

Quadrupedal Locomotor Characteristics of Uner Tan Syndrome Cases, Healthy Humans, and Nonhuman Primates in Evolutionary Perspectives

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Quadrupedal Locomotor Characteristics of Uner Tan Syndrome Cases, Healthy Humans, and Nonhuman Primates in Evolutionary Perspectives

Author(s): Tan U

Coverletter

08 December 2015

Dear Editor:

I would like to submit my paper entitled "**Quadrupedal Locomotor Characteristics of Uner Tan Syndrome Cases, Healthy Humans, and Nonhuman Primates in Evolutionary Perspectives**, for possible publication in the Journal of WebmedCentral). This is a revised version of my article appeared in WMC (Tan U. Gait Analysis in Uner Tan Syndrome Cases with Key Symptoms of Quadrupedal Locomotion, Mental Impairment, and Dysarthric or No Speech. WebmedCentral NEUROSCIENCES 2015;6(11):WMC005017), revised according to the Reviewer's comments.

Uner Tan syndrome was first identified in 2005 as a unique syndrome characterized by the habitual use of quadrupedal locomotion, severe truncal ataxia, dysarthric or no speech, and severely impaired intellectual abilities. No quantitative gait analysis was carried on these cases until 2014, when the QL was characterized by others as lateral sequence similar to healthy human adults, but in a small sample size from only one family. The submitted work included a representative sample size from 10 families hitherto discovered in Turkey, and reports a new quantitative gait analysis of Uner Tan syndrome cases, healthy human infants, healthy human individuals and nonhuman primates. It addresses the fact that UTS cases walk with straight rather than flexed legs, and the results show that while the QL is mostly lateral sequence, there are similarities in gait characteristics with terrestrial primate locomotion, whereas the QL in healthy individuals had similarities with arboreal primate locomotion. These findings have implications in the evolution of bipedal locomotion in human beings and in the quadrupedal locomotion in UTS cases.

I hope this revised version of my article will meet with your approval.

Yours faithfully,

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Abstract

Introduction: Uner Tan syndrome (UTS) consists of quadrupedal locomotion (QL), impaired intelligence, and dysarthric or no speech. Previously, I described the walk of cases with UTS as diagonal sequence (DS) because of ipsilateral limb interference, which is mostly observed in nonhuman primates with DS QL. The only gait analysis previously performed for UTS was of a few cases from only one family. They exhibited lateral sequence (LS) QL. The current work presents a gait analysis of UTS in more cases from more families, to obtain a representative sample.

Methods: Hip and knee angles during quadrupedal standing were measured in UTS cases, healthy controls with requested QL, and nonhuman primates. Limb phases were assessed from video footages, as the percent of the hind limb's stride durations.

Results: UTS cases and nonhuman primates exhibited quadrupedal standing with straight legs nearly perpendicular to the ground. Healthy individuals could not walk quadrupedally like the UTS cases, but could perform QL only with flexed legs. UTS cases and healthy individuals with free (flexed-leg) QL used predominantly lateral sequence-diagonal couplet (LSDC) walks. Terrestrial primates preferred DS gaits. The healthy individuals with free QL were similar to arboreal primates in quadrupedal posture.

Conclusions: Healthy individuals could not imitate the QL of the UTS cases, so a comparison of the UTS cases with healthy individuals is not justified. Although these results do not seem to support the thesis of locomotor evolution in reverse, nobody knows with certainty who our ancestors were or how they walked, and so the possibility of UTS as an example for the ancestral reappearance of QL in human beings cannot be positively excluded. This locomotor evolution in reverse was supported by experimental evidence that proved reverse evolution occurs as a scientific fact.

Introduction

In 1887, Eadweard Muybridge reported the first case of a child walking on all four extremities with a paralyzed leg (Muybridge, 1901). In this context, Price (1997) noted "...not only was the regular system of limb movements used, but the support of the body devolved, in their proper sequence, on the lateral and on the diagonals," which possibly highlighted a locomotor de-evolution in human beings.

A man with healthy legs walking on all four extremities was discovered by Childs (1917), a famous British traveler and writer, in the middle Black-Sea region of Turkey. Childs described this man as follows: "*I saw that he was without thighs; that the knee-joint was at the hip, the leg rigid, and only half the usual length. With his grim bearded face thrust upwards, and the odd movements of his little legs, he lacked only a stump of tail to make me think I had come upon a satyr in life.*" This man actually exhibited habitual QL with straight legs. He had tattered and torn trousers (**Illustration 1**). He was probably the first UTS case with habitual QL, perhaps a slight mental impairment, truncal ataxia, and poverty (see for a review: Tan et al., 2012).

