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Review Article

The WNT/β-catenin Pathway and Matrix Metalloproteinase-9 in hypermobile Ehlers-Danlos Syndrome and Autism Spectrum Disorder: A Possible Connection

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Abstract

Hypermobile Ehlers-Danlos Syndrome (hEDS), a connective tissue disorder also known as Ehlers-Danlos Syndrome Type III or Ehlers-Danlos Syndrome Hypermobility Type, and Autism Spectrum Disorder (ASD), a neurodevelopmental disorder, present notable symptom overlap and higher than expected level of comorbidity. A recent systematic review and meta-analysis found that the overall prevalence of joint hypermobility in autistic individuals was 22.3%, rising to 31% when clinically assessed. The overall prevalence of Ehlers-Danlos Syndrome or Hypermobility Spectrum Disorder was 27.9%, rising to 39% when clinically assessed rather than self-reported. This comorbidity is likely underrepresented due to factors including gender-related underdiagnosis, limited awareness, and fragmented care. Despite this, research at the disorders' intersection remains limited. In this narrative review, we aim to (i) examine hEDS and ASD from a clinical and molecular perspective; (ii) review literature regarding the WNT/β-catenin pathway and matrix metalloproteinases' involvement in fibroblast phenotypes, extracellular matrix regulation, and synaptogenesis; and (iii) evaluate how pathway dysregulation may connect each disorder's tissue and neurodevelopmental traits. Although both disorders remain pathophysiologically elusive, we hope to shed light on their co-occurrence and promote future research by exploring how these disorders are possibly linked, specifically via WNT/β-catenin and matrix metalloproteinase activity.

Keywords: Autism Spectrum Disorder, Ehlers-Danlos Syndrome Hypermobility Type, Matrix metalloproteinases, microRNAs, Wnt Signalling Pathway

Introduction

In 2017, the International hypermobile Ehlers-Danlos Syndrome diagnostic criteria were published. Since then, an increase in research and public awareness has followed as researchers and clinicians have been able to more easily define this complex syndrome[1]. Interestingly, hypermobile Ehlers-Danlos Syndrome (hEDS), also known as Ehlers-Danlos Syndrome Type III or Ehlers-Danlos Syndrome Hypermobility Type, has a high co-occurrence with neurodevelopmental disorders. Despite the growing research on hEDS itself, this connection and its potential molecular basis have remained relatively unexplored. In a recent systematic review and meta-analysis, Baeza-Velasco et al. (2025) reported that the overall prevalence of joint hypermobility in Autistic individuals is 22.3%. This prevalence of joint hypermobility rose to 31% when only studies that clinically assessed joint hypermobility were used[2]. They also found that the overall prevalence of Ehlers-Danlos Syndrome (EDS) or Hypermobility Spectrum Disorder (HSD), a hypermobility disorder debated to be closely related to hEDS[3,4], is estimated to be 27.9% when Autistic individuals self-report. The prevalence of EDS or HSD rose to 39% when individuals were clinically assessed[2]. Furthermore, Casanova et al. (2019) reported

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in a survey-based study that 20% of mothers with hEDS or HSD give birth to Autistic children[5]. They report that this statistic is comparable to the 19% of Autistic mothers who reported giving birth to Autistic children. Collectively, these findings raise the possibility of shared genetic or biological factors. In a 2020 review, Casanova et al. even described Ehlers Danlos Syndrome/Hypermobility Spectrum Disorders as a possible subtype of Autism[6].

Although hEDS is a connective tissue disorder and Autism Spectrum Disorder (ASD) is a neurodevelopmental condition, they both involve early-life developmental processes[7,8]. They also present a number of shared symptoms, yet the symptoms and disorders themselves are often diagnosed and treated by different specialists[9]. Often also underdiagnosed individually[10–12] the underrepresentation of their co-diagnosis may be further perpetuated by the fact that up to 90% of hEDS cases are in female patients[13,14], a population in which ASD symptoms are commonly missed[15]. Possibly influenced by cultural norms, Autistic women's conscious and unconscious ability to "socially camouflage" or "mask"[16], and their historical underrepresentation in ASD research[15], has affected the public's understanding of what ASD "looks like" in the female population and has led to ASD often being missed in women.

The complex and spectrum-like nature of both disorders, the relatively recent discovery of their comorbidity, and the individual and simultaneous underdiagnosis have meant that research concerning their common, underlying mechanisms remains virtually non-existent. Therefore, in this review, we aim to explore how hEDS and ASD may be connected by examining the WNT/β-catenin pathway and matrix metalloproteinases as a possible common thread. We hope to bring attention to the high co-occurrence of these disorders and encourage further research into potential shared mechanisms.

Methods

In our initial search regarding the background of hEDS, we discovered a review article by Chiarelli et al. (2019)[17]. In this review article, they reference one of their own research studies completed in 2016. In reference to this study, they discussed their belief that the WNT/*β*-catenin pathway may be implicated in hEDS. Based on the abundant evidence that the WNT/*β*-catenin pathway is also essential to neurodevelopment, we chose to focus our search on this pathway in both disorders[18].

In order to identify relevant literature that may help elucidate how these disorders may be connected, a multi-step search strategy was completed using PubMed as the database. First, key words related to hEDS and ASD were identified, including by using MeSH.

For key words related to hEDS, we chose to include terminology commonly used before the 2017 international criteria were published. This includes terms and their affiliated acronyms such as "Joint Hypermobility Syndrome;" "Benign Joint Hypermobility Syndrome;" and "Benign Hypermobility Syndrome." We chose to include these pre-2017 hEDS related terms as the literature landscape surrounding hEDS post-2017, although rising, is still limited. Further, before 2017, some researchers used this terminology in reference to hEDS or even in combination with post-2017 terminology (see Chiarelli et al. (2016)). Including the pre-2017 definitions also account for the transitional period after the 2017 international classification was published where some literature continued using these older terms.

We also chose to include "Hypermobility Spectrum Disorder" and its acronym, "HSD." Currently, a debate exists on whether HSD is simply a more mild form of hEDS rather than a distinct diagnosis with differing etiology. This begs the question of whether literature and research regarding HSD and hEDS should be combined or separated. Upon initial search, we discovered that key pathophysiological research on hEDS often also includes HSD (see Zoppi et al. (2018) and Ritelli et al. (2024)). In 2022, Ritelli et al. found common cellular traits between hEDS and HSD fibroblasts[19]. These common cellular traits may support the idea that hEDS and HSD should be categorized as one, "spectrum-like" disorder rather than entirely separate. This led us to include HSD in our search strategy.

