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REVIEW

ÜNER TAN SYNDROME: A REVIEW OF THE SYNDROME AND REVERSE EVOLUTION

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ABSTRACT

Üner Tan syndrome is a rare genetic condition that primarily affects individuals from consanguineous families, marked by a distinct quadrupedal gait, intellectual disability, and limited speech. First identified in Türkiye in 2005, Üner Tan syndrome has since been recognized in various regions with similar patterns of consanguinity. Those with Üner Tan syndrome commonly exhibit a diagonal-sequence quadrupedal gait, which led Üner Tan to propose the theory of "reverse evolution," suggesting that affected individuals represent a regression to a more primitive state, losing advanced human traits such as upright walking, speech, and cognitive abilities. This theory has sparked significant debate in both medical and evolutionary circles. Neurological and genetic studies have pointed to certain mutations that play a role in the syndrome, with cerebellar hypoplasia frequently detected in brain scans. The disorder sets itself apart from other conditions like cerebral palsy and congenital ataxias due to the absence of congenital hypotonia and the preservation of muscle strength. However, affected individuals often struggle with bipedal movement, instead relying on quadrupedalism as their primary means of locomotion. This phenomenon is linked to the dysfunction of central pattern generators, neural networks that typically coordinate rhythmic movements like walking. In Üner Tan syndrome patients, these central pattern generators appear impaired, leading to a preferance for quadrupedalism over bipedalism.

Despite the severity of intellectual impairment, the exact cause of the cognitive dysfunction in Üner Tan syndrome remains elusive, though it is thought to involve a combination of genetic mutations affecting brain development. In addition to cerebellar atrophy, imaging often shows mild cerebral atrophy. The rarity of Üner Tan syndrome, its overlap with other conditions, and the absence of clear diagnostic criteria make it challenging to diagnose, further complicating clinical understanding of the syndrome. The concept of reverse evolution in Üner Tan syndrome has also led to interesting discussions in evolutionary biology. There is a controversial notion that challenges traditional ideas about evolution by suggesting that mutations can cause the loss of higher-order human traits and revert individuals to a more ancestral form. This idea parallels some observations in other biological processes, such as the metabolic shifts seen in cancer cells, where cells revert to more primitive states to survive. However, it's important to take this notion into consideration with caution since it is still a subject of debate. In conclusion, Üner Tan syndrome is a complex condition that offers valuable insights into human development, genetics, and the potential for reverse evolutionary processes. Further research is needed to clarify its genetic underpinnings and its implications for understanding human evolution and disease.

Keywords: Ataxia, consanguinity, hypotonia, intellectual disability

INTRODUCTION

Üner Tan syndrome (UTS) is a syndrome characterized by diagonal-sequence quadrupedal gait, intellectual disability, and rudimentary speech (1). Üner Tan first discovered a family that had members thought to have UTS symptoms in İskenderun, a region in Hatay, Türkiye in 2005. In 2006, new families with members that had the same symptoms were discovered in the cities, of Adana and Gaziantep. Later on, cases in cities such as Çanakkale and İstanbul proved that the syndrome was not a special condition within a specific geographic region, as they weren't in Southern Türkiye like the previous cases (1). The Anatolian region has a long history of quadrupedalism; in fact, the first person to use their four limbs and have UTS symptoms was discovered in the Havza region of Samsun. This person was photographed by a British photographer, W. J. Childs, in 1917. This man was thought to belong to a consanguineous Greek family as Greek people tended to live in that region during the Ottoman Empire's reign in isolation and practiced

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incestual relationships (2). UTS is an autosomal recessive disease, it is almost exclusively seen in consanguineous families and is seen in closed populations that practice intrafamilial marriages (3). Üner Tan himself described the syndrome as a "backward (reverse) evolution" (4). This sparked controversy among evolutionary scientists and medical authorities as the irreversibility of evolution has been a staple theme for a long time (5).