About a century later, in the years 2004-2005, Turkish media reported five siblings of a consanguineous family with 19 children, residing in a small village near Iskenderun in Southern Turkey to the west of the Syrian border. These five siblings exhibited habitual QL, accompanied by severe mental retardation, truncal ataxia, and dysarthric speech. All of them could stand up and walk bipedally, but only with great difficulty due to severe truncal ataxia, contrary to their easily performed QL. These cases showed a novel neurological syndrome, which was then proposed as Uner Tan syndrome, after its discoverer and reporter (Tan, 2005, 2006, 2008; see for reviews: Tan, 2010; Tan et al., 2012). There was a sixth sibling (a brother) in this family, who used QL during childhood (according to the parents' report), but changed to ataxic bipedal locomotion (BL) after puberty (late-onset bipedal locomotion). Otherwise, he exhibited all of the symptoms of UTS.

Interestingly, the mother in this family suffered from Type-1 diabetes, which is known to be associated with neurological disorders including ataxias (Urduingulo et al., 2009) and autosomal recessive syndromes through epigenetic changes (Morell et al., 1986).

All of the UTS families found in 2004 and later (10 families in all) had low socio-economic status, which

can also induce epigenetic changes affecting the brain development and result in neural disorders, including—in this case—UTS, because of the strong association of poverty with epigenetic patterns (Borghol et al., 2011).

With regard to the locomotor aspects of UTS, we did not perform a biomechanical gait analysis on any of the UTS cases, despite having extensive video recordings. Instead, we made a simple analysis by exploring their QL in regard to ipsilateral hand-foot interferences. We found all of them exhibited ipsilateral hand-foot interferences during QL, and described their walk as DS because the ipsilateral limb interference frequently occurs in nonhuman primates with DS gait, and the ipsilateral limb interference was reported to be a potential drawback of a diagonal walk (Hildebrand, 1967; Cartmil et al., 2002; Wallace and Demes, 2008). As noted by Hildebrand (1976) and Larson (1998), DS walking often results in ipsilateral limb interferences (see also Young et al., 2007). Moreover, Larson (1998) stated: "*a diagonal sequence/diagonal couplet walking gait creates a strong potential for interference between the ipsilateral hind and forelimbs.*" Wallace and Demes (2008) also highlighted the ipsilateral limb interference in DS gait. According to Shapiro and Raichlen (2006), "*ipsilateral interlimb interference is very high for DSDC walking.*"

However, the idea that nonhuman primates exclusively prefer DS walking gait is not in accord with the scientific literature. Namely, Sellers et al. (2013) found a mixture of DS and LS gaits in nonhuman primates when they used a computer simulation of chimpanzee locomotion. Moreover, Hildebrand (1967) and Cartmill and Demes (2002) also found a broad spectrum of gaits with footfall overlaps in nonhuman primates.

With regard to UTS, Shapiro et al. (2014) carried out a biomechanical gait analysis in a few UTS cases belonging to a single family and a few healthy individuals requested to use QL. They reported the UTS cases exhibited LS walks almost exclusively, unlike the DS walking gaits of their nonhuman primates. Considering this result, these authors noted UTS may not be related to a locomotor evolution in reverse, which was defined as a reappearance of ancestral human QL (see Tan, 2005, 2006). In my opinion this approach is not justified, since the living nonhuman primates cannot be taken as our ancestors. Therefore, this interesting topic needs further evaluation to determine the evolutionary origins of human bipedalism with regard to our real ancestors (who we do not yet know with certainty), and to be conclusive about their walking gaits.

Analyzing gaits in UTS, Shapiro et al. (2014) found

nearly exclusively LSDC gaits in their few UTS cases, and this seemed to contradict my observational analyses of the pictures of the cases, which showed ipsilateral hand-foot interference. It is questionable whether their small sample ($n = 5$ from only one family) would be representative of all of the UTS cases ($n = 33$ from 10 families) reported in two review articles (Tan, 2010; Tan et al., 2012). Therefore, more families with more cases need to be subjected to a quantitative gait analysis to be conclusive on this topic.

Following the above considerations, I designed a more comprehensive study to include more cases from more families. The essential questions of this work to be answered were: (i) Do the UTS cases use LS and/or DS walking gait? (ii) How might the QL of UTS cases be related to that of healthy individuals and the living nonhuman primates, erroneously reported as our ancestors? (iii) Might the locomotor characteristics of the UTS cases be considered examples of a locomotor evolution in reverse in human beings?

Methods

To assess the quadrupedal posture while standing on all four extremities, the hip and knee angles were measured using the "Universal Desktop Ruler v3.6.3481" software. These measurements were performed on pictures of the UTS cases from 10 families ($n = 32$), healthy adults with requested straight-leg QL to imitate the UTS cases ($n = 27$), healthy adults with freely moving flexed-leg QL ($n = 53$), adult terrestrial primates (bonobos, baboons, chimps, gorillas, and rhesus monkeys; $n = 24$), and adult arboreal primates (loris, lemur, propithecus, and marmoset; $n = 31$), and healthy human babies with straight-leg QL ($n = 24$).

