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In-Depth Look into Genetic Influences on Postural Orthostatic Tachycardia Syndrome and Ehlers-Danlos Syndrome: A Comprehensive Review

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Postural Orthostatic Tachycardia Syndrome (POTS) is a prevalent but underrecognized cardiovascular autonomic disorder characterized by an excessive heart rate increase upon standing and symptoms of orthostatic intolerance. Predominantly affecting women aged 15–45, POTS can be debilitating and economically burdensome, particularly impacting young adults in their prime educational and professional years. The etiology of POTS remains elusive, with both genetic and non-genetic factors, such as trauma, infections, and pregnancy, potentially contributing. Genetic mutations have been implicated,particularly in the norepinephrine transporter (NET) gene. NET plays a critical role in norepinephrine reuptake, and its dysfunction can lead to heightened sympathetic nervous system activity, contributing to POTS symptoms. Specific polymorphisms, like rs7194256 in the NET gene, have been linked to impaired norepinephrine clearance and increased sympathetic activity. Epigenetic modifications and regulatory mechanisms involving transcription factors and microRNAs also influence NET gene expression. Additionally, conditions like Ehlers-Danlos Syndrome (EDS) often coexist with POTS, suggesting a complex interplay between connective tissue disorders and autonomic dysfunction. While the genetic basis of POTS, including the role of NET gene variations, is not fully understood, preliminary evidence suggests these variations may affect norepinephrine modulation and autonomic function. Further research with larger, more diverse cohorts and advanced genetic analyses is needed to elucidate the mechanisms by which NET gene variations contribute to POTS. Understanding these mechanisms could improve diagnostic and therapeutic strategies, ultimately enhancing patient outcomes.

Keywords: Norepinephrine transporter (NET) gene, Ala457Pro mutation, genetic polymorphisms, SLC6A2 gene, genetic connective tissue disorders**.**

Postural orthostatic tachycardia syndrome (POTS) represents a frequently encountered yet less recognized form of cardiovascular autonomic dysfunction. An unusually high heart rate characterizes Postural Orthostatic Tachycardia Syndrome (POTS) upon standing, along with symptoms of intolerance to an upright position and occasional fainting episodes. POTS primarily