Separately, throughout this article, we will use terminology from the original source we are citing as a guide for what terminology is appropriate in that moment (i.e. "JHS and hEDS fibroblasts" (Chiarelli et al. (2016)) vs. "hEDS and HSD fibroblasts" (Chiarelli et al. (2019)). For example, we will distinguish hEDS specific findings from mixed hEDS/HSD findings from historical JHS cohorts.

Key words were then assembled into three search strategies (Supplementary Table 1). Search strategy I was employed with no limits or filters. Inclusion and exclusion criteria were manually applied during screening. Articles relevant to both hEDS/HSD/JHS/BJHS and ASD were included. Authors AD and DS then hand-searched relevant literature found via strategy I, and during background research, for articles specifically relevant to the pathophysiology of hEDS/HSD/JHS/BJHS and ASD. Relevant articles were included if they were peer-reviewed and priority was given to original research published during or after 2017. Articles that were not peer-reviewed and not relevant to hEDS/HSD/JHS/BJHS and ASD were excluded.

Based on background research and studies found in search strategy I, search strategy II (regarding hEDS/HSD/JHS/BJHS) and III (regarding ASD) were then created, using key words related to the WNT/β-catenin pathway and MMP-9. Relevant, peer-reviewed articles were included. For strategy II, priority was again provided for those published during or after 2017. No limits or filters were applied to strategy II or III. The date of the last search (strategy III) was November 15, 2025. AD and DS also

hand-searched relevant literature found in strategies two and three for other relevant literature.

Hypermobile Ehlers-Danlos Syndrome Overview

Epidemiology and Genetics

Prevalence

There are thirteen subtypes of Ehlers-Danlos Syndrome (EDS). Hypermobile Ehlers-Danlos Syndrome (hEDS) is considered the most common subtype, representing 80-90% of all EDS cases[20]. Despite this, there is limited epidemiological data on hEDS before or after 2017[21]. In 2002, the minimum prevalence of EDS (all subtypes) was estimated at 1 in 5,000[22]. Given this information, Tinkle et al. suggested that the prevalence of hEDS was presumed not to be lower than 1 in 5,000 at that time[23]. Since then, data has been extrapolated and information used as a proxy to predict hEDS prevalence. For example, in 2013, Mulvey et al. completed a large epidemiological study that suggested 3.4% of a population of 12,853 had joint hypermobility with widespread pain[24]. More recently, a national cohort study in Wales, United Kingdom, found that EDS and JHS had a combined diagnosed prevalence of 1 in 500[14]. These researchers used this data as a proxy to represent the prevalence of hEDS or HSD within the 2017 classification, noting that these disorders may not be as "rare" as once believed[14]. Although there is no definitive epidemiological data on hEDS or HSD, it is unclear if an epidemiological study would clarify its exact prevalence due to many patients going undiagnosed due to the "spectrum-like" nature of the disorder, lack of healthcare provider awareness, and no available genetic test[25].

Association

hEDS is most highly associated with a patient's gender. Women reportedly represent up to 90% of all hEDS cases[13,14]. Other studies suggest that joint hypermobility is also more commonly found amongst Africans rather than Caucasians[26]. hEDS is also associated with a high level of multi-morbidity with over 98% of patients reporting at least 4 comorbid conditions[27]. For more information about associated conditions and symptoms, please see section "Symptomatology" below.

Familial Clustering

Of the EDS subtypes, hEDS is the only one to not have an identifiable, pathogenic gene or molecular marker[1,28]. This means that diagnoses are purely clinical, as no molecular genetic tests are currently available to identify hEDS in a patient. Despite this, some data suggest that hEDS is inherited in an autosomal dominant manner whereas others report a more complex inheritance pattern including compound heterozygosity, separate gene variants that perturb the same pathway, and "additive high-damage variant loads"[25,28]. According to Petrucci et al., up to 76% of hEDS patients report a family history of hEDS[27]. Despite this statistic, the disorder presents with variable expression and penetrance, meaning family members may have varying symptom severity[27]. For example, families with hEDS-like phenotypes may present with different variants of the same gene, such as TNXB[29,30]. To help elucidate the genetic complexities of hEDS, the Ehlers Danlos Society began the Hypermobile Ehlers-Danlos Genetic Evaluation (HEDGE) study in 2018. Using large-scale whole-genome sequencing, their goal is to uncover the genetic basis of hEDS.

Mechanistic Inference

The HEDGE study shows great promise in better understanding hEDS genetic basis and therefore possibly inferring its pathophysiological mechanism. However, it may not be able to identify the more subtle contributors such as epigenetics or post-transcriptional alterations. Thus far, hEDS has not been clearly linked to a single collagen gene defect unlike several other EDS subtypes[31]. Due to the lack of genetic epidemiology research completed on hEDS, it is difficult to make an inference about what its etiology may be. Most recently, Shirvani et al. analyzed genetic variants from 86 hEDS patients. They found significant enrichment of variants associated with collagen synthesis, the adaptive immune axis, and mitochondrial respiratory chain[25]. However, this is the first study of its kind. The authors also admit that these associations require validation and functional studies before mechanistic or clinical conclusions can be made.

Symptomatology

Hypermobile Ehlers-Danlos Syndrome primarily manifests as generalized joint hypermobility and recurrent subluxations, dislocations, and soft tissue injuries from minimal trauma[23,32]. Distinct from the listed, acute injuries, widespread musculoskeletal, visceral, and/or neuropathic chronic pain is also common[33,34]. Patients may also have abnormal scarring, mildly hyperextensible skin that is easily bruised, has trouble healing, and can appear soft or "velvety"[32,35]. Additionally, hEDS is associated with frequent multisystem involvement, including gastrointestinal (functional bowel disorders), cardiovascular (autonomic dysfunction, mitral valve prolapse, aortic root dilation), urogynecologic (pelvic organ prolapse), inflammatory (mast cell activation disorders), and neurobehavioral disorders (anxiety disorders, ASD, Attention-Deficit/Hyperactivity Disorder)[28,36,37]. Fatigue, headaches, and sleep issues are also often experienced by hEDS patients[38–40].

