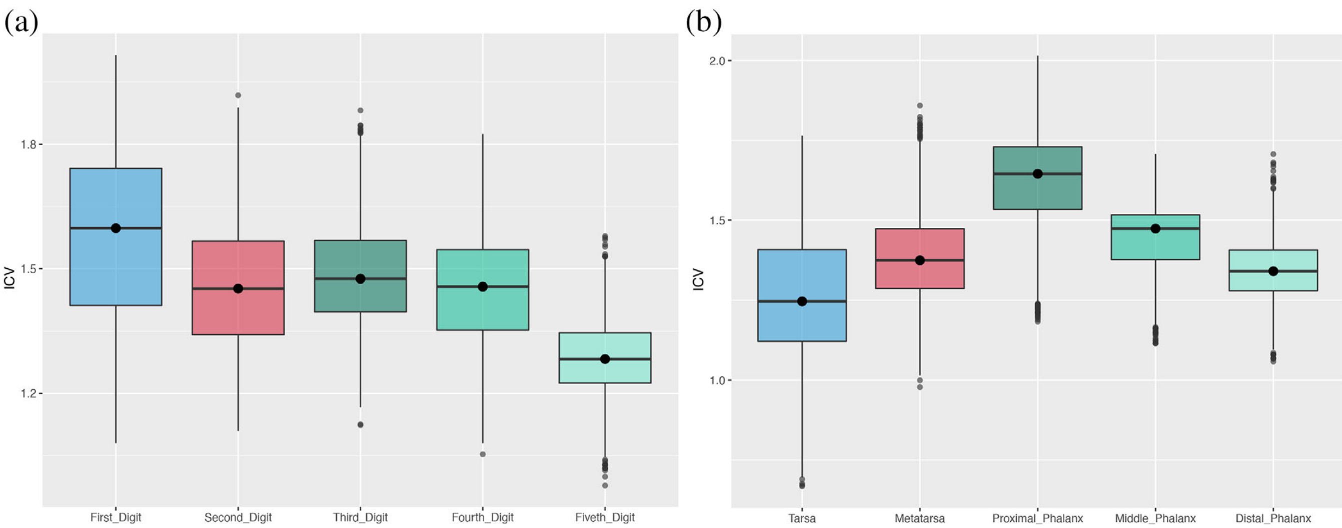

FIGURE 2 Integration by digit (left) and by modules (right). (a) the medial column represented by the first digit is the most integrated, and the lateral one represented by the fifth digit the least. (b) proximal phalanges are the mostintegrated elements, decreasing toward distal phalanges and proximal (tarsal) positions.

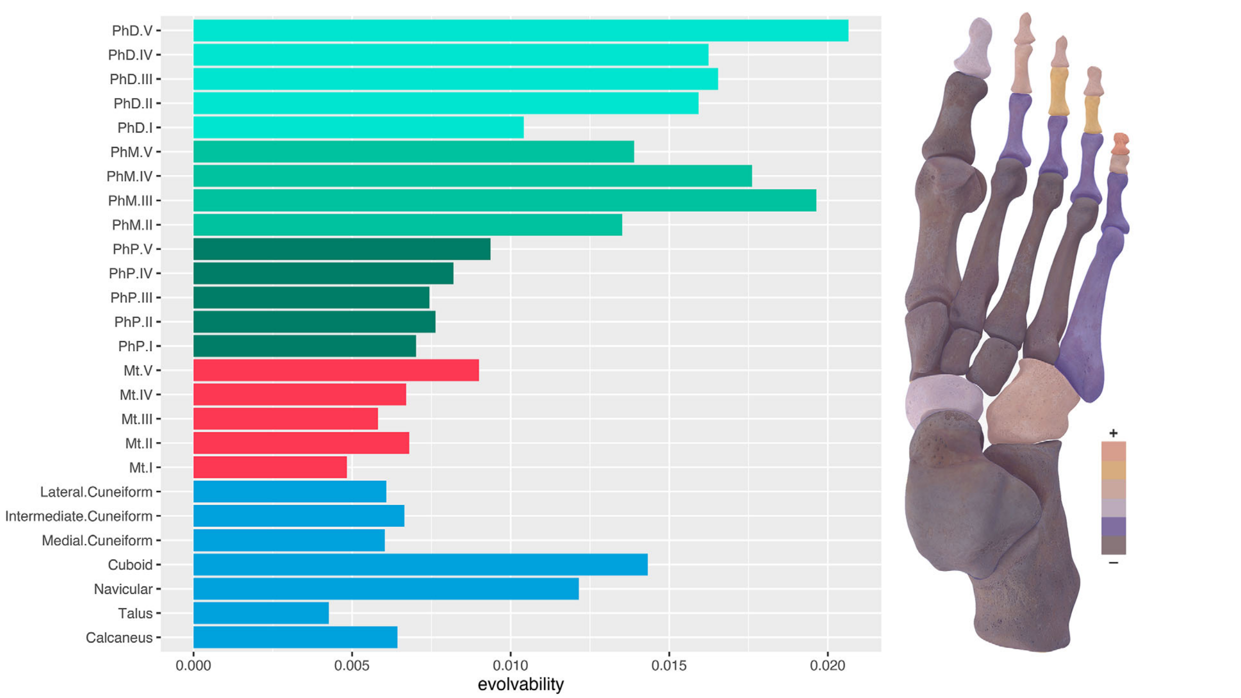

FIGURE 3 Magnitudes of evolvability in the modern human foot. The diagram on the left represents the values of evolvability obtained from each pedal bone. Acronyms consistent with key in Table 2: Mt, metatarsal; PhP, proximal phalanx; PhM, middle phalanx; and PhD, distal phalanx. Each color represents an anatomical module, tarsals (blue), metatarsal (red), and proximal, middle, and distal phalanges in different shades of green. The foot on the right represents a heat map of evolvability in all pedal elements. Orange color indicates the highest and dark-brown the lowest values. The fifth distal phalanx is the most evolvable skeletal element and the talus the least.

magnitudes of integration increases from medial (first ray) to lateral positions (fifth ray). On the other hand, there is another trend where the level of integration increases from distal to proximal phalanges and then decreases toward the tarsal bones, which are, on average, the lowest integrated bones in the entire foot (Figure 2).