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impacts individuals aged 15 to 45, with a marked preference for females, who comprise 80% of cases in this age group. [1] The precise incidence rate of postural orthostatic tachycardia syndrome (POTS) remains uncertain, and its specific etiology is also unknown. POTS is a frequent disorder. POTS may be extremely crippling and financially disastrous because it primarily affects teenage or young adult women who would normally be in the middle of their studies or early professions. Postural Orthostatic Tachycardia Syndrome (POTS) was first recognized in 1982 and further defined in 1993.[2] POTS may have become more common during the past 20 years owing to more knowledge of the illness, while the present epidemiology is unknown. By definition, postural orthostatic tachycardia syndrome (POTS) is a clinical condition of orthostatic intolerance marked by an increase in heart rate (HR) of 30 beats/min or higher, often resulting in standing HRs surpassing 120 beats/min within 10 minutes of standing or head-up tilt (HUT). This occurs without orthostatic hypotension, which involves a drop in blood pressure (BP) of 10 mm Hg or more in the diastolic range. The current diagnostic rule for adults requires a heart rate increase of at least thirty beats per minute when standing or tilting the head up (HUT) for the first ten minutes without experiencing orthostatic hypotension. POTS may be predisposed to both genetic and non-genetic causes, including trauma, infection with germs or viruses, and pregnancy. A genetic mutation in NET has been linked to a family occurrence of postural orthostatic tachycardia syndrome (POTS). The NET protein, also known as the norepinephrine transporter, is involved in the reuptake of norepinephrine from the synaptic cleft, playing a crucial role in neurotransmission. [3-6] The hallmark of postural orthostatic shock (POTS) is an elevation in resting heart rate without concomitant hypotension. [7] Between 500,000 and 1,000,000 people are thought to suffer from POTS in the US; the illness is present in 0.2% of the total population. Although people of either gender can develop postural orthostatic tachycardia syndrome at any age, the majority of patients are diagnosed between the ages of 15 and 25. However, 75% to 80% of cases are in women.[8] The origins of POTS vary among individuals, and researchers have not yet fully understood the causes of this disorder. There is ongoing debate regarding the classification of POTS; however, most experts acknowledge distinct characteristics of POTS, which manifest more prominently in certain patients than in others. It's important to understand that these characteristics can overlap, as individuals with POTS may have multiple simultaneously: Neuropathic POTS is linked to damage to small fiber nerves (small-fiber neuropathy), regulating blood vessel constriction in the limbs and abdomen. Hyperadrenergic POTS involves heightened levels of the stress hormone norepinephrine. Hypovolemic POTS is associated with low blood volume (hypovolemia). Secondary POTS indicates POTS associated with another condition that could potentially cause autonomic neuropathy, such as diabetes, Lyme disease, or autoimmune disorders like lupus or Sjögren's syndrome. [9] Certain research indicates a potential genetic influence on autonomic function in individuals with OD (orthostatic dysfunction). This effect might entail the heterotrimeric guanine nucleotide-binding protein (G-protein), which comprises three subunits (alpha, beta, and gamma) and interacts with seven transmembrane receptors, like adrenoceptors, in intracellular signaling cascades. These cascades are pertinent to a range of physiological functions, including those related to the cardiovascular system. The identification and comparison of circulatory responses to rapid standing involved examining gene polymorphisms in components of the autonomic nervous system, specifically G protein â subunit (GNAS1) T131C and G protein â subunit (GNB3) C825T.[10] Genomic DNA analysis revealed several gene polymorphisms, including those associated with angiotensin-converting enzyme, angiotensinogen, angiotensin II receptor type 1, and the serotonin transporter. While the genetic basis of orthostatic hypotension remains incompletely explored, small population-based studies suggest that G protein-related gene polymorphisms (such as GNAS1 and GNB3) impact cardiovascular tone and reactivity.[11,12] A recent release of data from a worldwide study of POTS patients indicates that the illness may be exceedingly burdensome and that patients with undiagnosed POTS are frequently referred to psychiatric treatment (77% before diagnosis).[13] Polymorphisms in the gene encoding this protein can lead to variations in its structure and function, potentially impacting neurotransmitter

uptake and affecting various physiological processes. The A457P mutation denotes a particular single nucleotide polymorphism (SNP) causing an alteration of the amino acid from alanine (A) to proline (P) at position 457 within the NET protein sequence.[14]

Genetic variants and polymorphisms in the NET gene

Changes in the norepinephrine transporter (NET) can lead to a decreased ability to remove norepinephrine, resulting in heightened activity of the sympathetic nervous system. Both uncommon mutations and more prevalent variations in the genes responsible for the norepinephrine transporter (NET) have been associated with POTS (Postural Orthostatic Tachycardia Syndrome). [15] The role of norepinephrine (NE) involves its uptake into presynaptic noradrenergic neurons, facilitated by the plasma-membrane norepinephrine transporter (NET) encoded by the SLC6A2 gene, commonly known as NET. The effectiveness of norepinephrine reuptake relies on the ability of the NET to efficiently retrieve norepinephrine released by sympathetic nerves, estimated to be approximately 90% for the heart.[16] The rise in NET expression noted in stimulated cells is strongly linked to the dissociation of the SMARCA2-methyl-CpG-binding protein 2 (MeCP2) corepressor complex.[17] When investigating the regulatory mechanisms, thorough analysis of CpG methylation through bisulfite sequencing confirms that methylation patterns in the NET gene are within normal ranges. Increased activation of the NET gene is associated with elevated acetylation of histone H3 lysines 9 and 14 (H3K9/14ac) and is correlated with histone H3 lysine 9 methylation (H3K9me3). Moreover, the separation of the MeCP2 corepressor complex demonstrates an inverse correlation with heightened histone acetylation. Further research in humans has suggested that epigenetic alterations impact the expression of the NET gene in individuals diagnosed with POTS. [18]