Pathophysiology

Researchers have identified the genetic markers of the 12 other EDS subtypes. Identifying these genetic markers

has also helped clarify their individual pathophysiology. For example, in classical EDS, dominant negative mutations or haploinsufficiency of the COL5A1 and COL5A2 genes lead to defects and/or deficits in type V collagen[41–45]. These perturbations alter fibril assembly and therefore the structural integrity of connective tissue[17,44–46]. Unlike the other EDS subtypes, the unknown genetic basis of hEDS presents a challenge in understanding its own pathophysiology. This challenge is only further complicated by varying clinical severity. Some research has even found that individual EDS phenotypes may not be directly determined by how or what is disrupted in the extracellular matrix (ECM)[8,47].

Despite these challenges, research regarding hEDS's pathophysiology has shown a few promising leads. Zoppi et al. in 2018 reported that dermal fibroblasts from a mixed hEDS/HSD cohort exhibited ECM component disorganization, α-SMA organization, OB-cadherin/ cadherin-11 expression, enhanced migratory capacity, altered CCN2/CTGF expression, and increased levels of matrix metalloproteinase-9 (MMP-9) when compared to controls *in vitro*[48]. The authors interpreted these findings as indicative of a fibroblast-to-myofibroblast transition. They also proposed that this transition is sustained by the αvβ3 integrin-ILK-Snail1/Slug signaling axis in hEDS/HSD cells. The myofibroblast phenotype exhibited by these cells is a unique feature not shared with any other EDS subtype and indicates that they may exist in an inflammatory, repair-like state. Normally, fibroblasts help maintain skin and connective tissue structure. A constant inflammatory state, such as that of the hEDS/HSD fibroblast, may help explain part of the symptomatologic and pathophysiologic picture of hEDS/HSD. However, these findings do not necessarily fully account for the disorder's complexity.

In 2016, Chiarelli et al. completed a transcriptome-wide expression profile on Joint Hypermobility Syndrome (JHS), now generally accepted as HSD, and Ehlers-Danlos Syndrome Hypermobility Type (EDS-HT), now generally accepted as hEDS, fibroblasts. As a result, they identified 19 microRNAs that were differentially expressed by the JHS/EDS-HT fibroblasts[49]. After transcription, microRNAs (miRNAs) can repress or activate gene expression by interacting with messenger RNA, playing a subtle but vital role in phenotype production. Of the miRNAs differentially expressed in the study, most fibroblasts overexpressed miR-378-3p, an miRNA moderating epithelial-to-mesenchymal transition and inflammation associated with the NF-kB and TNFα pathways; miRNA-224, an miRNA activating the WNT/β-catenin pathway; and miRNA-23a, also activating the WNT/β-catenin pathway. In 2022, Ritelli et al. put forward a hypothesis based on Chiarelli's previous research and their own RNA-sequencing data. They suggested that a combination of disordered ECM, abnormal signaling, and increased inflammation may be fostering a cycle that alters connective tissue's structure and function, possibly leading to the multisystem presentation seen in HSD/hEDS patients[19].

However, this hypothesis or the exact mechanism by which hEDS develops has yet to be proven.

Autism Spectrum Disorder Overview

Epidemiology and Genetics

Prevalence

Globally, it is estimated that ~1 in 127 people meet the Autism Spectrum Disorder (ASD) criteria[50]. In the US, it is estimated that about 1 in 31 children at age eight and 1 in 45 adults ages 18-84 meet the criteria for ASD[51,52]. ASD is also nearly three to four times more prevalent in boys than in girls[51,53].

Association

The association between sex and ASD diagnosis, as stated earlier in this paper, may be due to women being underdiagnosed or misdiagnosed. Historically, women have been underrepresented in ASD research leading to limited awareness of the various ways ASD may present. For example, the "social camouflaging/masking" phenomenon can make it difficult to discern an individual's true presentation during ASD clinical evaluations. Increased risk of ASD is also associated with prenatal exposure to valproic acid, thalidomide, chemical pollutants, maternal infections, and intestinal pathogens[54–57]. Advanced parental age and a family history of mental and/or neurological disorders also increases one's odds of ASD[53,58]. ASD is also associated with high levels of comorbidity, with one study finding that 74% of an ASD patient cohort had at least one comorbidity[59]. For more information about associated conditions and symptoms, please see section "Symptomatology" below.

Familial Clustering

Researchers have found that there is a clear genetic component to ASD as well. Although it tends to cluster in families, its inheritance pattern remains unknown. In 2019, Bai et al. estimated that the heritability of ASD was approximately 80%[60]. Twin studies show heritability between 60-90% with concordance being especially high amongst monozygotic twins[58]. Almost 1200 risk genes have been identified[53]. However, risk genes that are believed to contribute to communication, cognition and behavioral deficits have been found to only account for 10-20% of ASD cases[61].

Mechanistic Inference

The diversity of risk genes and environmental contribution makes ASD present as a rather heterogenous condition. A similar genetic background between patients does not guarantee a similar clinical phenotype[54,62]. Despite this, the data generally has shifted consensus to converge on pathways affecting processes such as transcription, translation, epigenetics, synaptic function, and immune responses[63].

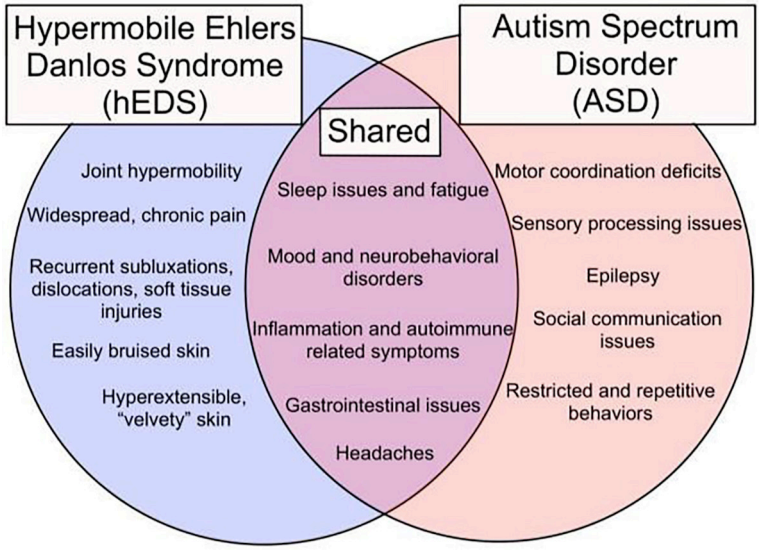

Figure 1. Hypermobile Ehlers-Danlos Syndrome (hEDS) and Autism Spectrum Disorder (ASD) present with significant symptom and co-morbidity overlap pointing towards a possible shared molecular pathway. Hypermobile Ehlers Danlos Syndrome (hEDS) and Autism Spectrum Disorder (ASD) present a number of overlapping symptoms and co-morbidities including sleep issues, fatigue, mood and neurobehavioral disorders, inflammation and autoimmune related symptoms, gastrointestinal issues, and headaches. Given the spectrum nature of both disorders and their high co-morbidity, it is also possible that patients with either given disorder present a symptom from the other, again pointing towards a possible shared molecular pathway.

