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Normal and five-fingered hand: comparative X-ray morphometry in the post-natal age

Running head: The controversial question of the thumb missing segment

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Abstract

Background: Five-fingered hand (5-FH) with complete developed phalanges is a rare phenotype observed so far only in humans and characterized by three phalanges of the 1st ray. A long-lasting, debated question is if the missing element of the normal hand 1st ray is the metacarpal or the phalanx. In this study, comparative X-rays morphometry of long bones in normal and 5-FH is carried out with the aim to face this question through homology analysis of long bone segments in the transverse and longitudinal line of normal hand and 5-FH.

Materials and methods: In the normal hand X-rays (n =20) and in a 5-FHX-rays series (n=9) the relative length of each segment on the ray total length and the index of growth rate (IGR) were assessed. The calculation of the first parameter in normal hand bi-phalangeal thumb was carried out on the 3rd ray total length in the same hand.

Results: The parameters relative length and the proximal/distal growth rate asymmetry in the post-natal period (assessed through the IGR) confirmed in 5-FH the homology of all the five segment on the transverse line. In the normal control hand, the relative length assessment methodology was biased by the missing segment of the thumb, therefore, the reference to the 3rd ray total length in the same hand (instead of the 1st), allowed the homology analysis of the thumb metacarpal and 1st phalanx with the lateral segments (2nd- 5th ray) of the same hand. The 5-FH analysis was used to choose the more appropriate reference ray for the normal hand group.

Conclusions: The relative length and IGR comparative analysis in the two groups suggested homology of the (anatomical) 1st metacarpal with the 2nd – 5th proximal phalanges in the same hand and that of the (anatomical) 1st proximal phalanx with the 2nd-5th mid phalanges. These data suggest that the missing segment of the thumb normal hand is the metacarpal.

Key words: five-fingered hand, triphalangeal thumb, hand post-natal ossification pattern, hand segments morphometry homology

INTRODUCTION

In the fetal period and after the formation of the primary ossification centers, it is possible to document that the length increment of the long bone cartilage anlagen in the hand occurs with a symmetric proximal and distal growth of the meta-epiphyses [1,2]. This process is controlled by the chondrocyte proliferation rate and orientation in the transition zones between the primary ossification center of the diaphysis and the epiphyses [2]. In a more advanced developmental stage (late fetal and post-natal period), a distinct ossification center is formed transforming the interposed cartilage layer between the ossified diaphysis and the epiphyseal ossification center into the metaphyseal growth plate cartilage. This provides the longitudinal growth until the skeletal maturity is reached. The opposite epiphyseal end undergoes to a different type of ossification indicated with the term of “pseudo-epiphysis” [3].

Therefore the pattern of longitudinal growth changes becoming asymmetric, with a higher distal growth rate in the 2nd- 5th metacarpals and an inverted proximal growth in the 1st metacarpal and in all the phalanges.

Five-fingered hand (5-FH) with completely developed phalanges (excluding delta or severely underdeveloped phalanges) is a rare phenotype. To the best of our knowledge, it has been observed only in the human species. X-ray morphometry of this phenotype has been used to compare length, shape and growth rate index (IGR) of each ray bone element without the bias of the missing segment of the thumb. The result of this study are considered in the context of the long lasting question if the missing 1st ray segment of the normal, human hands a metacarpal or a phalanx [4,5]. No morphometric analysis of this type has been so far carried out on 5-FH phenotype because its uncommon occurrence prevented the collection of a sufficient number of X-rays for the analysis. The aim of this paper is to document through published X-ray images of 5-FH reported cases [6,7,8,9,10] the length homology of the hand segments in the transverse line, the length proportions along the ray longitudinal line, and the pattern of growth which determine the overall shape of each segment class. These data were compared with the normal hand population. In this context, the 5-FH phenotype deserves a remarkable interest because it can be related to the evolution of the opposable thumb in hominids and some anthropoid species.