3.2 | Responses to selection

In this section, we will describe the results obtained from the four indexes of responses to selection, evolvability, conditional evolvability, flexibility, and constraints, and their correlation with integration.

3.2.1 | Evolvability

The results from the analysis of evolvability, which represents the ability of a structure to evolve in the direction of selection, are presented in Table 2 and Figure 3. There are significant differences in the magnitudes of evolvability among modules, except between the middle and distal phalanges and between proximal phalanges and tarsal bones (Table S11). On average, the distal and middle phalanx

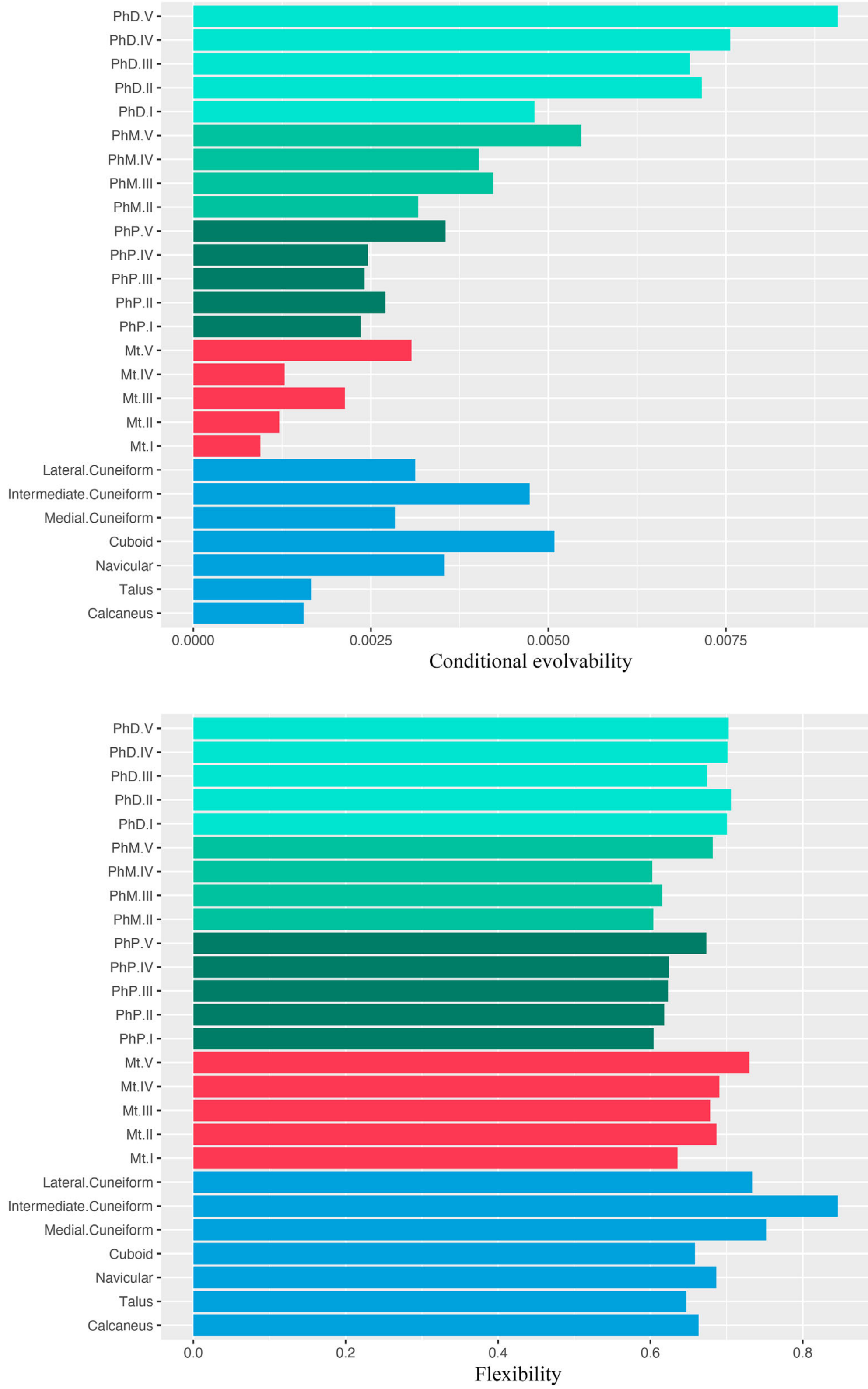

FIGURE 4 Scores obtained by each single pedal element in three different indexes of response to selection. Each color represents an anatomical module, tarsals (blue), metatarsals (red), and proximal, middle, and distal phalanges in different shades of green.