Symptomatology

Similar to hEDS, ASD presents as a spectrum disorder in that the phenotypical and clinical manifestations can vary considerably from one patient to another. The DSM-5 characterizes the core diagnostic features as persistent social communication and interaction deficits and a number of restricted or repetitive behaviors, interests, or activities. As a neurodevelopmental disorder, the deficits may present very early in a child's life, such as by 1 or 2 years old; may only manifest when social demands exceed their capacity; or may be "socially camouflaged/masked" by learned strategies[7].

Patients with ASD are also at increased risk for comorbid disorders. In the study that found that 74% of their ASD cohort had at least one comorbidity, researchers assessed 42,000 individuals with ASD and over 11,000 of their non-ASD siblings. With these same cohorts, they also found that the ASD cohort averaged more comorbidities than their non-ASD siblings[59].

Common comorbidities amongst ASD individuals include immune hypersensitivities, sleep disorders, headaches, psychiatric and other neurological disorders, such as anxiety or attention-deficit hyperactivity disorder, and gastrointestinal problems (many of these symptoms and comorbid disorders overlap with hEDS's own symptoms/comorbidities)[64,65]. Mohammed Al-Betagi notes in his 2021 review of ASD's medical comorbidities, "comorbid conditions may be markers of [ASD's] underlying pathophysiology." Following this logic, it is therefore vital to investigate how disorders like hEDS may be related to ASD, so that better therapeutic approaches can be developed and delivered to patients (Figure 1).

Pathophysiology

Similar to hEDS, the heterogeneity of ASD has made understanding its pathophysiology challenging. The most widely discussed hypotheses are those that involve altered neuron connectivity and synaptogenesis. Some studies suggest that individuals with ASD present with increased neuronal density due to insufficient synaptic pruning of non-functional or unnecessary neurons during development[66]. An excess of poorly refined neural connections may disrupt more important connections essential for communication between brain regions. For example, disruptions may occur in the intrahemisphere and prefrontal cortical microcircuits which help us consolidate and integrate information from our environment[67,68]. This disruption may also be compounded by misplaced neurons due to altered neuronal migration[69]. It has also been reported that ASD patients' neurons show altered

dendritic morphology and spines[70].

As noted earlier, ASD patients often show some level of immune dysregulation, albeit to varying degrees[71]. This immune dysregulation may extend to neuroinflammatory processes involving neuroglia. The immune system and glia are essential to normal neurodevelopment as they contribute to synaptic remodeling and developmental apoptosis.

Importantly, key signaling pathways have been linked to the neurodevelopmental nature of the disorder. For example, a number of high risk ASD genes have been found to converge on WNT/β-catenin signalling[72]. Albeit, there is debate about how the WNT/β-catenin pathway is dysregulated within ASD and ASD models. Some researchers have found evidence for enrichment of the pathway while others have found evidence for its downregulation[72–74]. Despite this, there seems to be a general consensus that the WNT/β-catenin pathway is somehow implicated in ASD. Further, a Danish Cohort study found that amniotic fluid in ASD cases contained elevated levels of matrix metalloproteinase-9[75].

WNT/β-catenin Pathway and Matrix Metalloproteinases in hEDS and ASD

The high co-occurrence between hEDS and ASD, as well as the symptom overlap and spectrum-like nature of the two disorders, raises the question of what underlying pathophysiology may be driving their connection. Between hEDS and ASD, one possible connection is WNT/β-catenin signaling and matrix metalloproteinases (MMPs), specifically matrix metalloproteinase-9 (MMP-9), an extracellular matrix (ECM) modulator. Given that WNT signaling and ECM modulation influence both musculoskeletal and neurological development, it is reasonable to explore how the two may be implicated in both disorders.

WNT signaling is a highly conserved developmental network that integrates extracellular cues to act as one of the few pathways that regulates cell fate throughout an animal's lifespan[76]. During development, when WNT ligands bind to their receptor, their downstream signaling cascades direct embryonic patterning by coordinating stem cell and progenitor cell fate, tissue polarity, body axis creation, and tissue/organ development. During adulthood, the WNT pathway regulates tissue homeostasis, cell renewal, and regeneration[76,77].

WNT signaling progresses through two possible pathways: the canonical and non-canonical branches. The canonical pathway is also known as the WNT/β-catenin pathway. B-catenin is a protein that serves multiple functions within cells. For example, β-catenin is vital in cell-to-cell adhesion, where it acts as part of the adherens junction connecting cadherins to the actin cytoskeleton[78]. Another function of β-catenin is to act as a transcriptional regulator of target genes[78]. Through the canonical pathway, when WNT ligand signals are absent, a "destruction complex" is formed. The destruction complex consists of axin, adenomatosis polyposis coli, glycogen synthase kinase-3β, and casein kinase 1 (CK1). This complex then phosphorylates β-catenin, marking it for degradation. In the canonical branch of WNT signaling, when WNT ligands and their signals are present, WNT ligands engage the Frizzled (FZD) receptor and low-density lipoprotein receptor-related protein (LRP5/6) co-receptors to inhibit the β-catenin "destruction complex." This ultimately prevents the phosphorylation and degradation of β-catenin, instead stabilizing it[79]. β-catenin then accumulates, translocates to the nucleus, and binds to TCF proteins. Once bound, transcription of programs often linked to cell cycle progression and progenitor self renewal are promoted[77]. Although its downstream effects are context dependent, the canonical WNT signaling process occurs similarly for both non-neuronal cells and neuronal cells.