MATERIALS AND METHODS

The search of published articles on the topic was carried out on PUBMED data base using the terms “triphalangeal thumb” or “five-fingered hands”. Five papers provided X-ray of image quality, which should allow reliable measurements: in all 9 hands in 8 reported cases were analyzed (Tab. 1). The low number of studied cases was due to the rarity of this mutation (basically a normal hand with three phalanges associated to a variable limitation of the opposition). A further limit was represented by the quality of the printed X-ray images, which required a further selection for a reliable morphometry. The selected X-ray images were digitalized in JPEG format with a scanner (when no PDF was available). Elaboration with Adobe Photoshop was carried out using only the brightness/contrast or the “relief” function of the program. Twenty normal hand X-rays of children between 8 and 15 years old was selected from the Pediatric Radiology archives (ASST Spedali Civili di Brescia). The radiographic survey had been carried out for trauma of wrist/finger because of a dubious fracture but not confirmed by X-rays; otherwise, for assessment of the skeletal age. X-rays were taken in anterior-posterior hand projection at the standard distance of 50 cm from the radiogenic tube. The research was approved by University of Brescia DSMC Council.

Length analysis

The length assessment of each hand segment (metacarpals and phalanges) was carried out on digitalized images measuring the distance from the proximal to the distal end along the longitudinal mid axis with the program "Cell" (Soft Imaging System GmbH, Munster, Germany). The epiphyseal ossification centers were included in the measurement: most of the selected X-rays were of adolescents or young adults, therefore with the full developed series of epiphyseal nuclei. The total ray length was calculated as the sum of the metacarpal and of the same ray phalanges. The relative length of each segment in the same 5-FH was calculated on the total length of its own ray. In the normal hand population, the relative length of the thumb segments was calculated on the 3^{rd} ray total length in the same hand, those of the other fingers on the total length of the corresponding ray.

Longitudinal fingers' growth rate index (IGF)

In metacarpals and phalanges X-rays, the narrower circumpherence of the diaphysis (deduced from the narrower A-P diameter in 2-D view) did not correspond to mid point of the segment length. In the early fetal period the primary ossification center develops at the mid point of the cartilage anlage and only later in the ensuing developmental stage became manifest the different longitudinal growth rate of the bone proximal and distal end. This specific character of long bone anlagen development was used to assess the longitudinal growth index of each hand segment: the narrower, transverse diameter of the diaphysis was traced on the digitalized X-ray image and the distance between this line and the proximal and distal ends was measured. When the definition of the narrower transverse diameter was uncertain, the proximal and distal boundaries of the narrow, central segment were traced: the mid point of the central segment was assumed as the level of the narrower diameter (Fig. 1). The ratio between the distance of the mid-point and the proximal/distal ends (IGF) expressed the differential growth after cessation of the bidirectional growth pattern which characterizes the growth phase of the post-natal age.

Statistical analysis

Repeated measurements of twenty normal hand X-ray images and of nine 5-FH X-rays were obtained independently by two investigators (AGS and AM). Each data set was measured twice at interval of one month in two series of paired measurements. The difference of each paired measurements (intra-observer and inter-observer) was plotted against difference in individual segments and total ray length. By analyzing the differences between the paired measurements, the only error which was likely to follow a normal distribution. The variation in the differences for both the two series of measurements was wider in the inter-observed paired data set than in the corresponding intra-observer set, however with a degree of agreement above 95 % of confidence interval for both [11]. The finger segments relative length and the IGF was expressed as mean ± SEM. Statistical analysis was performed with a statistical package (Graph Pad prism 5, Graph Pad Software, San Diego, CA, USA). Non parametric data were analyzed by a Kruskall-Wallis test followed by Dunn's test or Mann-Withney test when appropriate.