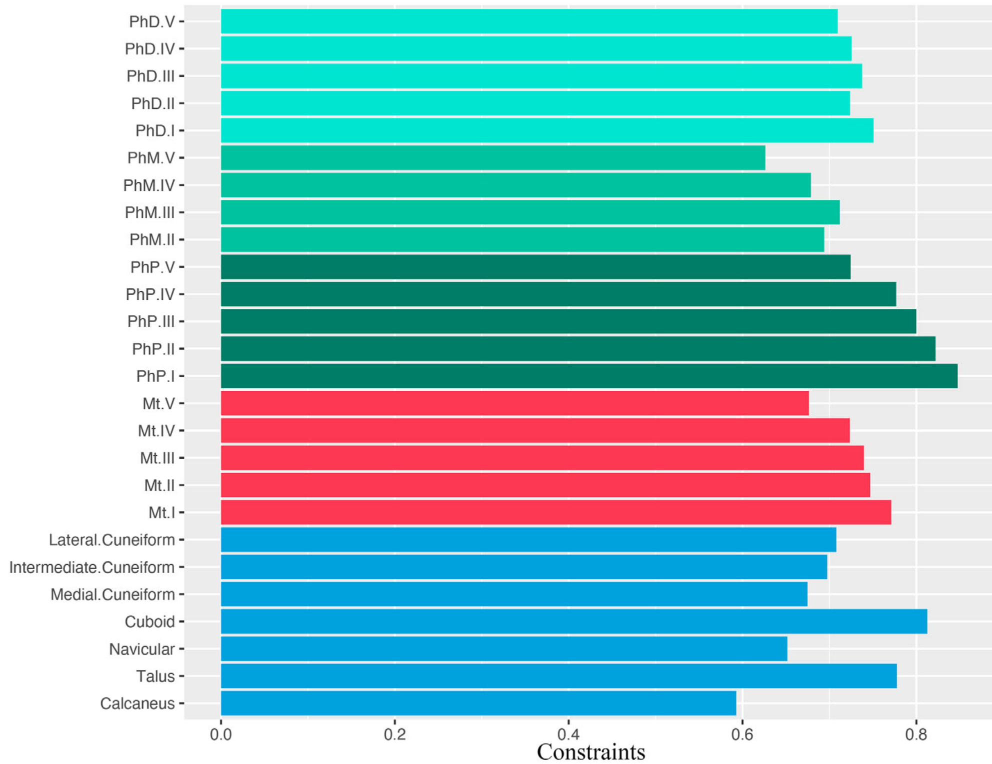

FIGURE 4 (Continued)

modules display the highest mean values (mean = 0.016), and the metatarsal the lowest (mean = 0.007; Table 3). Comparisons between different digits reveal significant differences in their selection index except between the third and fourth rays. The results revealed that, except for the middle phalanx, the most evolvable is the fifth digit, and the least evolvable is the hallux. The difference in the degree of evolvability between the first and fifth elements is especially remarkable in the distal phalanxes. Regarding the middle phalanx module, which diverges from the general trend, those from the third and fourth digits show the highest values, and from the second the lowest (Figure 3). The talus is the least evolvable element in the tarsal module, and the navicular and cuboid show relatively high values compared with the rest of the module. Generally speaking, and except for the middle phalanx module, we can observe a general trend in which the ability to evolve in the direction of selection of the human foot decreases from distal to proximal positions and also in the lateral direction from the fifth toward the first elements (Figure 3). Except for the cuboid and navicular, the tarsal bones also generally show low values. Indeed, regarding this general tendency, the talus is the least evolvable element from the entire foot, and the fifth distal phalanx is the most.

3.2.2 | Conditional evolvability

The results from the conditional evolvability index, which represents a structure's ability to evolve in the direction of selection when under stabilizing selection, are shown in Table 2 and Figure 4. These results show similar trends to those observed in the evolvability index. The degree of evolvability decreases in two directions, from distal to proximal autopods and from lateral to medial elements. In the case of conditional evolvability, this pattern is even more evident as the middle phalanx module does not deviate from the general trends. Indeed, there are also significant differences between the third and fourth digits, which yielded non-significant results in the evolvability index (Table S11). Finally, the tarsal module yields relatively higher values relative to the rest of the elements compared to those obtained by evolvability.

3.2.3 | Flexibility

The results from the index of flexibility—the ability of a structure to track the direction in which selection is acting—are reported in Table 2. Among anatomical modules, they show significant differences from each other except for between the middle and proximal phalanges (Table S10). The tarsal bones yield the highest mean values (mean = 0.713), with the three cuneiforms being the most flexible elements of the entire foot (Table 3). Regarding the rest of the modules, the distal phalanges are the most flexible elements, followed by the metatarsals with the middle and proximal phalanges showing similar lower values. Broadly, the fifth bone element from each module is the most flexible and the first the least. In the case of the proximal phalanx, these differences are subtler, without significant differences among those from the central digits (i.e., second, third, and fourth).