A gait analysis was performed on videos in which the participants were filmed with a digital video camcorder at 25 frames/sec. Limb phases were measured from the video footage, "as the percentage of a hind limb's stride duration that the touchdown of a forelimb follows that of the hind limb on the same side of the body" (Shapiro et al., 2014). Gait numbers (limb phases), were as follows: 0 (or 100) corresponds to a pace, 1-24 represents LSLC, 25: LSSF, 26-49: LSDC, 50: trot (diagonal limbs landing simultaneously), 51-74: DSDC, 75: DSSF, and 76-99: DSLC walking gaits. LS, LC, DS, SF, and DC were abbreviations for lateral sequence, lateral couplet, diagonal sequence, single foot, and diagonal couplet, respectively. Sequence meant the order of footfalls in time. In a DS walk, a reference hind limb touches the ground and then the contralateral forelimb touches the ground. In an LS

walk, a reference hind limb touches the ground and then the ipsilateral forelimb touches the ground (see Shapiro et al., 2014). Gait analysis included only the symmetrical walking strides between 40 and 60% for the fore and hind limbs (see Hildebrand, 1976).

Informed and written consent was obtained from a responsible person before the investigations. The study was approved by the ethics committee of Cukurova University, following the Helsinki declaration. Statistical analyses were performed using SPSS V. 22 (IBM Corp., 2012, USA).

Results

Hip and knee angles during standing on all fours

Illustration 2 depicts quadrupedal standing postures of the UTS cases (**A1-A4**), healthy individuals with requested QL like UTS cases (**B1-B4**), terrestrial nonhuman primates (**C1-C4**), humans freely standing on all fours (**D1-D4**), and arboreal primates (**E1-E4**). The UTS cases stood on all fours with straight legs nearly perpendicular to the ground. The healthy individuals with requested straight-leg quadrupedal posture could not bend at the hip as much as the UTS cases. The terrestrial nonhuman primates were able to stand on all fours with straight legs like the UTS cases. The healthy individuals with free QL used bent (flexed) legs, contrary to the UTS cases and terrestrial nonhuman primates, but similar to the arboreal primates with a flexed-leg quadrupedal posture.

Means with SDs of the hip and knee angles of the UTS cases, healthy individuals with requested QL using straight legs, adult terrestrial primates, healthy individuals with free quadrupedal standing using flexed legs, and adult arboreal primates were presented in **Illustration 3**.

Univariate ANOVA showed significant differences in mean hip angle (dependent variable) between groups ($F_{1,162} = 86.7$, $p < .000$). Multiple comparison tests indicated no significant difference between the mean hip angles of the UTS cases and terrestrial primates or between the mean hip angles of the healthy individuals with free QL (flexed-legs) and arboreal primates: $p = 1.000$. Multiple comparisons further indicated the mean hip angle was significantly greater in healthy individuals with requested straight-legged quadrupedal standing than UTS cases ($p < .000$). The mean hip angle was significantly greater in UTS cases than healthy individuals with free (flexed-leg) QL, with $p < .000$, and significantly greater than that of the arboreal primates with $p < .05$.

Illustration 4 depicts the mean hip (open circles) and

knee angles (filled circles) in UTS cases (UTS), healthy individuals with requested QL (HEALTHY1), terrestrial primates (PRIMATES1), healthy individuals with free QL (HEALTHY2), and arboreal primates (PRIMATES2). Univariate ANOVA indicated the mean knee angle, as the independent variable, was significantly associated with groups ($F_{1,62} = 200.8$, $p < .000$). Multiple comparisons yielded the following results for knee angles: UTS cases > healthy individuals with free QL; UTS cases > arboreal primates; healthy individuals with requested QL > healthy individuals with free QL and arboreal primates; terrestrial primates > healthy individuals with free QL and arboreal primates; healthy individuals with free QL (flexed leg) < UTS cases; healthy individuals with requested (straight-leg) QL < terrestrial primates.

Gaits

The univariate ANOVA test of between subjects effects indicated significant associations of the mean limb phase values with groups ($F_{4,84} = 37.1$, $p < .000$). **Illustration 5** shows the mean limb phase values (%) with their ± 2.0 SDs for the UTS cases (UTS), healthy individuals with requested QL (forced QL), and free QL (free QL), babies (babies QL), and terrestrial primates (primates QL). The groups entirely above or below the 50% reference line were the terrestrial primates (PRIMATES QL), and healthy individuals with requested QL (FORCED QL), respectively. Otherwise, the mean limb phase value was significantly greater in UTS cases than the healthy individuals with requested QL, but significantly smaller than the healthy individuals with free QL, babies with free QL, and the terrestrial primates ($p < .000$).

Illustration 6 presents the stride numbers and percentages of the LSDC and DSDC walks, including minimum and maximum limb phase values (%) in all five groups. The limb phase values of the UTS cases mainly indicated LSDC gaits (94.9%) with a small percentage of DSDC gaits (5.1%), but the healthy individuals with requested straight-leg QL exclusively exhibited LSDC gaits. The individuals with free flexed-leg QL used a mixture of walking gaits: 67.6% LSDC and 32.4% DSDC. Babies with free QL exhibited a similar gait pattern to the healthy individuals with free QL, being 70.0% LSDC and 30.0% DSDC. The terrestrial primates exclusively exhibited only DSDC gait.