NET gene expression and regulation

The regulation of the NET gene involves multiple factors, including transcription factors such as AP-2, Sp1, CREB, and Nurr1. Epigenetic modifications like DNA methylation and histone acetylation can impact NET gene expression by modifying the accessibility of the promoter region. Alternative splicing can generate different isoforms of the NET protein with varying functions and localizations. Post-translational modifications, such as phosphorylation, ubiquitination, and glycosylation, play roles in modulating the activity, stability, and trafficking of the NET protein. MicroRNAs, small non-coding RNAs, can bind to the 3' untranslated region of NET mRNA, inhibiting its translation or promoting its degradation, thus influencing NET gene expression.[19]

Norepinephrine Transport and Autonomic Dysfunction about POTS

Norepinephrine transport is the process of removing norepinephrine from the space between nerve cells, where it acts as a chemical messenger, by a protein called the norepinephrine transporter (NET). Both the central and peripheral nerve systems express NET, and several variables, including genetic abnormalities, can affect how it functions, epigenetic modifications, and environmental stressors. One of the possible causes of POTS is a deficiency or dysfunction of NET, which leads to impaired clearance of norepinephrine from the nerve synapses. The sympathetic branch of the autonomic nervous system, which controls the fight-or-flight response, is overactive or overly activated as a result. This may result in aberrant reactions to stress, including variations in heart rate, blood pressure, and metabolism. For example, a deficiency of NET can cause orthostatic intolerance and tachycardia, which are symptoms of POTS.[20,21] An imbalance between the sympathetic and parasympathetic branches of the autonomic nervous system, which typically cooperate to maintain homeostasis, is another potential explanation of post-trial hypotension. The parasympathetic branch is responsible for the rest-and-digest response, and it uses acetylcholine as its main neurotransmitter. When the autonomic nervous system malfunctions, there may be too much release of norepinephrine and epinephrine from the sympathetic branch and/or too little release of acetylcholine from the parasympathetic branch, causing the symptoms of POTS.[22] NET gene variations may contribute to the pathophysiology of POTS by impairing NE reuptake and enhancing NE-mediated effects on the cardiovascular system. The 3' untranslated region (UTR) of the NET gene, for instance, has a polymorphism called rs7194256 that is more common in POTS patients than in healthy controls. By creating a binding

site, this polymorphism inhibits the expression and function of NET by binding to a microRNA (miR-19a-3p). Individuals with POTS may be more susceptible to cardiovascular illness due to a potential potentiation of the sympathetic neurochemical signal caused by a deficiency in NET activity.[23] Although there is a decrease in sympathetic outflow and a corresponding decrease in effective baroreflex sensitivity, the absence of NE clearance by NET leads to increased plasma NE levels, contributing to an elevated heart rate. [24]

SLC6A2 Polymorphisms in POTS

Modifications in synaptic NE levels and â-AR activation may result from genetic or acquired abnormalities in the NET, which might impact NE homeostasis. The SLC6A2 gene[25,26], which is found on human chromosome 16q12.2.[27], encodes the NET, a member of the SLC6A2 family. The 16 exons that encode this gene cover a distance of 45 kilobases between the start and stop codons. [28] Five SNPs in the SLC6A2 gene have been found to cause substitutions in amino acids. Just a small percentage of these variants have had their functional changes investigated; the majority were generated from certain psychiatric and cardiovascular characteristics.[29-30] Even though there are many contributing factors to hypertension, functional SLC6A2 SNPs may have an impact on blood pressure.[31,32] Out of all the SNPs found in SLC6A2, only rs168924 was found to be associated with the incidence of essential hypertension.[33] The discovery of a connection between hypertension and SLC6A2 gene mutations in POTS, which leads to a reduction in NE uptake activity, raises the possibility that a dysfunctional NET could be the source of compromised cardiac 123I-mIBG uptake. It's noteworthy to observe that NE spillover varies throughout organs. Myocardial NE re-uptake is generally quite efficient, and only 2% to 3% of the systemic NE spillover (i.e., plasma) can be traced back to the origin of the heart. [34]