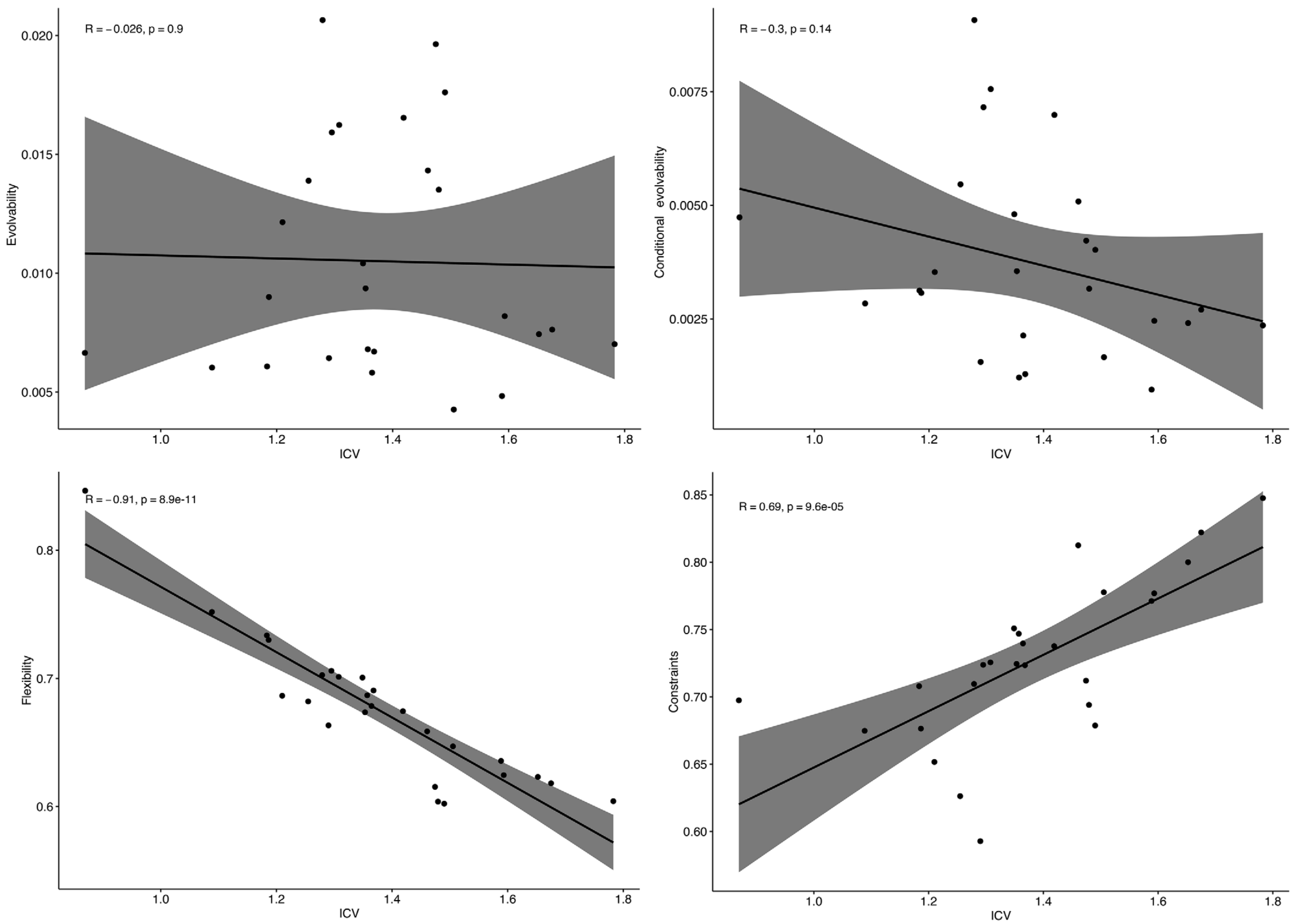

FIGURE 5 Scatterplots showing the correlation between integration and different indexes of response to selection in the entire modern human foot.

3.2.4 | Constraints

The results from the index of constraints are shown in Table 2. Among anatomical modules, the proximal phalanges show the highest mean values of constraints (mean = 0.794), and the middle phalanges the lowest (mean = 0.678). Comparing individual elements, the calcaneus is the least constrained bone (mean = 0.593), followed by the fifth middle phalanx (mean = 0.626), and the first proximal phalanx is the most constrained anatomical element from the entire foot (mean = 0.848). There is a general pattern, where the degree of constraint significantly decreases from medial to lateral digits (Table 3).

In sum, our results indicate that more medially located digits, especially the hallux, are more integrated and are less evolvable than their lateral counterparts. This general trend is also observable between the phalanges, where more distally located phalanges are less integrated, more evolvable, and more flexible than proximal ones. Within the tarsal module, the talus and calcaneus are significantly the most integrated and the least evolvable and flexible (Table 3). These results support our first hypothesis that hallux, which is located medially in the foot, displays larger magnitudes of integration due to its critical functional role in human bipedal locomotion. Also, they support our second hypothesis that the degree of integration in the phalanges decreases from proximal to distal elements following their developmental process. Finally, the results obtained here also support the third hypothesis that elements from the lateral column of the foot are the most evolvable after the observations made in the fossil record, where the first morphological changes in the hominins foot occurred in the lateral region.

3.2.5 | Correlation of integration versus responses to selection

The correlation of integration to responses to selection in the entire foot reveals that integration correlates significantly with flexibility (negative correlation) and constraints (positive correlation). In contrast, evolvability and conditional evolvability do not show significant results (Figure 5). However, this analysis performed by anatomical modules separately reveals a different scenario (Table 4). On the one hand, metatarsals and proximal phalanges show a highly significant negative correlation between integration and evolvability. On the other hand, tarsals, medial and distal phalanges, do not correlate with

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TABLE 4 Correlation between integration and the indexes of selection in the entire foot, the anatomical modules, and the digits.