RESULTS

The genetic transmission of 5-FH phenotype has been documented by the study of gene mutations in several cases with a large genealogical tree [10,12,13,14,15]; one of these hands X-ray image entered into the criteria of this study and could be analyzed with morphometry. A further case reported by Heiss [6] documented bilateral 5-FH either in the mother (Fig. 2) and her new-born, confirming the genetic transmission. The relative length measurements of the 5-FH segments showed along each ray longitudinal axis same progression with Mtc > Ph-p > Ph-m > Ph-d. The comparison between the corresponding segments relative length in the transverse line (from ray 1 to ray 5) was variable, but with no-significant differences (Tab.2, relative length). The IGF variance was wider among the distal phalanges, not significant among mid/proximal phalanges and metacarpals. The index of all metacarpals was > 1 in contrast with that of all the phalanges which resulted < 1 (Tab.2, IGF). Comparing 5-FH and normal hand segments, the 2^{nd}-5^{th} ray showed no significant difference of relative length and

IGF between corresponding segments (Tab. 3, relative length). The normal hand thumb ray (with the missing segment) was obviously much shorter than the 5-FH 1st ray. Correction of the "missing element bias" of the normal hand 1st ray segments with calculation of the relative length on the 3rd of the same hand (instead of the 1st), homology resulted between the normal hand thumb metacarpal (anatomical) and the lateral proximal phalanges as well as between the thumb proximal phalanx (anatomical) and the lateral mid-phalanges (Tab. 3, relative length).

The IGF of normal hand 2nd – 5th metacarpals was > 1, that of the 1st < 1, such as all the phalanges (Tab. 3, IGF). Both relative length and IGF of the thumb parameters were significantly different in the normal hand and in 5-FHseries.In the latter (n= 9), three cases were reported as not-opposable thumb, in the remaining six hands this character was not reported. In the Heiss case report the hands of the mother showed a synostosis of the right hand trapezius-metacarpal joint, however, also the flat and enlarged joint between the trapezius and the 1st – 2nd left hand proximal metacarpals (Fig. 3) indicated a not-opposable thumb [6].

DISCUSSION

The concept of homology and its application in developmental biology is a cornerstone in the study of organismic diversity and evolution [16]. The issue of the limb bone segment development in the vertebrates offers an ideal field for the application of X-ray morphometry, in particular for what concerns the most distal limb sector, (the autopod) and the evolution of primates and the hominin family.

The measurement of the hand segments relative length on the total ray length was an unavoidable methodology to apply morphometry to published X-ray images of 5-FH because of the rare observation of this human phenotype and the consequent difficulty to collect the original documentation of old cases. Moreover, the morphometric comparison with the normal-hand population was complicated by the "thumb missing segment bias" of the latter population which reduced the total length of the 1st ray (thus increasing the relative length of the ray segments). Therefore, a correction factor was introduced in the normal-hands population calculating the relative length of the thumb segments on the 3rd ray of the same hand total length. The choice of the 3rd ray was based on the observation that in the 5-FH series the 3rd ray total length gave the best approximation to that of the thumb without a missing element.

Shape and topology were the currently used criteria to recognize the individuality of the hand segments as the metacarpals and respectively the proximal, mid and distal phalanges. The morphometric analysis of 5-FH confirmed with the parameters relative length and IGR the homology of the segments at the same level in the transverse line of metacarpals and phalanges. In the human hand evolution, the loss of one segment of the 1st ray and the acquired ability of the thumb opposition has raised a long lasting discussion on the thumb segments homology with that of the lateral four metacarpals and phalanges [5,17].
The unanswered question in this discussion was if the proximal segment of the thumb should be considered as a true metapodial or a phalanx and if the missing segment was the metacarpal or alternatively the proximal or the mid phalanx.

The 5-FH phenotype has been considered the result of a repeated, occasional gene mutation in the chromosomal region 7q36 [18,19] and it was suggested that it could be an ancestral phenotype in the evolution of anthropoids and hominids [20,21,22,23]. However, to the best of our knowledge no observations of this autopod pattern have been reported in paleontology or in the phylogenesis of vertebrates. These considerations were used to support the theory that the proximal thumb segment in the modern humans was a modified metapodial [17], but it does not give an explanation of the thumb missing segment (accordingly to this theory the proximal or the mid phalanx).
The comparative relative length analysis between the 1st ray segments of normal-hand and that of the 5-FH series suggested homology between metacarpal ≈ proximal-phalanx and proximal-phalanx ≈ mid-phalanx.