Magnetic Resonance Imaging (MRI)

Illustration 7 depicts the sagittal and coronal MRI scans of a healthy individual (A, B), a UTS case (C, D), and a sagittal MRI of a rhesus monkey (E). The UTS case exhibited hypoplasias in the cerebellum,

pons and medulla, and simplification of the cortical gyri compared to the healthy individual and the rhesus monkey. The MRI scans of the UTS case is typical of the MRI scans of other UTS cases, except that some of them showed an additional hypoplasia of the corpus callosum, and one case of a total of 33 cases had a normal cerebellum.

Discussion

Quadrupedal locomotion

The individuals with UTS kept their legs straight during quadrupedal standing and QL. When the healthy individuals were asked to walk on all four extremities with straight legs to imitate the UTS cases they were almost unable to do so. They instead made very small steps and only with great difficulty, despite being given a warm-up period of five minutes. This is contrary to the conclusion of Shapiro et al. (2014) that: "*the quadrupedalism exhibited by individuals with UTS resembles that of healthy adult humans.*" The contradictory result may be because their healthy controls were not asked to imitate the UTS locomotion on all four extremities with straight legs perpendicular to the ground. Instead, they most likely walked on all fours with bent (flexed) legs as this is more natural for healthy individuals. Shapiro et al. (2014) did not mention the leg posture of their participants and did not provide pictures and/or video of them to confirm their posture. In light of the extreme difficulty of adopting UTS-like locomotion it seems likely that they analyzed the gaits of healthy individuals with flexed legs. Therefore, their conclusion "*...although the habitual use of quadrupedalism by adults with UTS is unusual, the form of this quadrupedalism resembles that of healthy adults and is thus not at all unexpected*" is not justified. On the contrary, the gait in UTS was indeed unexpected, so that this syndrome evoked a world-wide interest among scientists.

Postural characteristics

The mean hip and knee angles were significantly smaller in the healthy individuals with free (flexed-leg) quadrupedal standing than in UTS cases and terrestrial primates, but the latter two groups had similar hip and knee angles and exhibited similar postural characteristics while standing on all fours.

The neural mechanisms of this postural behavior would be the same throughout tetrapods (Reilly et al., 2006; Patrick et al., 2009). In essence, many basic features of the neural networks controlling the locomotor system have been preserved during evolution across the lower vertebrates to human beings (Falgairolle et al., 2006). Stuart (2005), emphasizing the phylogenetic importance of posture

and movement, stated: *“Neural mechanisms that integrate posture with movement are widespread throughout the central nervous system.”*

The mean hip and knee angles were not significantly different between the healthy individuals freely standing on all fours with flexed legs and the arboreal primates, which also used flexed legs. These results add support to the hypothesis that bipedal locomotion in human beings originated from arboreal primate life. In this context, Schmitt (2003) highlighted the evolutionary importance of the stiff-leg QL and stated: *“...the evolution of bipedalism in humans involved a simple transition from a relatively stiff-legged quadrupedalism.”* This author also pointed out that *“laboratory based studies of primates also suggest that human bipedalism arose not from a terrestrial ancestor but rather from a climbing, arboreal forerunner.”* The flexed-leg quadrupedal posture of healthy humans naturally adopted when they were requested to use QL, supports this statement.

Gait analysis

The UTS cases predominantly used LSDC walking gaits (92.4%) with the remainder (7.6%) being DSDC. The healthy individuals with requested straight-leg QL used only LSDC walking gaits, but the mean limb phase was significantly different to that of the UTS cases. The distribution of mean limb phase values in healthy individuals using free QL was also significantly different to that of the UTS cases. These results indicate UTS was unique in the biomechanical features of QL, contrary to Shapiro et al.'s (2014) claims.

The limb phase values showed overlaps among groups. In nonhuman primates all limb phase values were greater than 50, indicating exclusively DSDC walking gaits. The UTS cases, healthy individuals with free QL, and babies, shared many limb phase values with nonhuman primates, with 42.9% of babies exhibiting LSDC and 57.1% DSDC. Similarly, Trettien (1900) also found a mixture distribution of walking gaits in human babies, with 50% using diagonal crawling on hands and knees, 20% lateral crawling on hands and knees, and 9% diagonal crawling on hands and feet. Righetti et al. (2015) reported crawling on hands and knees in infants was very similar to the locomotion in nonhuman primates. Patrick et al. (2009) found infants on hands and knees all inclined to move their diagonal limbs together, and concluded: *“human crawling shares features both with other primates and with nonprimate quadrupeds, suggesting similar underlying mechanisms.”* So, the scientific literature is consistent with similarities between humans and nonhuman primates with regard to quadrupedal

locomotor characteristics and their underlying neural controls.