Experimental Reverse Evolution and Reverse Evolution in Nature

Reverse evolution is explained as the reacquisition of at least one of the ancestral traits by derived populations, thereby resembling ancestor populations to a certain degree (5). In the laboratory, the possibility of reverse evolution can be easily examined by creating mutants resistant to antibiotics and allowing them to develop in environments deprived of antibiotics. Although phenotypic reversion of antibiotic resistance has been documented, evolutionary reversions involving the spread of antibiotic- sensitive wild-type alleles are quite rare in nature and only take place in highly selective environments with high mutation rates such as laboratory studies that introduce specific alleles in antibiotic-free environments (6).

When discussing reverse evolution, two different types of genetic mechanisms need to be recognized: those that aid the process of reversal and those that totally prevent or partially prevent the process of reversal. Generally, pleiotropy and random mutations aid in reverse evolution (5). Total reverse evolution in multicellular organisms is particularly difficult because of epistasis, the interaction between genes at different loci, where the expression of one gene depends on the presence of alleles at another gene locus (5, 7).

Attempts to reversely evolve viruses and bacteria have been made in the past with few of them succeeding, reverting the organism close to the ancestral levels (5). It has been demonstrated in some studies that evolution in reverse is possible in both short-term, experimentally controlled studies of populations and over long evolutionary histories encompassing the diversification of large groups of species. These studies have focused on opposite extremes of the reversibility spectrum with respect to time span (8). A study made on *Plasmodium vivax* to understand the mechanism of microbial resistance has found that a particular single-point mutation, the amino acid at position 117 that is changed from serine to asparagine (S117N), serves as a turning point in the evolution of high resistance regions by generating epistatic interactions that obstruct the reverse evolution of the gene back toward the wild-type ancestor which doesn't have antimicrobial resistance (9). An experiment used an ancestral form of *Pseudomonas fluorescens* in an attempt to investigate evolutionary diversification when faced with geographical heterogeneity. Asexually reproduced bacteria in a different culture than their ancestors' developed a wrinkly fuzzy form in 7 days, differing from their smooth ancestors. However, when these "evolved" bacteria were put into their ancestor's culture, and then these bacteria "reverted" their ancestral smooth form which was more suitable for the culture.

This suggests that the wrinkled phenotype was not a fixed product of evolution (10). In another study, the researchers worked with *Helicobacter pylori (H. pylori). H. pylori* is a bacterial species that includes strains resistant to antibiotics such as Kanamycin and Clarithromycin. The researchers explored horizontal gene transfer, finding that higher transformation rates can spread non-resistant alleles and partially reverse antibiotic resistance in some populations (6).

Some laboratory experiments have been conducted on sexually reproducing multicellular organisms as well to determine whether reverse evolution in a highly selective environment is possible (11). In an experiment conducted in 2002 on *Drosophila* (fruit flies), these flies shared a common ancestry but were raised under different selective pressures, such as late-life fertility, starvation resistance, and accelerated development. The animals were then placed in the same ancestral environment and bred for 50 generations. The experiment concluded that some aspects of male fitness reverted to their ancestral levels such as survival time, offspring's viability, and mating success; female flies didn't show such strong evidence of reverse evolution of fitness. Although the fitness of female flies didn't show significant change, some groups of the population had limited differentiation observed in fecundity characteristics but this differentiation wasn't widespread as well (11, 12). The outcome might be explained by theories like differences between the inheritance of male and female traits and/or having different environmental sensitivity levels than males (11).

In another study, the reversal of adaptation to the ancestral state by back amino acid replacement has also been documented. *Rhodopsin1 (RH1)* gene sequences that encode rhodopsin, a protein that makes it possible to form images in light-deficient environments, from cichlid fishes across four tribes in Lake Tanganyika, each inhabiting different depth habitats, have been studied. The species generally exhibited two RH1 variants: 292A for shallow-water species and 292S for deep-water species, tailored to their respective light environments as confirmed by pigment absorption spectra.

Findings reveal two distinct patterns of parallel adaptive evolution to the depth of water: the A292S substitution occurred independently at least four times, facilitating adaptation from shallow to deep water environments. Conversely, the reverse substitution S292A occurred three times, enabling adaptation from deep to shallow water habitats. This dual adaptation demonstrates a complete reverse evolution scenario where adaptive mutations in RH1 pigments coincide with shifts in species' habitats, marking a notable example of genetic adaptation to environmental changes (13).