In contrast, the non-canonical arm signals independently of β-catenin and includes pathways such as the planar cell polarity module and the WNT/Calcium pathway. The planar cell polarity module governs cytoskeletal polarity through small GTPases and the JNK/ROCK pathway[80]. The WNT/Calcium pathway regulates migration and morphogenesis by activating Calcium/Calmodulin-dependent protein kinase II, protein kinase C, and calcineurin-NFAT[81,82]. Importantly, the branches within the non-canonical arm can inter-regulate each other as well as the canonical pathway, which tunes dose, duration, and cellular outcome related to the intended outcome of each pathway[77,82]. The tight regulation of each WNT pathway is essential to proper patterning and homeostasis, meaning that subtle changes within the pathways can have large downstream consequences.

It is well established that during the proliferative phase of wound healing, the WNT/β-catenin pathway is activated and β-catenin is upregulated. As a result, increased β-catenin levels drive myofibroblast differentiation[83–85]. β-catenin is therefore considered a central mediator of the profibrotic state, especially in dermal fibroblasts[86].

Chiarelli et al. (2016) found that JHS/EDS-HT fibroblasts differentially expressed 19 miRNAs. They also reported that these fibroblasts exhibited altered expression of canonical WNT pathway–related genes, including SFRP2, PRICKLE1, and FZD3[49]. In a later review, Chiarelli et al. (2019) specifically discussed how given these findings, they believed that WNT/β-catenin pathway may be dysregulated and therefore may contribute to the disorders' pathophysiology[17]. Taking these findings together, it may be possible that the unique myofibroblast phenotype of hEDS and HSD skin fibroblasts, as identified by Zoppi et al., in part results from dysregulation of the WNT/β-catenin pathway. However, it is likely not this straightforward. In the same paper from 2018, Zoppi et al. also reported that the fibroblast-to-myofibroblast transition exhibited by hEDS/HSD fibroblasts was likely

sustained by αvβ3 integrin-ILK-Snail1/Slug signaling[48].

The WNT/β-catenin and ILK pathways are deeply interconnected, functioning as mutually reinforcing loops that independently and concurrently activate shared downstream targets. For example, when the αvβ3 integrin interacts with the ECM, it activates the integrin-linked kinase (ILK). ILK can then directly phosphorylate and inhibit GSK-3β of β-catenin's "destruction complex," thus stabilizing β-catenin[87,88]. Stabilizing β-catenin cross-activates the WNT/β-catenin pathway without any WNT ligand binding. Additionally, both β-catenin and ILK's other downstream effectors, such as NF-kB (another factor related to one of the miRNAs that Chiarelli found to be modulated in JHS/EDS-HT cells), can activate Snail1 and Slug transcription, indicating another point of convergence[89–91].

The pathway's interconnectedness is also illustrated by the discovery that inhibiting ILK suppresses β-catenin's ability to translocate to the nucleus and Snail1's transcription[89].

Although αvβ3 integrin-ILK-Snail1/Slug signaling has been shown to sustain the myofibroblast phenotype, WNT/β-catenin's own, proven role in wound healing may play a concurrent and synergistic role. As noted previously, Chiarelli et al. (2016) demonstrated that JHS/EDS-HT fibroblasts feature increased levels of miRNAs associated with upregulating the WNT/β-catenin pathway, providing evidence for its possible involvement in hEDS and historical hEDS-related pathophysiology. Evidence that the myofibroblast phenotype is sustained by αvβ3 integrin-ILK-Snail1/Slug signaling does not necessarily preclude WNT/β-catenin pathway contribution.

Fibroblasts are the key moderators of ECM and tissue homeostasis[92]. As such, the "wound-healing" program observed in hEDS/HSD fibroblasts may contribute to many of the symptoms that hEDS patients suffer from. Such symptoms could include chronic inflammation, gastrointestinal issues, organ "weakness," and fibrosis[93]. Furthermore, the activation of the myofibroblast phenotype may be aided by profibrotic factors such as MMPs. In fact, Zoppi et al. (2018) also found that the hEDS/HSD fibroblasts exhibiting the myofibroblast phenotype also showed elevated MMP-9 levels[48].

Both WNT/β-catenin signalling and αvβ3-integrin activation can independently, and synergistically, promote MMP-9 expression. The elevation of MMP-9 in hEDS/HSD fibroblasts may suggest a shared downstream endpoint of this signaling convergence rather than a single upstream abnormality. This provides a possible mechanistic framework that can be compared to ASD, where alterations in WNT/β-catenin signaling and MMP-9 levels influence neurodevelopmental processes.

In humans, MMPs are a group of 23 zinc-dependent endopeptidases belonging to the metazincin protease superfamily[94]. Although originally thought to function solely as collagen-degrading enzymes, MMPs are now known to play broad roles in ECM remodeling. They also play roles in key developmental and physiological processes, including angiogenesis, embryogenesis, morphogenesis, wound repair, signaling, immunity, and transcriptional regulation[95–97]. MMPs are categorized into collagenases, gelatinases, stromelysins, matrilysins, membrane-type MMPs, or "other" based on their substrate. Despite these categorizations, all MMPs share a common core containing an 80 amino acid propeptide, a 170 amino acid catalytic metalloproteinase with catalytic zinc, a hinge region of varying lengths, and ~200 amino acid hemoplexin-binding domain[94–98].

Importantly, MMPs and the WNT/β-catenin pathway are closely tied. Within the Hydra model, Veschgini et al. (2023) found that WNT/β-catenin signaling triggers remodeling that is correlated with MMP concentration along the Hydra body axis[99]. Their findings propose that the regulation of protease activity by the WNT/β-catenin pathway generates changes within the ECM. They report that this may indicate that the relationship formed between the WNT/β-catenin pathway and MMPs was a key evolutionary transformation for animal tissue development. MMP-9 expression, specifically, is regulated through both parallel and convergent mechanisms by the WNT/β-catenin and αvβ3 integrin-ILK-Snail1/Slug pathways[100,101].

Through canonical WNT signaling, endothelial cell-derived WNTs can activate FZD receptors, stabilize β-catenin proteins in T-Cells, and thereby induce MMP-9 expression through tandem TCF sites[100]. In contrast, through the αvβ3 integrin-ILK-Snail1/Slug pathway, ILK can activate the AP-1 transcription factor, which then binds to the MMP-9 promoter, thereby also inducing MMP-9's expression[102]. The paths converge through their activation of Snail1[90,103]. Once expressed, Snail1 can collaborate with other transcription factors, including EGR-1 and SP-1, to directly activate the transcription of MMP-9[104].