Using hands and feet instead of hands and knees, the babies in the present study constituted a group different from the UTS cases, with a significantly greater percentage of DSDC walking gaits and significantly greater mean limb phases. These results also support the conclusion that the UTS cases belong to a unique group with regard to their gait characteristics.

A small percentage of the UTS cases shared limb phase values with those of nonhuman primates. In accord, the spinal and supraspinal motor control mechanisms are also shared among human adults (Dietz, 1992, 1997), infants (Yang et al., 1998; Pang and Yang, 2000), and all quadrupeds (Grillner, 1981), but primates constitute a more or less distinct group because their upper limbs are specialized for skilled hand movements with specific supraspinal motor control (Dietz, 1992).

Neural mechanisms

As Falgairolle et al. (2006) noted, *“rhythmic arm movements are under the control of cervical forelimb generators in quadrupeds as well as in humans,”* suggesting phylogenetic conservation of the preserved spinal network organization. These evolutionarily conserved locomotor neural networks may also play a role in the re-emergence of quadrupedalism in human beings with UTS, which may be described as locomotor evolution in reverse (see Tan, 2014).

With regard to the neural mechanisms of human quadrupedalism, Ivanenko et al. (2013) concluded: *“human quadrupedalism is a behavior that can result from adaptive processes triggered by disorders in postural tone and environmental cues.”* Dietz (2002) and Patrick et al. (2009) reported that the shared features of the crawling of humans and locomotion of quadrupeds may suggest the existence of similar underlying locomotor mechanisms. Dietz (2002) and Righetti et al. (2015) also concluded that similar supraspinal and spinal locomotor controls exist in human infants, adults, and quadrupeds, accentuating the importance of the neurophysiological mechanisms that play a role in the emergence of the QL, but not the biomechanical features, contrary to Shapiro et al. (2014), who concluded, *“quadrupedalism in healthy adults or those with a physical disability can be explained using biomechanical principles rather than evolutionary assumptions.”*

In a study by Zampagni et al. (2011), human expert climbers exhibited a prominent diagonal gait resembling the diagonal walking gait of nonhuman

primates, but the non-climbing individuals with QL on the ground in the present study used primarily LSDC, with a small percentage of DS. Similarly, nonhuman primates do not always use purely LS or DS, but also exhibit a mixed pattern of diagonality. Primates alternating between DS and LS gaits have been reported in several studies (Hildebrand, 1967; Tomita, 1967; Rollinson and Martin, 1981). Wallace and Demes (2008) investigated the walking gaits of two primates (*Cebus apella*) as they moved across terrestrial and simulated arboreal substrates and found they used DS gait on the arboreal substrate and LS gait on the ground. Thus, the locomotion of the UTS cases, with predominantly LS walking gaits resembles that of arboreal nonhuman primates such as *Cebus apella*, traveling on the ground.

Evolution in reverse

As a result of their gait analysis and noting non-similarities between the UTS cases and the nonhuman primates, Shapiro et al (2014) rejected the idea of locomotor evolution in reverse in human beings, i.e., the reappearance of quadrupedalism in UTS cases. By definition, the theory of backwards evolution or de-evolution or reverse evolution means “a reacquisition of the same character states as those of ancestor populations by derived populations” (Teotonio and Rose, 2001). I followed this definition in my studies regarding the locomotor evolution in reverse in human beings. This was merely an endeavor to be able to better understand the transition from quadrupedalism to bipedalism in pre-human beings.

Reverse evolution is, in fact, not a simple hypothesis, but there are reports based upon experimental works supporting this concept (see e.g., Teotonio and Rose, 2000, 2001; Porter and Crandall, 2003; Tan and Gore, 2012). Moreover, as an example of reverse evolution, Bekpen et al. (2009) discovered a gene associated with Crohn’s disease in humans, that was deleted 50 MYA in primates, could be resurrected during human evolution. In addition, chickens without teeth probably have ancestral genes that could be switched back on (Harris, 2006). The ancestral four-winged flies emerged following mutations in the *Ubx* gene (Lewis, 1978). Dinosaurs also showed devolution by exhibiting the characteristics of their ancestors (Zheng, Jin, and Xu, 2015). In line with these studies, the re-emergence of QL in UTS may also be described as a locomotor evolution in reverse in *homo sapiens sapiens*. This does not mean, however, that the QL in UTS is derived from the QL in living nonhuman primates, because they were not our ancestors, and we do not know yet with certainty who our common ancestors

were. Moreover, a reverse evolution need not reflect the original copy of a behavioral or structural condition because of the unpredictability of the evolutionary outcomes, due to the self-organizing processes occurring within dynamical systems. A locomotor reverse evolution would not therefore mean a blueprint of the ancestral QL. A phenotypic re-emergence of QL, for instance, would be enough to show the reverse locomotor evolution by definition, without considering its details.