Cancer and Reverse Evolution

Cancer is greatly connected to many biomechanisms, one of them being reverse evolution. The study of evolutionary reversibility in enzymes has shown how genetic pathways can

shift in response to environmental pressures, a principle that can also apply to multicellular organisms where cells may "reverse" to a more primitive, survival-driven state (14). Cancer is caused by various factors, including genetic mutations, viral, bacterial, fungal, and parasitic infections, environmental agents like toxins and radiation, and lifestyle factors such as smoking, alcohol, poor diet, obesity, and inactivity (15).

Interestingly, similar to the adaptive gene network reversals observed in yeasts, which switch their metabolism to enhance survival under stress, cancer cells also undergo metabolic reprogramming, allowing them to more efficiently utilize energy for rapid growth and survival (16). The idea that cancer develops by disturbing the genetic network underlying multicellularity is supported by the discovery of an increased percentage of cancer promoters on branches linked to the formation of metazoan multicellularity (17).

Cancer cells use glycolysis to provide energy to the cell even in the presence of oxygen, this is less effective than oxidative phosphorylation. This phenomenon is known as the "Warburg effect" (18). Warburg effect is thought to occur for different reasons, one of them being the fast and uncontrolled proliferation of cancer cells; glycolysis is faster than oxidative phosphorylation, thus allowing faster growth (19). In addition, cancer cells usually overgrow their blood supply, meaning that the oxygenation of cells will not be sufficient after some point, and oxygen will be scarce. Using glycogen for adenosine triphosphate (ATP) production resolves this issue (20). Increased lactate will acidify the cell eventually and this will promote metastasis while also suppressing immune response (20, 21). Switching to the Warburg effect, meaning the preference for glycogen instead of oxygen is a sign of cells acquiring a more primitive state in terms of metabolism (18). Mitochondria being rendered useless because of the preference for glycogen has some scientists claim that cells undergo "de-endosymbiosis", further claiming this shift in cancer cells proves reverse evolution in cancer cells (18).

UTS and Human (De-)Evolution

UTS patients are usually unable to move bipedally and usually they have never exhibited such behavior (22). The development of extensor motor system dominance over the flexor motor system during sitting, standing, and walking led to the emergence of bipedalism. The dominance of the extensor motor system over the flexor motor system is attributed to the skeletal muscles, which are responsible for maintaining upright posture by acting against gravity alongside a healthy nervous system (23).

There are various hypotheses exploring the purpose and advantages of bipedalism of humans. The emergence of bipedalism dates back to around 7 million years ago. This shift from quadrupedalism likely involved a gradual transition from more compliant, ape-like gaits to the stiffer, more efficient bipedalism seen in modern humans, driven by anatomical adaptations that facilitated upright posture and movement, a process that may have been influenced by environmental and functional factors (24). People with UTS generally use quadrupedalism as a way of locomotion with skill and ease. Some patients may use quadrupedalism habitually, switching between bipedalism and quadrupedalism while some never gain the ability to ambulance bipedally (25). Üner Tan used the term "evolution in reverse" for UTS because it seemed as if this "mysterious condition" took away all the great gifts of evolution: speech, bipedal locomotion, and intelligence (26).

Intelligence is almost always impaired severely with very few exceptions and speech is always rudimentary if not absent (25). Üner Tan has postulated that quadrupedalism in people with UTS happens in three stages.

The first phase, termed primary variability, occurs during fetal development and infancy, encompassing both typical and abnormal cases such as UTS. In this phase, the neural foundation for locomotion is established based on evolutionary epigenetic mechanisms inherited from primitive tetrapods that lived approximately 400 million years ago. Through self-generated motor activity and afferent information transmission within the neural system, the groundwork for quadrupedal locomotion is laid down, drawing upon ancient neural networks (27).

The second phase involves a neuronal selection process occurring during infancy. Here, the most effective motor patterns and associated neuronal groups are chosen based on experience. In normal cases, this phase leads to the selection of neural networks conducive to bipedal walking. However, in UTS cases, where certain neural structures necessary for upright walking are compromised due to conditions like cerebellar hypoplasia, the selection process diverges, favoring the enhancement of neuronal groups related to diagonal-sequence quadrupedal locomotion (27).