	Evolvability	Cond. evolvability	Flexibility	Constraints
Entire foot	−0.03	−0.3	**−0.91****	**0.69****
Anatomical modules				
Tarsals	0.23	−0.33	**−0.95****	0.47
Metatarsals	**−0.94***	−0.83	**−0.99****	**0.92***
Proximal phalanges	**−0.98****	**−0.90***	**−0.99****	**0.98****
Medial phalanges	0.50	−0.87	**−0.99****	0.91
Distal phalanges	−0.36	−0.48	**−0.92***	0.70
Digits				
First digit	−0.65	−0.67	**−0.99**	0.93
Second digit	−0.47	−0.43	−0.82	0.69
Third digit	−0.15	−0.29	−0.74	0.77
Fourth digit	−0.23	−0.49	−0.86	0.37
Fifth digit	0.08	−0.13	−0.85	0.57

Note: Significant values are indicated in bold.
**$p < 0.01$; *$p = 0.01–0.05$.

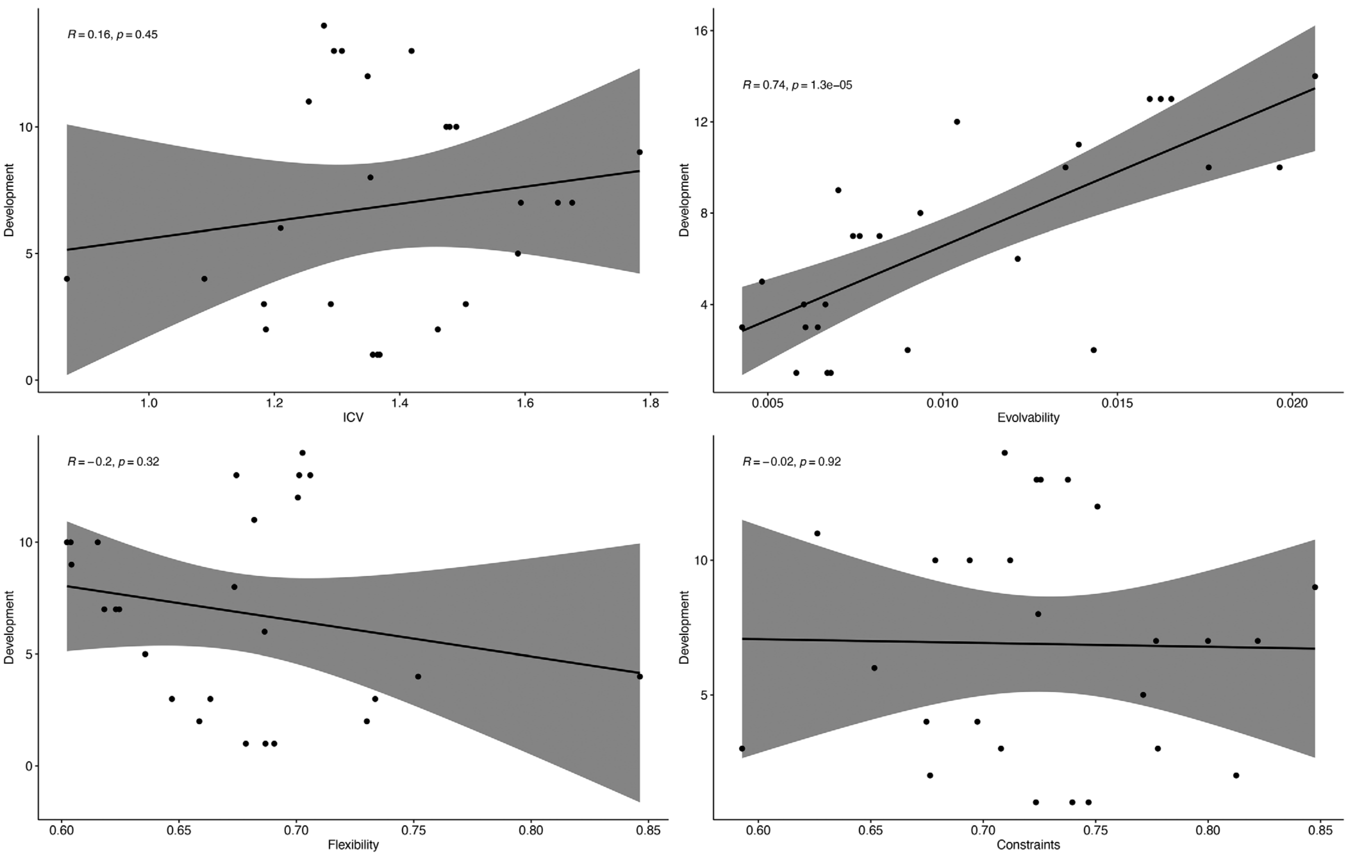

FIGURE 6 Scatterplots showing the correlation between the early stage of development and different indexes of response to selection in the entire modern human foot.

constraints. Finally, analyzed by digits, those from the medial column show a higher negative correlation of integration with evolvability, though these results are not significant. The absence of significance in these results is probably due to the low number of bones included in each analysis (Table 4). The results of correlation of the foot early development stages to integration and responses to the selection show that only evolvability and conditional evolvability are significantly highly (positive) correlated with the entire foot ($r = 0.74$ and

TABLE 5 Correlation between early stages of development and values of integration and responses of selection in the entire foot, the forefoot (metatarsals and phalanges), phalanges and tarsal bones.