Emergent properties of UTS

Uner Tan syndrome was found to be associated with mutations in several genes (*VLDLR*, *WDR81*, *CA8*, *ATP8A2*), suggesting a genetic heterogeneity of the syndrome (see Onat et al., 2013). Thus, single genes were associated with UTS, and with the possible reappearance of an ancestral locomotor trait. These nonspecific mutations were attributed to the emergence of a neural disorder facilitating the emergence of UTS (see Onat et al., 2013). However, the same mutations may be responsible for many conditions other than UTS. That is, a genetically disordered nervous system may produce vulnerability for a range of pathological conditions, despite a neural disorder extended throughout the brain. Why? The answer may be the unpredictability of the self-organizing processes creating attractors within a highly complex dynamical system such as the brain. That is, no one can predict the outcome of such a dynamical system by merely detecting the affected brain regions.

By definition, the self-organization is a dynamical and adaptive mechanism with a spontaneously emerging output property, occurring without any external control. From the system-theoretical perspective, the outcome of a dynamical system with self-organizing properties is unpredictable (Moore, 1990). Accordingly, the rarely occurring emergence of habitual QL in the UTS cases may then be explained by the physical properties of the self-organizing processes within the human brain, which is a highly complex dynamical system. The locomotor neural networks, such as the ancestral central pattern generators (Grillner, 1981; Falgairolle, 2006; Guertin, 2013) can provide a neural basis for the emergence of the attractor state QL. These mechanisms were previously discussed in several articles to explain the dynamics of UTS (Tan, 2010; Tan et al., 2012; Tan, 2014). In this context, any attempt to explain human QL as a simple adaptation to cerebellar ataxia (see Shapiro et al., 2014) would be too simple: there are many cerebellar ataxias, but only rarely with emergence of UTS and its quadrupedal locomotion. UTS can thus be regarded as the

unpredictable outcome of an adaptive self-organizing process, within a genetically disordered brain.

Darwinian Medicine

The idea of evolution in reverse can also be considered within the framework of evolutionary or Darwinian medicine (Rapoport, 1988), which was suggested as a foundation for all medicine (Zampieri, 2009). This was originally proposed to answer the question why serious diseases still exist despite natural selection. A number of diseases and conditions were considered as Darwinian disorders, such as tuberculosis, Huntington's disease, depression, obesity, anxiety, pain, nausea, cough, fever, vomiting, fatigue, epilepsy, obsessive compulsive disorder, schizophrenia, and Alzheimer's disease as a phylogenetic regression (Eskenazi et al., 2007; Scorza et al., 2009; Abed and Pauw, 1998; Pearlson and Folley, 2008). In this context, Ghika (2008) stated: "*The highest level of gait disorders including Uner Tan syndrome, with its simian-like gait and posture or apraxia, i.e., the re-emergence of old automatism of pre-human gait, may also be considered under these phylogenetic diseases.*"

Although these considerations are in accord with my theory of "human locomotor evolution in reverse" (see Tan et al., 2012), it was criticized by Shapiro et al (2014) by comparing the gaits of a few UTS cases with living nonhuman primates. Here, I would like to refer to two points: (i) Shapiro et al. (2014) tested the theory of "human locomotor evolution in reverse" or, in short, "human locomotor devolution." This is acceptable despite these authors having tried to disprove it, since a theory is scientific only if it is falsifiable or testable, and if not it is unscientific (Popper, 1999); (ii) Shapiro et al. (2014) appeared to consider living primates as our ancestors. Although I can agree with the first point, I cannot agree with the second, because our ancestors are not known with certainty, and they are not the living primates. In this context, Huxley (1860) stated: "*...the stock whence two or more species have sprung, need in no respect be intermediate between these species.*" The paleontological discoveries made on African fossils have not yet identified with certainty our proposed common ancestors (White et al., 2015), and consequently, any gait analysis on living nonhuman primates would not be sufficient to reach an acceptable conclusion about the walking patterns of our ancestors. On the other hand, Dawkins (2004) pointed out that one possibility to explain bipedal locomotion in humans was that "*chimpanzees and gorillas descend from more human-like, even bipedal ancestors, and have reverted to all fours more recently,*" suggesting an evolutionary route contrary to

our general understanding. In brief, living primates cannot constitute a model to study our ancestors' locomotor characteristics.

Conclusion

The locomotor characteristics of the UTS cases, healthy human individuals, healthy human babies, and terrestrial and arboreal nonhuman primates were the main subjects of the present work. The results, in general, did not support Shapiro et al.'s claims. Individuals with UTS stood and walked on all four extremities with straight legs almost perpendicular to the ground, but healthy individuals asked to use straight leg QL could not mimic the QL of UTS cases, indicating that quadrupedal locomotion in healthy human individuals is not at all similar to the UTS cases: the UTS quadrupedal style was unique in this context, contrary to Shapiro et al. (2014). The quadrupedal standing of UTS cases was similar to that of terrestrial primates. The quadrupedal standing of healthy individuals with free (flexed-leg) QL showed similarities to the arboreal primates, supporting the hypothesis of arboreal locomotor origins of pre-humans.