Interestingly, Chiarelli et al. (2021) discovered that doxycycline, an antibiotic that suppresses MMPs, including MMP-9, partially reversed the myofibroblast phenotype of hEDS cells[105]. Although the αvβ3-ILK-Snail1/Slug pathway may be important to hEDS and hEDS-related pathophysiology, Chiarelli et al. noted that the actual mechanism may be more complicated as the myofibroblast phenotype was only partially reversed. If blocking MMP-9 is insufficient in restoring these cells, such as is shown in Chiarelli's work, it may mean that somewhere upstream, a phenotype is being reinforced. Given this, and the evidence for possible multi-pathway involvement in hEDS, the convergence and parallel amplification of the WNT/β-catenin pathway and ILK pathway may be what creates this irreversible phenotype. Understanding how these upstream pathways work together could be important for clarifying how they may be involved in hEDS and how they may also connect to ASD. Figure 2 details both established pathways in hEDS and ASD, as well as points of proposed convergence inferred from the evidence discussed above.

MMP-9 is secreted by a wide number of cells, such as neutrophils, macrophages, and fibroblasts[106]. It is primarily known for its involvement in ECM degradation and tissue

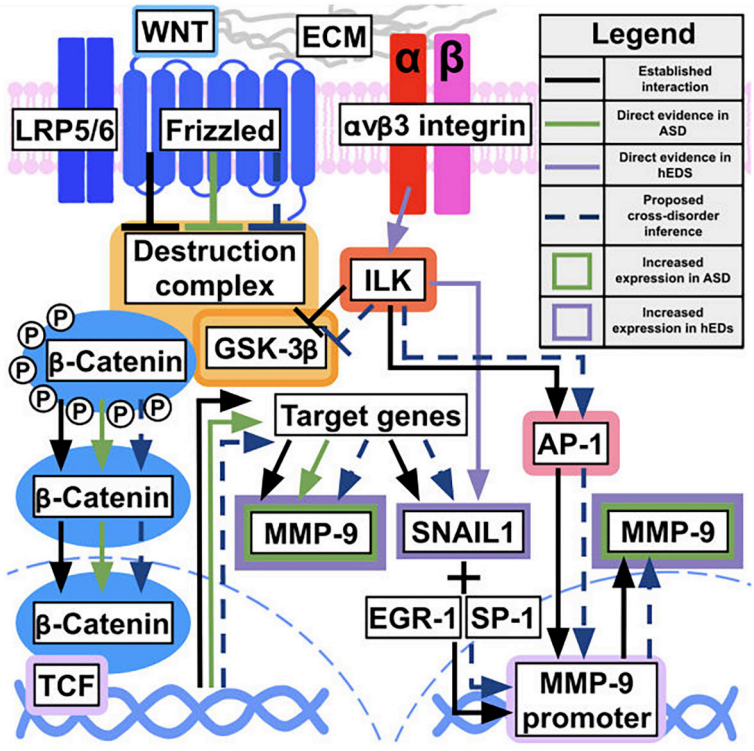

Figure 2. Proposed Convergence of Canonical WNT/β-catenin and αvβ3-integrin/ILK/Snail1 Signaling on MMP-9. The WNT/β-catenin pathway is an established pathway with established interactions (black lines) in both neuronal and non-neuronal tissue. Within this pathway, when a WNT ligand binds to the Frizzled receptor with LRP5/6 present, the destruction complex is inhibited. Inhibition of this complex prevents the phosphorylation and subsequent degradation of β-catenin. β-catenin is then able to translocate into the nucleus, bind to TCF, and stimulate the transcription of target genes, including Snail1 and MMP-9. In the context of Autism Spectrum Disorder (ASD), there has been direct evidence (green lines) of WNT/β-catenin pathway perturbations and increased expression of MMP-9 (green box). Separately, the unique myofibroblast phenotype of hypermobile Ehlers-Danlos Syndrome (hEDS) and Hypermobility Spectrum Disorder (HSD) fibroblasts has been shown to be sustained by the αvβ3 integrin-ILK-Snail1/Slug axis (purple lines). hEDS/HSD fibroblasts have also been shown to exhibit an increased expression of Snail1 and MMP-9 (purple box). Taking this together, there are a number of possible points of convergence between established ASD and hEDS pathways. Starting with the WNT/β-catenin pathway side, microRNAs associated with the WNT/β-catenin pathway have also been found to be differentially expressed in Joint Hypermobility Syndrome and Ehlers-Danlos Syndrome-Hypermobile Type fibroblasts. Given that MMP-9 expression is increased in both disorders, and there is evidence for possible WNT/β-catenin pathway involvement, it is feasible that the WNT/β-catenin pathway is contributing to such a phenotype in both ASD and hEDS (blue dashed line). As discussed above, one of the known downstream effectors of the WNT/β-catenin pathway is Snail1. Therefore, Snail1 may provide another point of convergence for the WNT/β-catenin pathway and established αvβ3 integrin-ILK-Snail1/Slug axis activated in hEDS. It has been shown that once activated, Snail1, in collaboration with factors EGR-1 and SP-1, can directly bind to the MMP-9 promoter and activate its transcription. Separately, when the integrin activates, ILK also becomes activated (as within the αvβ3 integrin-ILK-Snail1/Slug axis in hEDS/HSD). It has been established that once ILK is activated, it then has the ability to inhibit GSK-3β, a part of the WNT/β-catenin pathway's destruction complex. As noted earlier, inhibiting the destruction complex prevents β-catenin's destruction and can therefore promote MMP-9 production. Additionally, it has also been shown that once activated, ILK can activate the transcription factor, AP-1. AP-1 is then able to bind directly to the MMP-9 promoter and increase its transcription. Here, we infer a number of mechanistic interactions and overlaps that may occur between the WNT/β-catenin and αvβ3 integrin-ILK-Snail1/Slug pathways and that may ultimately converge both on Snail1 and most importantly, MMP-9. In this manner, a positive feedback loop may be created between the two pathways, which can mutually amplify and reinforce MMP-9 expression. Aberrations in either or both of these pathways may lead to a notable increase in MMP-9, as is shown in both ASD and hEDS.

remodelling during processes such as embryogenesis, neural development, immune cell function, and wound healing[98,107–109]. Direct regulation of MMP-9 by both the ILK and WNT/β-catenin system may explain why Zoppi et al. discovered elevated MMP-9 levels in hEDS and HSD cells. The convergent and separate but synergistic nature of WNT/β-catenin and αvβ3-ILK-Snail1/Slug pathways on MMP-9 might underlie its upregulation in hEDS. Excessive MMP-9 can lead to abnormal tissue remodeling, increased collagen and ECM degradation, altered fibril assembly, and a myofibroblast "wound-healing" phenotype[110]. Connecting this to symptoms seen in hEDS patients, upregulation of MMP-9 in hEDS fibroblasts may explain the decrease in tensile strength among skin, joints, and organs of hEDS patients[111].