In this context, the IGF (which can be easily determined in the human hands post-natal X-rays) offered further insights in this discussion. The development of the human autopod was characterized by two different growth patterns. a) the first with a symmetric proximal and distal length growth of the cartilage anlage and the formation of the primary ossification center in the embryonic and early fetal phase. b) the second with the appearance of the epiphyseal ossification center in the late fetal and post-natal age [1,2]. The narrower mid-transverse section of the primary ossification center corresponded to the mid-point of the cartilage anlage characterized by the symmetric length growth of both ends during the whole fetal phase and until the epiphyseal centers development. Therefore, the post-natal X-rays of both 5-FH and normal hands after the formation of the single epiphyseal center (and of the related growth plate cartilage) can be used to measure the distal and proximal segmental growth. It is worth to underscore that this parameter is independent from the relative length measurement.

Since IGF > 1 in 5-FH was the typical pattern of metacarpals, opposed to IGF < 1 of all the phalanges, the observation of the ratio < 1 in the normal-hand series 1st ray proximal segment (a metacarpal accordingly to the current anatomical nomenclature), further reinforced the homology suggested by the thumb relative length measurement, that is a correspondence metacarpal = proximal phalanx and proximal phalanx = mid phalanx.

This study presents some limitations, as frequently observed in comparative metanalysis. First of all, and since the topic refers to a rather infrequent condition, some papers included in this analysis are not very recent and thus include older elaboration techniques for x-ray images which may influence the included data. Secondly, we opted for the measurement of the 3rd ray together with a correction factor in order to achieve the most accurate approximation measurement.

CONCLUSIONS

The relative length and IGR comparative analysis in the two groups suggested homology of the (anatomical) thumb metacarpal with the 2nd – 5thray proximal phalanges in the same hand and that of the (anatomical) thumb proximal phalanx with the 2nd-5thray mid phalanges. These data suggest that in the human hand the missing segment of the thumb is the metacarpal.

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Figure 1. Method for the growth rate index (IGR) measurement in long bones of post-natal hand X-rays. The narrower, transverse diameter of the diaphysis was traced in on the

digitalized X-ray image and its distance from the distal and proximal end epiphyseal ends measured: AB/AC=IGF. When the definition of the narrower diameter was uncertain, the proximal and distal boundaries of the narrower central segment were traced: the mid-point of the latter was assumed as the narrower diameter (examples of measurement in metacarpal, mid and distal phalanx).