The analysis of the locomotor characteristics in the UTS cases demonstrated this syndrome may constitute a unique group among individuals with or without requested QL. In accord, Guertin (2013) also described UTS as "*a recently identified, and uniquely different neurological disorder.*"

The results were interpreted in line with locomotor reverse evolution and Darwinian medicine. It should, however, be noted that no one is certain who our real ancestors were, which makes it impossible to be conclusive in this context. On the other hand, the scientific literature showed that evolution in reverse is an experimentally proven fact.

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Illustrations

Illustration 1

First discovered man with habitual QL in Turkey in 1917 by Childs. Notice the hip (1) and knee (2) angles.



Illustration 2

Quadrupedal postures in the UTS cases (A1-A4), healthy individuals with straight- leg quadrupedal posture (B1-B4), nonhuman primates (C1-C4), healthy individuals with free quadrupedal postures (D1-D4), and nonhuman primates with arboreal QL (E1-E4. Notice primates with large (C1-C4: terrestrial) and small (E1-E4: arboreal) bodies.

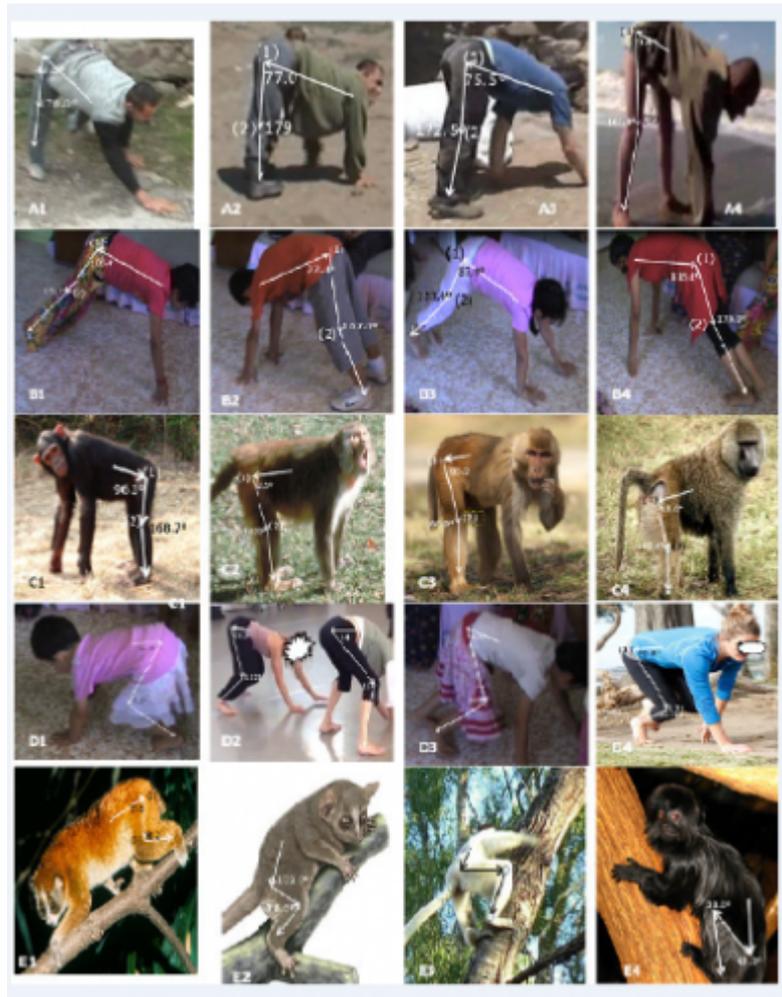


Illustration 3

Means and SDs of the hip and knee angles

Groups	N	Hip Angle		Knee Angle	
		Mean	SD	Mean	SD
1: <u>UTS</u>	32	69.6	<u>12.2°</u>	171.8	<u>5.5°</u>
2: <u>Healthy1</u>	27	120.6	<u>19.0°</u>	173.7	<u>2.6°</u>
3: <u>Primates1</u>	53	74.8	<u>12.0°</u>	169.8	<u>6.3°</u>
4: <u>Healthy2</u>	24	52.0	<u>11.7°</u>	115.1	<u>16.0°</u>
5: <u>Primates2</u>	31	57.2	<u>18.1°</u>	106.8	<u>24.4°</u>

SD: standard deviation; 1: UTS cases; 2: (Healthy1): healthy individuals with requested quadrupedal standing with straight legs; 3 (Primates1): terrestrial primates; 4: (Healthy2): healthy individuals with flexed-leg (free) quadrupedal standing; 5: (Primates2): arboreal primates.