	Entire foot	Forefoot	Phalanges	Tarsals
Integration	0.16; $p = 0.45$	−0.54; $p = 0.82$	**−0.74**; $p = 0.002$	−0.48; $p = 0.28$
Evolvability	**0.74**; $p = 1.3\text{e-}05$	**0.78**; $p = 9\text{e-}05$	**0.76**; $p = 0.002$	0.10; $p = 0.83$
Cond. evolvab.	**0.75**; $p = 9.2\text{e-}06$	**0.84**; $p = 7.3\text{e-}06$	**0.76**; $p = 0.002$	0.00; $p = 0.99$
Flexibility	−0.20; $p = 0.32$	−0.04; $p = 0.86$	**0.72**; $p = 0.003$	0.28; $p = 0.55$
Constraints	−0.02; $p = 0.92$	−0.15; $p = 0.54$	−0.49; $p = 0.076$	−0.52; $p = 0.23$

Note: Significant values are indicated in bold.

0.75 respectively; Figure 6), and the forefoot (Table 5), revealing that those skeletal elements that develop earlier are less evolvable and vice-versa. The phalanges show the highest correlation with development, which correlates significantly with integration (negative), evolvability, conditional evolvability, and flexibility (positive). The tarsal bones do not significantly correlate with any index (Table 5).

4 | DISCUSSION

4.1 | Medio-lateral pattern: Foot columns

The results of magnitudes of integration revealed two main trends, first from lateral to medial positions and second in the proximo-distal direction (Figure 2). The first trend showed that the hallux is the most integrated toe and the fifth digit is the least, with the middle digits showing similar intermediate integration values. This first integration trend mainly corresponds with the results obtained by the response to selection indexes, which showed that overall, less integrated digits are more evolvable, more flexible, and less constrained to respond to selection demands. That is, the hallux is the most integrated and constrained but also the least evolvable and flexible ray. In contrast, the fifth digit shows opposite values; it is the least integrated and constrained and the most flexible and evolvable (Figure 3).

It is remarkable that the highest values of integration mainly correspond with the areas of maximum weight transmission throughout the foot during the stance phase of the gait (Crompton et al., 2008). The hallux and the medial column in general, which supports the highest percentage of the total peak force during walking (∼60%), is the most integrated, and its counterpart, the fifth digit, which supports the lowest weight (∼6%), the least (Hughes et al., 1990). Similarly, in the middle and hindfoot, those elements that play an active functional role are the most integrated tarsal bones (i.e., the talus, cuboid, and calcaneus). For example, in the early phase of bipedal gait, the talus, the most integrated tarsal bone, is in charge of bearing at first instance, all the body weight from the tibia and the cuboid and calcaneus lock together to transfer the body mass to the medial column of the forefoot, transforming the foot into a rigid lever in the push-off phase (Blackwood et al., 2005; Bojsen-Møller, 1979; Lewis, 1980). Then, during the early to mid-stance phase, the bodyweight is borne by the lateral column and then by the medial column in the last phase just previous to the toe-off (Elftman & Manter, 1935a, 1935b; Hayafune et al., 1999; Hills et al., 2001; Kidd et al., 1996; Ledoux & Hillstrom, 2002; Lewis, 1980; Reeser et al., 1983; Susman, 1983). This finding supports our first prediction that, in general, those elements that support higher peak forces during the different phases of gait would show higher magnitudes of integration.

This overlap between the pattern of integration in the *Homo sapiens* foot and the lateral-to-medial shift of the center of pressure during gait indicates that plausibly, functional factors related to locomotion could have influenced the magnitudes of integration of the foot skeletal elements depending on its role in the gait. On the one hand, by increasing the level of integration in those units that support higher stress (hallux and talus), and on the other hand, decreasing it in those digits where functional selection pressure for locomotion was relaxed (fifth toe). Conversely to modern humans, quadrupedal great apes lack the longitudinal arch but present a midtarsal break that allows them to dorsiflex the foot at this level during gait (DeSilva, 2010; Holowka et al., 2017). This results in a median plane distribution of the pressure along the foot (Crompton et al., 2008), which could also be represented in their pattern of magnitudes of integration. Based on this indirect evidence, it is reasonable to hypothesize that in quadrupedal primates in general, the middle digits will show the highest integration, lowering the strength of integration toward the medial and lateral positions. This could represent the primitive pattern of morphological integration in the forefoot of this group, meaning that hominins would have deviated from the primitive pattern by increasing integration in the medial column. Indeed, a recent study on the midfoot has found that modern humans medial column is highly integrated compared to other great apes (Komza et al., 2022). We suggest that selection for bipedalism would have reorganized the V/CV matrices of the foot bones, especially those from the medial column in the forefoot, by coordinating their traits to work in the same direction and thus, increasing their strength of integration. However, further studies including data on the entire foot of non-human primates are needed to shed light on this hypothesis.