Minocycline, a tetracycline antibiotic similar to doxycycline in its ability to suppress MMP-9, though with different penetrations, has been shown to improve behavioral symptoms in Fragile-X syndrome patients[112,113]. Fragile-X syndrome is the most common monogenic cause of ASD. Individuals with Fragile-X who meet ASD criteria frequently display social communication deficits and restricted, repetitive behaviors[114]. Similar to hEDS, marked upregulation of MMP-9 is observed. In Fragile-X patients, this upregulation is due to loss of the FMRP translational repressor[115]. Clinically, Fragile-X patients share significant symptom overlap with hEDS patients, including joint hypermobility and behavioral symptoms, including mood, sleep, and memory consolidation issues[114].

With such improvement due to minocycline in Fragile-X patients, some groups have attempted similar clinical trials using minocycline in ASD patients. In 2013, a group at Johns Hopkins completed a pilot open-label trial of minocycline in ten ASD children with regressive features for six months. However, they measured no significant changes in plasma MMP levels or clinical improvements in sociability[116]. In 2023, another group at the University of Cincinnati completed a four-week minocycline treatment trial on a group of twenty-four 12-22 year-olds with ASD. This group also did not find any significant clinical improvements as measured by an "aberrant behavior checklist"[117]. Both groups admit their studies may be underpowered, which may have affected the results. It is also important to consider that none of these groups investigated clinical signs outside of neurological/ psychiatric symptoms, such as gastrointestinal issues, sensitivity issues, pain, or other symptoms that may overlap with hEDS patients.

Developmentally, MMPs are essential to the maturity of both non-neuronal and neural tissue. During brain development, MMP-9 directed proteolysis plays a vital role in ECM remodeling, as it causes the release of factors, like TGF-β, required for proper synaptic plasticity, dendritic outgrowth, and circuit formation[118–120]. However, when MMP-9 is overexpressed, the resulting increase in growth-factor release may promote dendritic overgrowth, a well-documented feature of ASD. Indeed, Gore et al. (2021) found that overexpressing MMP-9 in Xenopus tadpoles during early neurodevelopment led to neural circuit hyperconnectivity, disrupted social behavior, and increased seizure susceptibility, all common features of ASD[121].

Many studies have attempted to understand the genetic underpinnings of ASD, but like hEDS, ASD exhibits a heterogeneous set of factors that may lead to its development. However, several risk gene "hubs" tied to particular signaling pathways have been identified, including chromatin remodeling, mitochondrial dysfunction, and WNT signaling[122,123]. Researchers have found the WNT/β-catenin pathway to be particularly relevant after identifying the ASD associated genes CHD8 and CTNNB1. These genes moderate the WNT/β-catenin pathway and MMP-9[72,124]. Alexander et al. (2020) found that mice overexpressing β-catenin exhibited ASD-like behaviors, including reduced social engagement and increased repetitive behaviors, as well as alterations in known ASD risk factor genes[73].

WNT/β-catenin pathway involvement in ASD's pathogenesis is plausible given the essential role of WNT signaling in synaptogenesis and differentiation during neurodevelopment. At the circuit level, both the canonical and noncanonical branches of the WNT pathway shape synapses. The canonical pathway functions as described earlier in this article, where WNT ligands bind to the FZD receptor when co-receptor LRP5/6 is present, β-catenin is then stabilized and able to translocate to the nucleus. β-catenin's transcriptional activation promotes rapid spine growth and AMPA receptor recruitment by facilitating long-term potentiation (LTP). In fact, blocking WNT or the FZD receptor impairs LTP-linked spine plasticity[125]. Interestingly, both gain- and loss-of-function mutations within the WNT/β-catenin pathway have been linked to ASD; gain-of-function mutations overlap between cancer and ASD[126], and loss-of-function mutations overlap between Alzheimer's disease and ASD[127]. ASD-associated miRNAs that upregulate or downregulate the WNT/β-catenin pathway appear to follow a similar pattern[128]. Given WNT/β-catenin's role in acting as a timing and "dosage" controller for neural progenitors in the developing forebrain, and that small shifts in β-catenin tone can greatly alter cortical size and layering, some researchers propose that the varied gain- and loss-of-function of the WNT/β-catenin pathway in ASD may explain both the high genetic and clinical heterogeneity[72,129]. Is it possible that a similar mechanism may explain hEDS's genetic and clinical heterogeneity?

Of other conditions for which the WNT/β-catenin pathway is implicated, several involve joint laxity as a symptom. For example, patients with the rare condition of Osteoporosis Pseudoglioma (OPPG) have mutations in the LRP5 gene[130]. The disorder is characterized by visual loss and skeletal fragility. Some case reports also discuss patients having joint laxity and up to 25% exhibiting cognitive impairment[130,131]. The autoimmune disorder, Rheumatoid

Arthritis (RA) manifests initially as multiple-micro arthritis in patient's joints. RA causes widespread pain and eventually damages ligaments and tendons, causing joint laxity[132]. Similar to hEDS, RA disproportionately affects women, occurring at a rate three to five times higher than in men[133]. The Wnt/β-catenin pathway has been identified as playing a key role in the pathophysiology of RA including as part of its maintenance, differentiation, proliferation, self-renewal, synovial inflammation and bone metabolism[134,135]. Immunohistochemistry showed that β-catenin expression within synovial lining cells of RA samples is significantly higher than that of osteoarthritis or trauma samples[136]. Interestingly, several large cohort studies show that mothers diagnosed with RA before delivery have an increased chance of birthing a child with ASD[137,138]. A finding similar to that of mothers with hEDS.

Throughout this article, the focus has been on WNT/β-catenin and MMP-9. However, this may not be the only feasible explanation for hEDS and ASD's possible overlap. Alternatively, the immune system may play a role. Immune-related disorders are significantly more prevalent in hEDS and ASD patients. For example, in a clinical survey, Daylor et al. found that immune related conditions such as allergies, asthma, mast cell activation syndrome, anaphylaxis, chronic sinusitis, chronic urticaria, and cold urticaria were more common in hEDS patients than HSD patients[139]. A number of studies have also shown that allergies and asthma also disproportionately affect ASD patients[71].