The third phase, termed secondary or adaptive variability, begins around two to three years of age and extends into adolescence. During this phase, secondary neural repertoires are developed through diverse motor experiences, allowing for the precise adaptation of movements to specific tasks. In individuals with UTS, this phase is hindered, leading to the retention of primitive motor repertoires from earlier phases and limiting the creation of secondary neural repertoires. Consequently, these individuals may continue to rely on ancestral neural groups associated with quadrupedal locomotion. The duration of this phase may vary, with some individuals experiencing delays in the emergence of well-balanced quadrupedal locomotion, which may only manifest late in adolescence (27).

As for the intelligence and dysarthric speech of people with UTS, several hypotheses have been proposed, but an exact cause has still not been found, as is the case with quadrupedalism. Intellectual disability seen in individuals with UTS is thought to stem from a combination of genetic, neurological, and developmental factors. Phenotypic changes that affect brain development and function, leading to structural abnormalities such as cerebellar atrophy and mild cerebral atrophy, are observed in magnetic resonance imaging examinations (28, 29).

Furthermore, neurological dysfunction, including severe intellectual disability and speech disturbance, is common in individuals with UTS. These cognitive impairments may result from disruptions in brain regions beyond the cerebellum, suggesting a multifaceted etiology that may include genetics, cerebral impairments, and environmental factors (22, 28).

Mental impairment, cerebellar hypoplasia, and varying walking gaits have been observed in UTS. These symptoms are obvious especially when it comes to gait as some patients habitually use quadrupedalism (30). Üner Tan proposed that central pattern generators (CPGs), a neural network system that is used to create rhythmic, coordinated movement, such as walking and running, may be the main etiological cause of UTS. One of the main theories in UTS is that quadrupedalism may be caused by malfunctioning CPG circuits. Cerebellar atrophy in these patients may result in loss of coordination and balance, making it difficult for them to walk normally on two feet and therefore making them favor quadrupedal gait. The CPG's function in movement implies that variations in UTS symptoms, such as the degree of quadrupedalism or motor impairment, could result from different spinal locomotor circuit dysfunctions (31). As an example of the various presentations of the syndrome, Üner Tan reports on some members of the Adana-1 family who are able to walk backward and forwards bipedally while still suffering from UTS (32).

On the other hand, UTS patients are frequently thought to represent a phenotypic diversity of cerebral palsy and many of them stay undiagnosed. Several congenital ataxias, including Cayman syndrome, Gillespie syndrome, Disequilibrium syndrome, and Joubert syndrome, have symptoms that overlap with UTS. The absence of congenital hypotonia, maintained muscle strength, early gait acquisition, and quadrupedal movement are important characteristics that set UTS apart. Furthermore, brain imaging of patients with UTS usually shows cerebellar hypoplasia (22).

The reverse evolution thought to take place in the UTS has been associated and explained with certain morphological, neural, and genetic factors. The brachial index, which has decreased throughout hominin evolution, in patients with UTS is more similar to that of Pan paniscus (bonobos), Australopithecus afarensis (A. afarensis, Lucy), Homo habilis, than Homo sapiens. Additionally, the body mass distribution in the footfall patterns of UTS patients reveals reduced support on their hands relative to their feet, a pattern consistent with observations in non-human primates. In accordance with the principles of Darwinian medicine, Özçelik et al. (32) also highlight morphological features such as the supraorbital torus. Furthermore, the genetic traits and functional characteristics associated with UTS have been proposed as indicators of reverse evolution, a concept that is further elaborated upon in the upcoming section (32).

Genetic Factors in UTS

Variations of presentations due to various genetic mutations prove this syndrome rather unique (Table 1) (30). The genetic examinations of the 33 primary cases included in Üner Tan's original study indicate the heterogeneous genetic background of the syndrome (32). In the İskenderun family, the genetic mutation involved the WD repeat domain 81 (WDR81). In the Çanakkale and Antep families, the affected region on the chromosome included the very low-density lipoprotein receptor (32). Carbonic anhydrase 8 (CA8) was affected in the Iraqi family. In addition to these cases, a case with inositol 1,4,5-triphosphate receptor type 1 (ITPR1) mutation from Brazil with UTS has been reported (22).