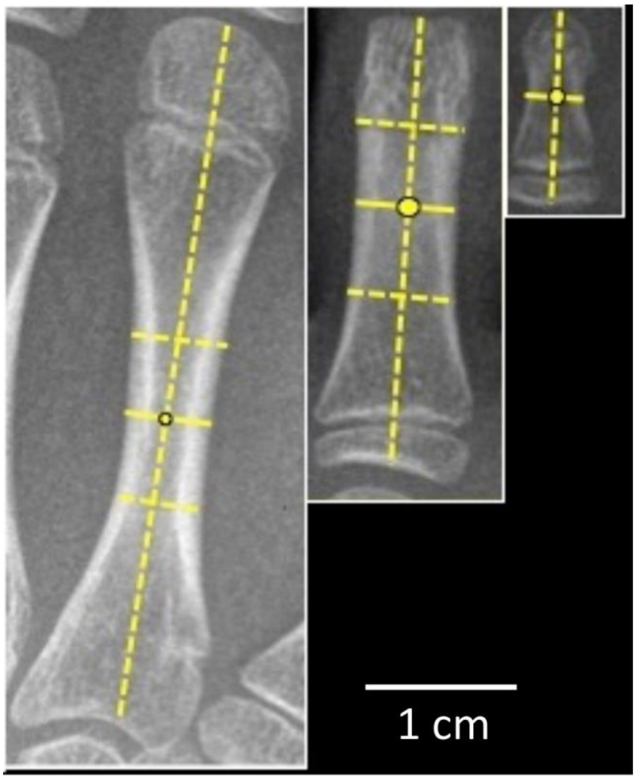
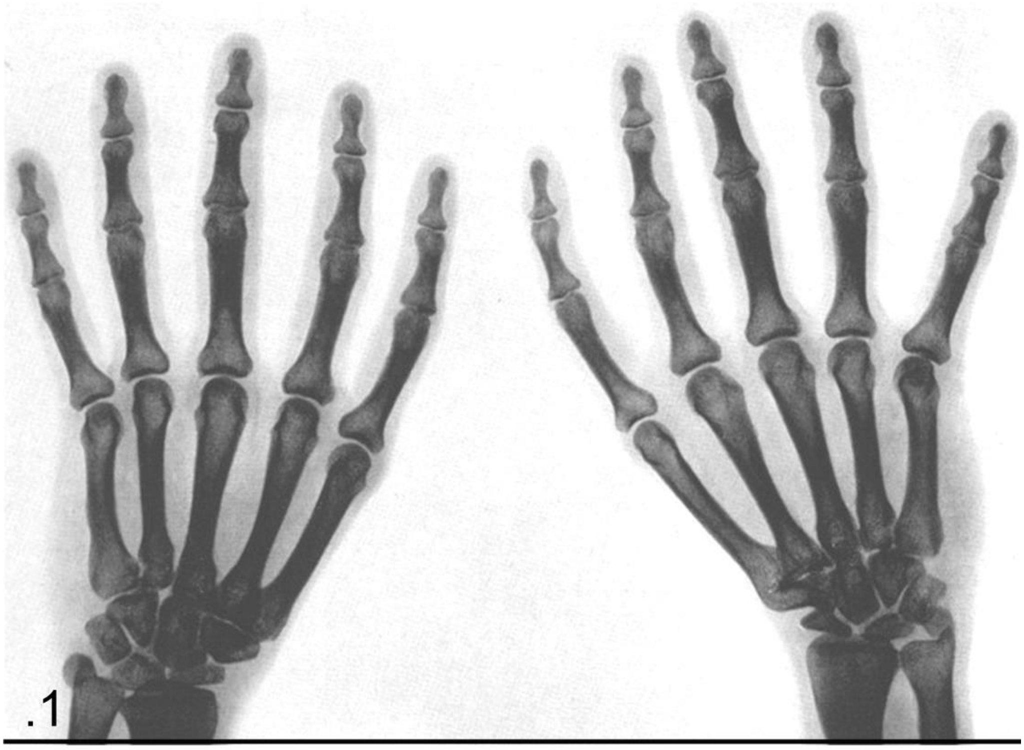


Figure 2. Image of 5-FH of the right and left hand of the mother (1) and of her newborn (2) reported by Heiss (1957). (reproduced from Zeitschrift fur Anatomieund Entwicklungsgeschichte with permission of Springer Nature - license n. 4334811065195).