Processes that bias the direction of variation result in morphological integration (Hallgrímsson et al., 2002). In this case, selection for functional specialization in the hallux might have constrained its ability to freely evolve in any direction of the morphospace, contributing to its high degree of integration. This is supported by the results obtained in the index of constraints, which shows a highly significant correlation with the magnitudes of integration, as also has been observed in previous studies (Arlegi et al., 2020; Goswami et al., 2014; Marroig et al., 2009; Porto et al., 2013). However, this does not necessarily mean that integration has restricted the capacity of the foot to evolve but that functional integration has driven selected traits along the path of the least evolutionary resistance in phenotypic space (Schluter, 1996), hampering traits from evolving in any other direction. Indeed, our results indicate no significant (neither positive nor negative) correlation between the indexes of integration and evolvability in the entire foot, the latter understood here as the ability to respond to selection demands in any direction of the morphospace. Though, when analyzing this influence by digits, we found that the evolvability of the hallux has been much more constrained by integration than the rest of the digits, driving its morphological evolution in the direction of functional selection. This is reflected in the exaggerated robustness of the hallux compared with the rest of the digits but also in the muscular architecture acting on the digits. While the hallux has its own extensor (*extensor hallucis longus*, *extensor hallucis brevis*) and flexor (*flexor hallucis longus* and *brevis*) muscles, the rest of the digits share the same muscles at origin that insert on each toe (*extensor digitorum longus*, *flexor digitorum longus*, and *brevis*) (Kelikian & Sarrafian, 2011). As an exception, there is also a dedicated flexor for the fifth digit, *flexor digiti minimi brevis*, not shared with the other digits. In sum, these results showing high integration and low evolvability in the modern human medial column indicate that the hallux has been under high—probably functional—selection pressures.

In addition, our results indicate that beyond functionality, the degree of integration of the digits is also influenced by their developmental process. For example, the chondrogenesis of the central digits (second, third, and fourth) occurs simultaneously and show similar magnitudes of integration (Table 2). As expected, anatomical elements that develop first show higher integration and vice-versa, except the hallux. The fifth digit develops after the central toes at all modular levels and shows lower integration values. In contrast, the hallux, which metatarsal and proximal phalanx are the latest to develop, is the most integrated. These results reveal the influence of the development process on the degree of integration in the digits, showing those digits that develop earlier have higher integration. Nonetheless, in elements under a strong functional selection as the hallux, this process can be altered by increasing the magnitudes of integration as a response to selection demands. Similarly, although there is no significant correlation between development and integration among the tarsals, the three bones that develop first (cuboid, calcaneus, and talus) show higher integration than the rest. As observed in the toes, functional factors also determine integration, which could explain the lack of correlation between development and integration in the tarsal module. These results suggest that development is not a unique factor determining integration, but together with functionality (and probably other factors), it highly influences its magnitude.

Differences in the morphology of the foot between great apes, extinct hominins, and modern humans suggest that selection for bipedalism has driven positively selected traits in the direction of robustness (DeSilva et al., 2013; Latimer & Lovejoy, 1989; Zipfel et al., 2011). Selection would have reorganized the internal structure of the selected foot bones, leading to a new internal architecture of the V/CV matrix and stronger integration of all the traits, which would have enhanced the rapid evolution of the hominin foot in that direction. It is worth remarking, though, that in this work, all the data have been scaled, and therefore, results are not influenced by differences in size between bones. Previous works that have analyzed morphological integration in primates have mainly focused on the entire autopod level, either comparing the levels of integration within or between hands and feet (Hallgrímsson et al., 2002; Rolian, 2009, 2020; Rolian et al., 2010; Young et al., 2010; Young & Hallgrímsson, 2005). For example, Rolian et al. (2009) found that function has an essential role in modifying the magnitudes of integration between species, having a larger effect than phylogenetic heritage in autopods variation. This (Rolian, 2009) and other studies (Young & Hallgrímsson, 2005) underline the rapidity with which integration evolves between species in an evolutionary context. Our results extend these findings, including all the bony elements of the foot in a single species, and also suggest that integration can also quickly be reorganized within the different units of a single species as a response to functional demands.

4.2 | Proximo-distal pattern: Anatomical modules

The second integration trend, which refers to anatomical modules (i.e., tarsals, metatarsals, proximal, middle, and distal phalanges), reveals that the tarsal bones are the least integrated elements, and the proximal phalanges the most (Figure 2). In the case of the phalanges, the degree of integration decreases from proximal to distal elements, leaving a general pattern in the foot where integration peaks in the proximal phalanges and decreases as it approaches more distal (third phalanges) or proximal (tarsal) positions. Our results correlating the early stages of development and integration in the phalanges show a highly significant correlation (Table 5). This result was expected as the development of the phalanges occurs from proximal to distal units (Kelikian & Sarrafian, 2011). Those metameric elements that develop earlier are expected to show higher integration, patterning the other serial elements (Kavanagh et al., 2013). Although the metatarsals form part of the digits (i.e., phalanges and metatarsals), they do not follow the phalanges proximal-distal increasing pattern of integration. It has been shown that whereas the development of each phalanx affects the other units of the toe, the metatarsals act as an independent module (Kavanagh et al., 2013).

On average, the tarsal bones develop earlier than the phalanges. However, they yielded lower values of magnitudes of integration. This results in a non-significant correlation between development and integration in the entire foot. The tarsal bones show large morphological variability among them, and thus, the variables analyzed are not homologous neither between them or with the metatarsals and phalanges. This fact could have influenced their (on average) lower integration values, or perhaps, simply that they are affected by functional or other factors that influence their degree of integration. Indeed, the intermediate cuneiform is the least integrated bone from the entire foot in modern humans. Similar results were also obtained in previous work (Komza et al., 2022), where they found that in humans, contrary to non-human apes, the intermediate cuneiform had the lowest magnitude of integration among medially located tarsals (the cuneiforms and navicular). Together with the second digit, the intermediate cuneiform constitutes the second ray. In modern humans, the second metatarsal is mortised between the medial and the lateral cuneiforms, making the second ray relatively immobile between the first and third rays and showing the lowest degree of motion of the five rays (Kelikian & Sarrafian, 2011). Here we suggest that the second cuneiform has been functionally selected against in hominins (Cheverud, 1996), lowering its magnitude of integration. Those elements with low integration values may show a relative morphological stasis, as they have all variations homogenously distributed in the morphospace (Gómez-Robles & Polly, 2012; Steppan et al., 2002). These results in the intermediate cuneiform correspond with the observations made in the hominin fossil record (Pablos, 2015; Pablos et al., 2012, 2017). These authors observed that middle Pleistocene hominins from Sima de los Huesos and Neandertals show more robust foot bones than modern humans except for a slender intermediate cuneiform.