Illustration 4

Error bars with ± 2.0 SE for the hip (open circles, red) and knee (filled circles, black) angles of the UTS cases (UTS), healthy individuals with requested QL, straight legs (FORCED QL), terrestrial primates with free quadrupedal standing (PRIMATE1), healthy individuals with free (flexed legs) QL (NORM QL), and arboreal primates with free quadrupedal standing (PRIMATE2)

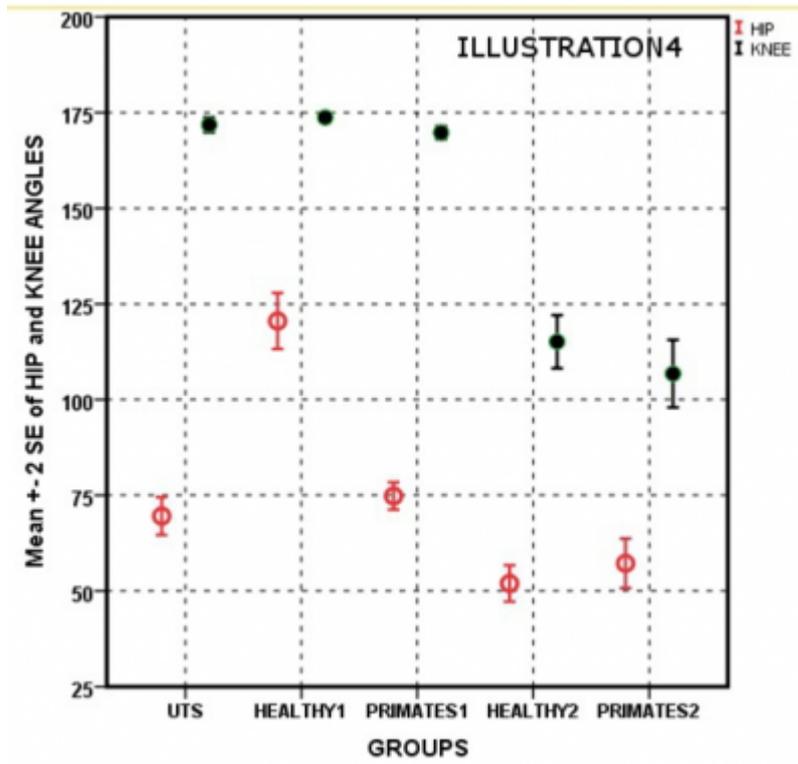


Illustration 5

Mean limb phases with ± 2.0 SDs for five study groups. UTS cases (UTS); FORCED QL: healthy individuals with requested straight-leg QL; FREE QL: healthy individuals with free QL; BABIES QL: babies with QL; PRIMATES QL: terrestrial nonhuman primates QL. Notice the differences and similarities in these subgroups.

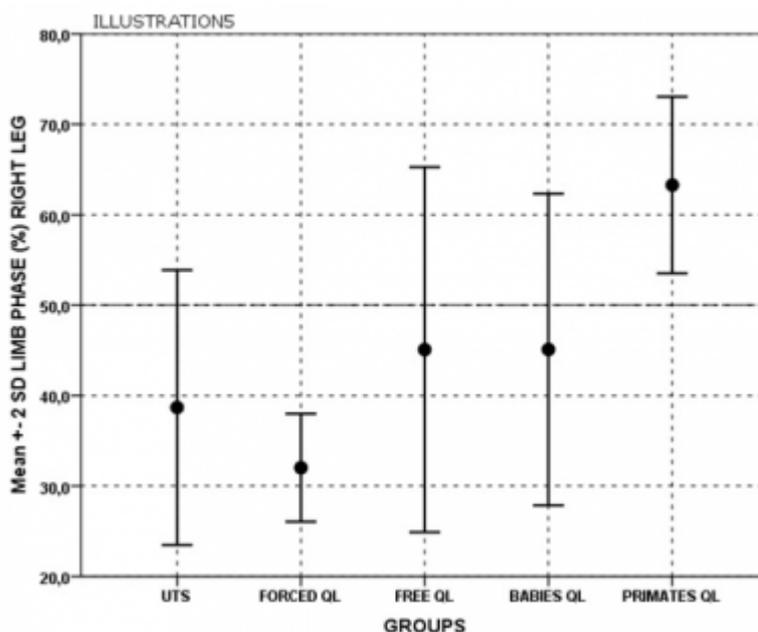


Illustration 6

Percentages and minimum-maximum limb phase values for five study groups

Groups	N	Limb phase LSDC		Limb phase DSDC		Limb phase (%)	
		N	%	N	%	Min.	Max.
UTS	32	319	94.9	17	5.1	25.6	59.2
Forced QL	27	254	100.0	0	0.0	25.9	39.0
Free QL	53	48	67.6	23	32.4	25.3	74.5
Babies QL	24	49	70.0	21.0	30.0	31.0	74.4
Primates QL	31	0	0.0	122.0	100.0	52.1	73.9

Illustration 7

Sagittal and coronal MRIs in healthy individuals (A, B), and UTS cases (C, D). E: sagittal MRI from a monkey brain, with Tammer et al.'s (2009) permission. CC: corpus callosum, CER: cerebellum.