.1

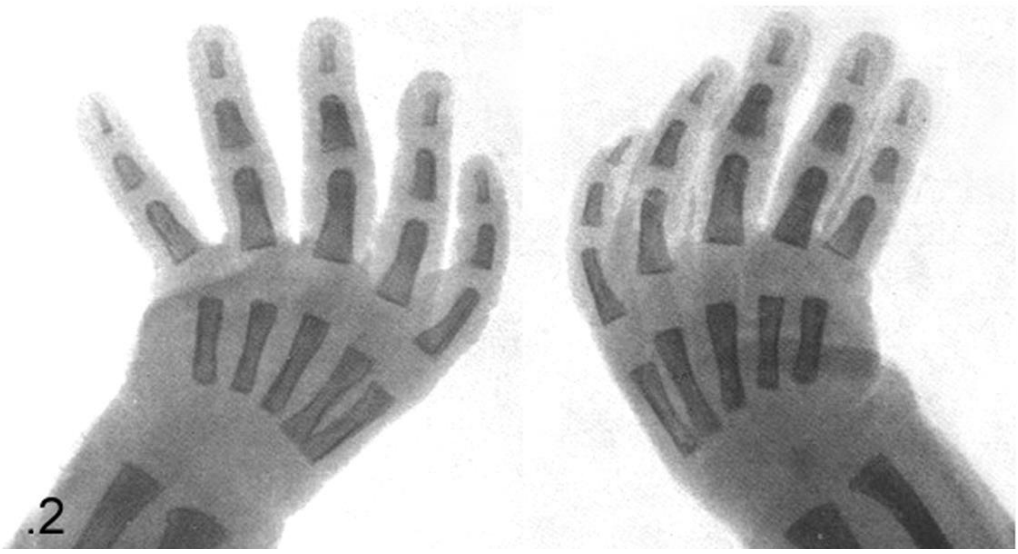

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Figure 3. Detail of Fig 2.1, elaborated with the “relief” function to enhance the relationship trapezius-1st and 2nd proximal metacarpals: synostosis trapezius-1st metacarpal in the right hand and a flat/enlarged trapezius joint surface with the 1st and 2nd metacarpals in the left hand. Both correspond to a not-opposable thumb.

Table 1. Selected case reports of 5-FH hand and data available from the articles (columns 1st-3rd), total number of subjects (column 4th), total number of scannerized hand X-rays where measurements and calculation of relative length and IGR assessment were carried out (column 5th).

Selected Case Reports	**Subject age**	**Parentage**	**Number of cases**	**Number of analyzed X-rays**
Heiss H. (1957)	adult	mother	1	1
	newborn	son	1	0
Qazi Q. & Kassner E G. (1988)	adult		1	2
	child		1	1
Zuidam JM et al (2006)	adult		1	1
Zuidam JM et al (2010)	adult		1	1
Zguricas J et al (1997)	adult		1	2
	adult		1	1
TOTAL			**8**	**9**

Table 2. Morphometric analysis of the hand segments relative length in the 5-FH series (n=9 hands). The segments mean relative length along the ray longitudinal axis decreased from the metacarpal to the distal phalanx: (MC) > proximal phalanx (Php) > mid phalanx (Phm) > distal phalanx (Phd). Only statistical comparison of the mean relative length between corresponding segments in the transverse line was carried out and resulting not significant. Analysis of the hand segments IGF in the 5-FH series (n=9 hands). All metacarpals (1th – 5th) have IGF > 1, all phalanges IGF < 1. This observation is relevant in the comparison with the normal human hand, whose thumb metacarpal (anatomical) has always IGF < 1 like that of all the phalanges. It corresponds to the asymmetrical growth pattern of the human autopod segments, which is characterized by the development of a unique, epiphyseal ossification center (see text). No other index inversions in the transversal line.

Relative length																
	MC				Php				Phm				Phd			
	mean		SD	P	mean		SD	p	mean		SD	p	mean		SD	p
R1	0.42	±	0.05	ns	0.32	±	0.05	ns	0.14	±	0.02	ns	0.12	±	0.01	ns
R2	0.49	±	0.04	“	0.27	±	0.02	“	0.17	±	0.01	“	0.07	±	0.02	“
R3	0.44	±	0.01	“	0.28	±	0.02	“	0.18	±	0.01	“	0.10	±	0.02	“
R4	0.42	±	0.02	“	0.30	±	0.02	“	0.18	±	0.02	“	0.11	±	0.03	“
R5	0.46	±	0.02	“	0.29	±	0.01	“	0.17	±	0.01	“	0.15	±	0.03	“

IGF												
	MC			Php			Phm			Phd		
	mean		SD	mean		SD	mean		SD	mean		SD
R1	0.92	±	0.06	0.84	±	0.05	0.63	±	0.03	0.33	±	0.04
R2	1.28	±	0.10	0.82	±	0.06	0.61	±	0.04	0.32	±	0.07
R3	1.31	±	0.08	0.83	±	0.05	0.62	±	0.06	0.32	±	0.07