If we observe the results from evolvability, there is also a general pattern from proximal to distal modules. Contrarily to what occurred with integration, in this case, this trend is observable in the entire foot. Distal bones (i.e., third phalanges) are more evolvable than proximal elements (i.e., metatarsals), showing a steady decrease in the strength of evolvability from distal phalanges toward the metatarsals and tarsal bones. In this case, our results analyzing the relationship between the ability of the foot to evolve (evolvability) and its development process show a highly significant correlation (Figure 6). Those bones that develop earlier have lower evolvability than those that develop later, without being affected by functional or other factors, as observed in the degree of integration (see above). These results suggest that early stages of development determine the ability of the foot bones to evolve in the direction of selection—either under directional selection or stabilizing selection—as development also correlates with conditional evolvability. In other words, early development acts as a constraint in the ability of the modern human foot to evolve, but not in its capacity to reorganize the integration pattern based on functional demands.

4.3 | Hominin evolutionary implications

The related concepts of integration, evolvability, and constraint can help to explain the emergence of novel morphologies across clades. Hominoids are well known for representing a derived group of primates in terms of posture and locomotion. A previous study suggests that an episode of relaxed integration early in hominoid evolution coincided with the appearance of multiple novel traits in this group (Parins-Fukuchi, 2020). Low magnitudes of integration are related to a larger degree of functional flexibility, which might have enhanced the large variability observed in hominoids. Regarding the hominin fossil record, the three main changes that occurred in the foot: the derived lateral push-off mechanisms of the lateral column, the adduction of the hallux, and short and strait pedal phalanges correspond to units that present either the highest values of integration or evolvability from the entire foot. Recent study on the midfoot found that *H. sapiens* medial column is highly integrated compared to nonhuman hominids, suggesting a link between hallucal abduction and reduced levels of morphological integration (Komza et al., 2022). The present study, including all the elements of the modern human foot, also found higher integration in the medial column compared to the lateral one. Altogether, these results suggest that the V/CV matrix of the foot has been reorganized, increasing the magnitudes of integration in the hallux, perhaps as an adaptation to functional demands related to bipedalism. This is also reflected in its low evolvability, which could reflect the high selection demands the hallux has been under. In addition, the high evolvability in the fifth digit may have facilitated the early stiffness of the lateral ray, which we suggest may have shown higher magnitudes of integration in this early stage previous to the adduction of the hallux, and progressively reduced as this increased its functional role in bipedal locomotion. Finally, the high degree of evolvability in the middle and distal phalanges may have facilitated their selection for endurance running, producing short and straight bones.

4.4 | Limitations of this study

This work is limited to the study of morphological integration and responses of selection in a single species, *H. sapiens*. The use of these approaches in an anatomical structure formed of homologous units allows us to elucidate potential variability and trends in the ability to respond to selection across single skeletal elements. Compared with the information provided by the fossil record, the results obtained from these approaches can be used to infer, how selection proceeds in the anatomical structure. However, to fully understand this process in a macroevolutionary context, it is necessary to analyze these indexes in phylogenetically closely related species to assess potential primitive patterns from which the species might have derived. In this sense, this work does not include other nonhuman hominids but uses the results obtained in a previous study in the midfoot to suggest evolutionary hypotheses in the evolution of modern humans' foot. Thus, further studies, including data on the entire foot of other great apes, are necessary to support the macroevolutionary hypotheses proposed in this study.

5 | CONCLUSIONS

Our results indicate that bones from the medial ray (e.g., hallux) show stronger integration and weaker evolvability than their counterparts from the lateral column (e.g., fifth ray), following this trend from medial to lateral positions. Also, they revealed that distal phalanges are less integrated, more evolvable, and more flexible than proximal elements (i.e., proximal phalanges and metacarpals).

Finally, among the tarsals, the talus and calcaneus are the most integrated, least evolvable, and flexible elements from that module. These results indicate that selection pressures have acted differently on each bone, reorganizing the V/CV matrix of the foot. In this vein, the hallux might have been under strong functional selection pressures for bipedal requirements, resulting in a strong integration and low evolvability. Also, differences in the developmental process of each bone seem to have played an essential role in the degree of evolvability, showing those elements that develop earlier have less ability to respond to selection demands. However, if selection puts an element under strong–functional–pressure (e.g., hallux), the influence of developmental factors will be overcome by this pressure. Thus, we conclude that selection for bipedalism would have reorganized the V/CV matrices of the foot bones in hominins, especially those from the medial column in the forefoot, increasing its magnitudes of integration and decreasing evolvability.

AUTHOR CONTRIBUTIONS

Mikel Arlegi: Conceptualization (equal); investigation (equal); methodology (equal); writing – original draft (equal); writing – review and editing (equal). **Adrián Pablos:** Conceptualization (equal); investigation (equal); writing – original draft (equal); writing – review and editing (equal). **Carlos Lorenzo:** Conceptualization (equal); investigation (equal); writing – original draft (equal); writing – review and editing (equal).

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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