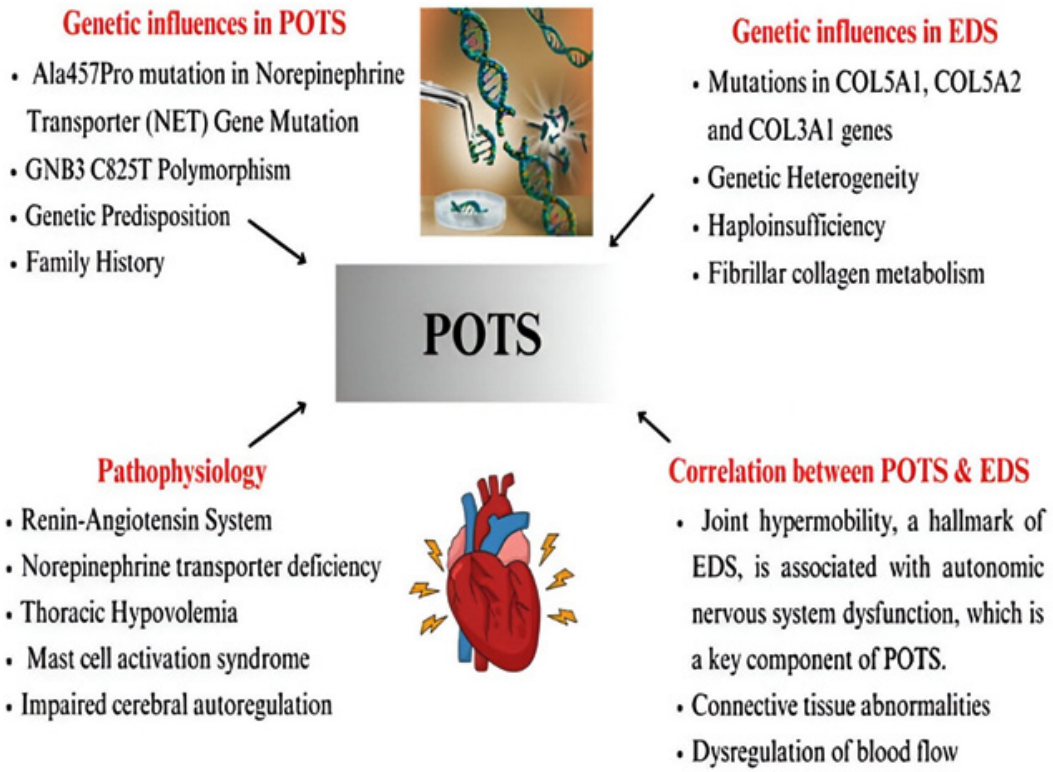

Fig. 1. Overview of Genetic Influence on POTS AND EDS

Mechanisms of Postural Tachycardia Syndrome Associated with Norepinephrine Transporter Deficiency

A presynaptic transporter in sympathetic neurons, synaptic norepinephrine release is dependent on the norepinephrine transporter (NET). A family with hyperadrenergic POTS has been shown to have a particular genetic defect.[35] The transporter becomes dysfunctional due to the Ala457Pro mutation, which is linked to changes in