R4	1.32	±	0.08	0.78	±	0.08	0.61	±	0.04	0.31	±	0.05
R5	1.35	±	0.08	0.82	±	0.05	0.62	±	0.05	0.32	±	0.05

*P < 0.05; **P < 0.01. ***P < 0.001; ns= not significant

Table 3. Relative length comparison in 5-FH (TPT) (n=9) and normal hand series (NH) (n=20). The relative length of the 1st ray segments normal hands was calculated on the total length of the 3rd ray in the same hand. Comparison of IGF in normal hand and in 5-FH series. In the first series the thumb metacarpal is < 1, the 2nd – 5th > 1, in the second all metatarsals IGF is > 1. All phalanges have IGF < 1 with an index gradient corresponding to metacarpal > proximal phalanx > middle phalanx > distal phalanx.

Relative lengh

	R1							R2							R3							R4							R5						
	TPT			NH				TPT			NH				TPT			NH				TPT			NH				TPT			NH			
	mean		SD	mean		SD	p	mean		SD	mean		SD	p	mean		SD	mean		SD	p	mean		SD	mean		SD	p	mean		SD	mean		SD	p
MC	0.42	±	0.05	0.28	±	0.1	ns	0.49	±	0.04	0.48	±	0.05	ns	0.44	±	0.01	0.43	±	0.01	ns	0.42	±	0.02	0.4	±	0.01	ns	0.46	±	0.02	0.44	±	0.02	ns
Php	0.32	±	0.05	0.19	±	0	***	0.27	±	0.02	0.25	±	0.08	ns	0.28	±	0.02	0.29	±	0.01	ns	0.3	±	0.02	0.29	±	0.01	ns	0.29	±	0.01	0.27	±	0.01	ns
Phm	0.14	±	0.02					0.17	±	0.01	0.16	±	0.02	ns	0.18	±	0.01	0.18	±	0.01	ns	0.18	±	0.02	0.18	±	0.01	ns	0.17	±	0.01	0.15	±	0.01	ns
Phd	0.12	±	0.01	0.14	±	0	ns	0.07	±	0.02	0.11	±	0.02	*	0.1	±	0.02	0.11	±	0.01	ns	0.11	±	0.03	0.13	±	0.01	ns	0.15	±	0.03	0.14	±	0.01	ns

IGF

	R1							R2							R3							R4							R5						
	TPT			NH				TPT			NH				TPT			NH				TPT			NH				TPT			NH			
	mean		SD	mean		SD	p	mean		SD	mean		SD	p	mean		SD	mean		SD	p	mean		SD	mean		SD	p	mean		SD	mean		SD	p
MC	0.92	±	0.06	0.91	±	0.1	ns	1.28	±	0.1	1.18	±	0.06	**	1.31	±	0.08	1.11	±	0.07	**	1.32	±	0.08	1.15	±	0.12	ns	1.35	±	0.08	0.99	±	0.04	***
Php	0.84	±	0.05	0.87	±	0.1	ns	0.82	±	0.06	0.87	±	0.06	ns	0.83	±	0.05	0.85	±	0.11	ns	0.78	±	0.08	0.83	±	0.1	ns	0.82	±	0.05	0.87	±	0.07	ns
Phm	0.63	±	0.03					0.61	±	0.04	0.86	±	0.09	***	0.62	±	0.06	0.83	±	0.11	**	0.61	±	0.04	0.92	±	0.15	***	0.62	±	0.05	0.84	±	0.1	***
Phd	0.33	±	0.04	0.84	±	0.2	***	0.32	±	0.07	0.35	±	0.1	ns	0.32	±	0.07	0.74	±	0.19	***	0.31	±	0.05	0.4	±	0.06	**	0.32	±	0.05	0.32	±	0.13	ns

*P < 0.05; **P < 0.01; ***P < 0.001; ns = not significant