On a molecular level, hEDS and HSD fibroblasts exhibit an inflammatory-like, repair state according to Zoppi et al. (2018)[48]. JHS and EDS-HT fibroblasts overexpressed miRNAs related to NF-kB and TNFα pathways according to Chiarelli et al. (2016)[49]. The brains of ASD patients have also demonstrated increased levels of TNF-α and proinflammatory cytokines like IL-6, IL-8 and IFN-γ[71,140,141]. As mentioned previously, MMP-9 is especially involved in the immune cell function and immune response both within dermal fibroblasts and in the brain[95,106,108,142]. Given this important factor, MMP-9 may play a central role in connecting hEDS and ASD either possibly via immune clustering, the WNT/β-catenin pathway, or both. However, this paper's intention is to bring awareness to the clinical overlap between ASD and hEDS and provide evidence that could spur hypotheses or future investigations. Currently, there is simply not enough research to create a definitive pathophysiological conclusion for the involvement of the immune system or WNT/β-catenin pathway. It is important for researchers in the future to explore all avenues that may connect the two disorders to help elucidate them independently and in combination with each other.

Conclusions

As noted earlier in this manuscript, for both hypermobile Ehlers-Danlos Syndrome (hEDS) and Autism Spectrum Disorder (ASD), the complicated and ambiguous nature of their pathophysiology and its translation to each disorders' phenotype underlines the importance of investigating their possible shared pathway and effectors. Despite arising in distinct tissue contexts, both disorders independently demonstrate possible dysregulation of the WNT/β-catenin pathway and abnormal MMP-9 activity; two systems acting as central regulators of ECM organization and neural circuit development.

Based on findings from mixed hEDS/HSD and historical JHS/EDS-HT fibroblast studies, it is possible that in hEDS, the convergent activation of WNT/β-catenin signaling and αvβ3 integrin-ILK-Snail1/Slug axis sustains the chronic repair-like myofibroblast phenotype accompanied by elevated MMP-9 expression. In ASD, these same molecular pathways dictate synaptic maturation, dendritic growth, and cortical patterning, and their disruption has been linked to circuit hyperconnectivity, altered synaptic pruning, and behavioral phenotypes that are characteristic of the disorder.

These parallels raise the possibility that biological pathways perturbed in mixed hEDS/HSD and historical JHS/EDS-HT fibroblast studies may overlap with pathways implicated in ASD. Although a common vulnerability may exist, this hypothesis will require direct testing in future studies. Here we have proposed a framework for how these disorders' mechanisms may converge. In highlighting their possible convergence, we hope to bring attention to the clinical overlap between these disorders, including mood disorders, elevated sensitivity to sensory input, sleep disturbances, autonomic symptoms, gastrointestinal dysfunction, and joint hypermobility.

Further research could move beyond examining isolated genetic studies and focus on pathway-level mechanisms, especially WNT/β-catenin signaling, ECM remodeling, and MMP-mediated proteolysis. By investigating pathway-level mechanisms, studies may be able to unify the connective tissue aberrations and neurological presentations seen in both hEDS and ASD. Recognizing hEDS and ASD as disorders with possibly converging molecular pathways has the potential to improve early identification, reduce underdiagnosis, stimulate therapeutic discovery, and enhance interdisciplinary and holistic care for individuals who fall at the intersection of these two complex syndromes.

Authors' Contributions

Anna C. Douglas and Daniel J. Staas contributed to the conception and design of the study. Both performed the primary literature search and data curation. Both authors contributed to the analysis and interpretation of the literature. Both drafted the initial manuscript. Anna C. Douglas illustrated figure 1 and figure 2 and created the figure captions. Both authors contributed to critical revision of the manuscript for important intellectual content and approved the final version for submission.

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Supplementary Table 1. Search Strategies Employed.

Search Strategy +Summary	Search String/Key Words	Filters Applied	Date Employed
I: hypermobile Ehlers-Danlos syndrome+related terms and Autism Spectrum Disorder	("hypermobile Ehlers-Danlos syndrome" OR "hypermobile EDS" OR "hEDS" OR "Ehlers-Danlos Syndrome, Hypermobile Type" OR "EDS, Hypermobile type" OR "EDS-HT" OR "Ehlers-Danlos syndrome Type III" OR "Ehlers-Danlos syndrome Type 3" OR "EDS type III" OR "EDS III" OR "EDS 3" OR "Ehlers-Danlos syndrome type 3"[Supplementary Concept] OR "Hypermobility spectrum disorder" OR "Hypermobility spectrum disorders" OR "HSD" OR "Joint Hypermobility syndrome" OR "JHS" OR "Benign Joint Hypermobility Syndrome" OR "BJHS" OR "Benign Hypermobility Syndrome" OR "BHS") AND ("Autism" OR "Autism Spectrum Disorder"[Mesh])	N/A	9-18-2025
II: hypermobile Ehlers-Danlos syndrome+related terms and WNT/β-catenin pathway and matrix metalloproteinase-9	("hypermobile Ehlers-Danlos syndrome" OR "hypermobile EDS" OR "hEDS" OR "Ehlers-Danlos Syndrome, Hypermobile Type" OR "EDS, Hypermobile type" OR "EDS-HT" OR "Ehlers-Danlos syndrome Type III" OR "Ehlers-Danlos syndrome Type 3" OR "EDS type III" OR "EDS III" OR "EDS 3" OR "Ehlers-Danlos syndrome type 3"[Supplementary Concept] OR "Hypermobility spectrum disorder" OR "Hypermobility spectrum disorders" OR "HSD" OR "Joint Hypermobility syndrome" OR "JHS" OR "Benign Joint Hypermobility Syndrome" OR "BJHS" OR "Benign Hypermobility Syndrome" OR "BHS") AND ("Wnt Signaling Pathway"[Mesh] OR "beta Catenin"[Mesh] OR "Matrix Metalloproteinase 9"[Mesh])	N/A	11-14-2025
III: Autism Spectrum Disorder and WNT/β-catenin pathway and matrix metalloproteinase-9	("Autism" OR "Autism Spectrum Disorder"[Mesh]) AND ("Wnt Signaling Pathway"[Mesh] OR "beta Catenin"[Mesh] OR "Matrix Metalloproteinase 9"[Mesh])	N/A	11-15-2025