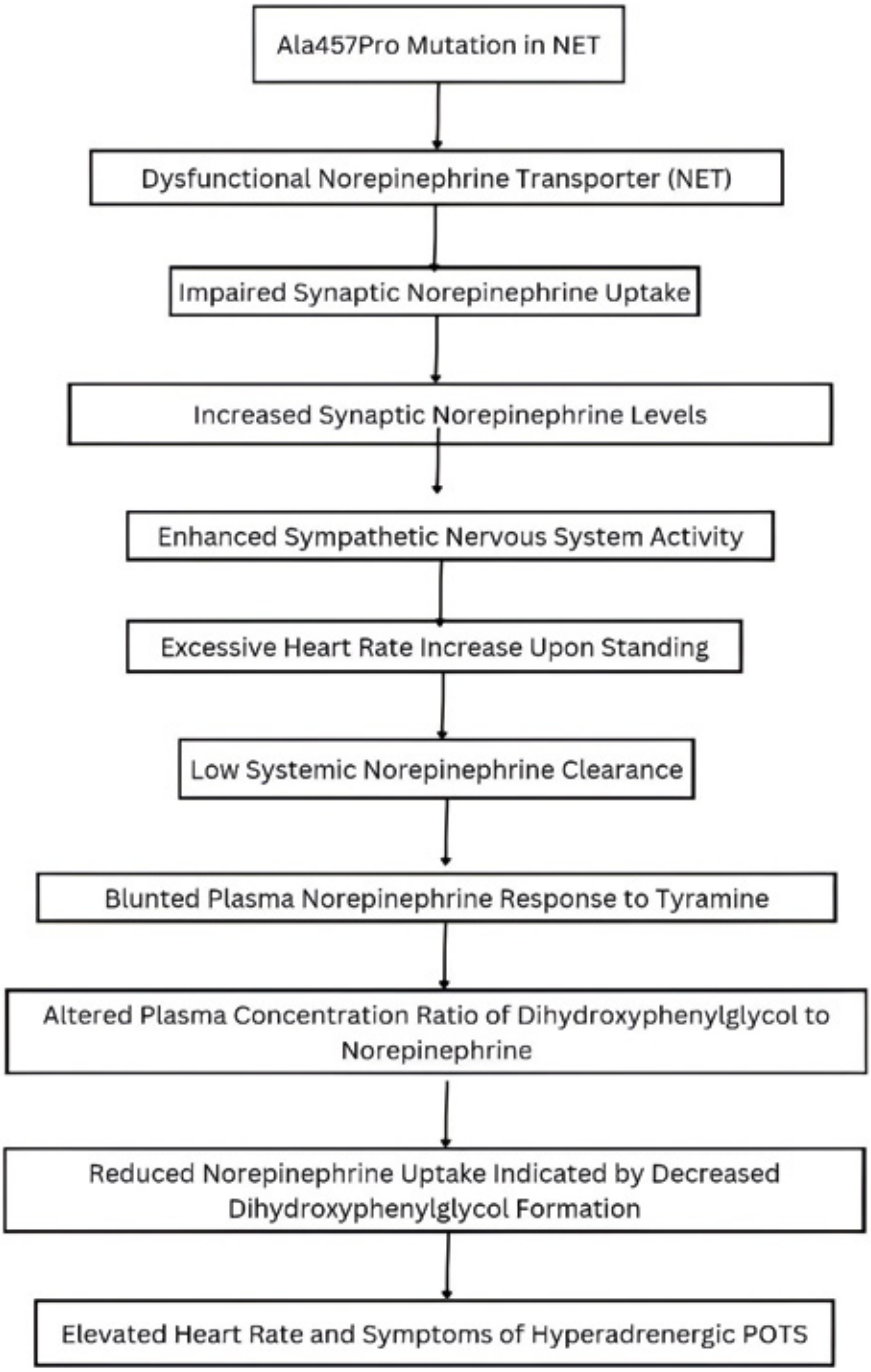

Fig. 2. Pathophysiology of Postural Tachycardia Syndrome due to NET Deficiency

norepinephrine metabolism and heart rate control. Due to her norepinephrine uptake deficiency, the patient's heart rate elevated dramatically when she got up from a supine position. It increased by about 10 beats per minute over the mean value for patients that were age-matched and normally constituted.[36] Norepinephrine uptake may have been compromised given the proband's low systemic norepinephrine clearance and the blunting of the rise in plasma norepinephrine following tyramine treatment. Further evidence of decreased norepinephrine absorption is provided by the aberrant relationship between dihydroxyphenylglycol and norepinephrine plasma concentrations. Monoamine oxidase converts most of the norepinephrine that the norepinephrine transporter takes up into neurons into dihydroxyphenylglycol in the vesicles, where it is stored for later release.[37] Once in the bloodstream, dihydroxyphenylglycol can be used as a marker for monoamine oxidase activity and norepinephrine uptake. [38]