WD repeat domain 81, VLDR, and CA8 are genes that have previously been associated with quadrupedal gait alongside ITPR1, tubulin beta 2B class IIb (TUBB2B), and ATP phospholipid transporting 8A2 (ATP8A2) (22). These individual genes are linked to the production of proteins crucial for the structural and functional organization of the brain, including the cerebellum, which governs locomotor coordination and trunk balance. It has been suggested that these mutations likely played a role in the development of quadrupedal locomotion in humans (32). Although this suggests a possible genetic background for UTS, many recorded cases lack a specific genetic diagnosis (22).

Table 1. Genetic mutations that are observed to cause UTS

Genes	Affected functions
ITPR1	Mutations might disrupt calcium homeostasis, leading to impaired function and degeneration of Purkinje cells (23).
TUBB2B	Mutations in the *TUBB2B* gene, which is involved with β-tubulin production, might cause disruptions in microtubule stability, causing impairments in neuronal migration and axonal development (30).
VLDLR	Mutations in the *VLDLR* gene might disrupt the Reelin signaling pathway, resulting in abnormal neuronal migration and cerebellar hypoplasia (34).
PIGG	Disruptions in glycosylphosphatidylinositol (GPI), which is encoded by the *PIGG* gene, might cause deficiencies in GPI-anchored proteins, preventing other proteins' binding ability to the cell. This might impair neurons and their function (35).
CA8	Mutations in CA8 might disrupt ion homeostasis and intracellular signaling, leading to cerebellar ataxia and cerebellar atrophy (23).
WDR81	Mutations might impair endosomal and lysosomal functions, leading to neurodegenerative changes and cerebellar atrophy (23).
ATP8A2	ATP8A2 protein ensures the asymmetry of phospholipids in the plasma membrane. Missense mutations disrupt protein's function, leading to defects in cell membrane structure and signalling (23).

ITPR1: Inositol 1,4,5-triphosphate receptor type 1, TUBB2B: Tubulin beta 2B class IIb, VLDLR: Very low-density lipoprotein receptor, PIGG: Phosphatidylinositol glycan anchor biosyhthesis, class G, CA8: Carbonic anhydrase 8, WDR81: WD repeat domain 81, ATP8A2: Adenosine triphosphatase phospholipid transporting 8A2, UTS: Üner Tan syndrome

Additionally, it has been suggested by Özçelik et al. (32) that maternal diabetes, type-1 diabetes in the case of the Iskenderun family, may add to the genetic defect via furthering prenatal neural damage.

CONCLUSION

Diagnosing UTS is challenging due to its rarity and consequent lack of awareness, limited research, overlapping symptoms with other neurological and genetic disorders, variability in symptom severity and comorbid conditions, absence of standardized diagnostic criteria, reliance on subjective assessments, complex and not well-understood genetic basis, need for a multidisciplinary approach, and the necessity for comprehensive evaluations including detailed clinical history, neuroimaging, and advanced genetic testing. Especially in countries where consanguineous marriages are common, doctors should be educated on UTS, through family history and the ability to obtain one is crucial when diagnosing hereditary rare disorders.

The consequences of consanguineous marriages extend beyond UTS, leading to a higher prevalence of various genetic disorders, congenital malformations, and developmental delays. Addressing these issues requires public health interventions, including genetic counseling and education to inform at-risk populations about the potential risks associated with consanguineous marriages. Additionally, promoting genetic screening and providing resources for family planning can help mitigate the incidence of inherited disorders in populations where consanguineous marriages are culturally prevalent.

Moreover, when discussing reverse evolution, it is important to recognize the genetic mechanisms that aid the process of reversal, such as pleiotropy and random mutations, as well as the inhibitory effects of epistasis in multicellular organisms. Experimental evidence of reverse evolution, including studies on Plasmodium vivax and ancestral forms of bacteria, provides valuable insights into the dynamic and context-dependent nature of reverse evolution in microbial populations. These insights contribute to the ongoing discourse in the scientific community and underscore the need for further research on the genetic mechanisms underlying evolutionary reversions.

Ethics

Informed Consent: *Not required.*

Footnotes

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