Ehlers-Danlos Syndrome-Related POTS

A set of genetic connective tissue disorders known as Ehlers-Danlos Syndrome (EDS) can present in a variety of ways, but they are all caused by sequence changes in the genes that code for fibrillar proteins and/or collagen processing enzymes, which decrease the structural integrity of connective tissue. Joint hypermobility is a defining feature of EDS type III and has been commonly associated with post-traumatic stress disorder (POTS). It is connected to sequence changes in tenascin X.[39,40] Two-thirds of individuals with hEDS are estimated to have orthostatic intolerance, and 41–49% of these individuals also have POTS. It is known that hypermobile EDS (hEDS) is inherited autosomally dominantly. Although certain cases and research have suggested potential genes associated with hEDS, conclusive evidence is lacking. For example, mutations in the gene responsible for encoding tenascin X (TNXB), an extracellular matrix protein, have been proposed as a potential contributor to hEDS genetics. However, in a limited number of instances, there seemed to be inadequate levels of tenascin X (TNXB), exhibiting partial penetrance in females and negligible impact in males. [41,42] Pharmacological treatments have been employed to manage pain in individuals with hEDS, following similar guidelines to those used for the general population. Available treatments comprise non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, topical analgesics, muscle relaxants, and opioids. [43] The initial non-pharmacological approach for managing POTS patients involves discontinuing any medications that might worsen their symptoms. These medications may encompass alpha- and beta-blockers, angiotensin-converting enzyme inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, diuretics, and sympathomimetics. [44] A presynaptic norepinephrine reuptake transporter (NET) deficit is the underlying genetic mechanism, which results in decreased norepinephrine clearance and extended sympathetic nervous system activation. Few POTS individuals and their families who had NET mutations provide evidence in favor of this theory [45, 46], or atypical expression of NET. [47–49] It's interesting to note that drugs that affect NET transporters and are used to treat fibromyalgia, depression, and attention deficit disorder can cause orthostatic tachycardia in people who don't have POTS or exacerbate it in people who do.[50,51] It's important to stress that POTS is regarded as a chronic ailment that, notably, does not correlate with greater death rates, even though there is now no known solution for it. The genetic basis of EDS, although incompletely understood, provides valuable insights into potential therapeutic targets and diagnostic markers. Moreover, the clinical overlap between EDS and POTS necessitates a multidisciplinary approach to patient care. Research efforts should focus on elucidating the specific genetic mutations and molecular pathways linking EDS to POTS. Large-scale genome-wide association studies (GWAS) and functional genomic analyses are needed to identify novel genetic variants associated with POTS susceptibility in individuals with EDS.

CONCLUSIONS

The research regarding NET gene variants and their potential association with Postural Orthostatic Tachycardia Syndrome (POTS) is intriguing, yet it remains unclear. These differences may influence norepinephrine regulation, which impacts autonomic function and may predispose individuals to POTS, according to preliminary research. More comprehensive and rigorous

research is required because the current data is still preliminary and confusing. To accurately identify the role of NET gene variants in POTS vulnerability, larger, more diverse cohorts, and sophisticated genetic investigations are required. Additionally, to verify and comprehend the mechanisms through which these differences could influence POTS development, functional assessments are required. A deeper understanding of the contribution of NET gene variants to POTS may change the way some therapies and diagnostic techniques are carried out. Future studies should concentrate on bigger, more varied populations and use cutting-edge genetic analyses to understand further how NET gene variants affect POTS susceptibility. Functional assessments are necessary to verify and clarify how these genetic differences may contribute to the illness. Growing knowledge of how NET gene variants affect POTS may transform the way we manage this crippling illness by opening new avenues for focused therapy approaches and diagnostic techniques. Progress in genetic research has the potential to revolutionize patient care and results, even though POTS is still a chronic illness with substantial morbidity.

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Informed Consent Statement

This study did not involve human participants, and therefore, informed consent was not required

Clinical Trial Registration

This research does not involve any clinical trials**.**

Author Contributions

Revanth Ramachandran: Conceptualization, Supervision, Methodology, Writing; Mouliprabakaran Sundarrajan: Data collection, Analysis And curation; Venkatesaprasath Ravichandran: Editing**,** Visualization, and Proof reading the manuscript; Each author mentioned has significantly and directly contributed intellectually to the project and has given their approval for its publication.

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