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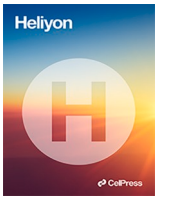

Research article

Folate-dependent hypermobility syndrome: A proposed mechanism and diagnosis

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ABSTRACT

Hypermobility involves excessive flexibility and systemic manifestations of connective tissue fragility. We propose a folate-dependent hypermobility syndrome model based on clinical observations, and through a review of existing literature, we raise the possibility that hypermobility presentation may be dependent on folate status. In our model, decreased methylenetetrahydrofolate reductase (MTHFR) activity disrupts the regulation of the ECM-specific proteinase matrix metalloproteinase 2 (MMP-2), leading to high levels of MMP-2 and elevated MMP-2-mediated cleavage of the proteoglycan decorin. Cleavage of decorin leads ultimately to extracellular matrix (ECM) disorganization and increased fibrosis. This review aims to describe relationships between folate metabolism and key proteins in the ECM that can further explain the signs and symptoms associated with hypermobility, along with possible treatment with 5-methyltetrahydrofolate supplementation.

1. Introduction

Hypermobility is becoming a better-recognized entity in the medical community, estimated to affect as much as 57% of the population [1,2]. While physicians identify other subtypes of Ehlers-Danlos Syndrome (EDS) with genetic testing, hypermobile-type Ehlers-Danlos Syndrome (hEDS) and Hypermobility Spectrum Disorders (HSD) do not have known significant genetic correlates [3]. Therefore, physicians rely on clinical presentation to reach a diagnosis, but the diagnostic criteria for hEDS and HSD are relatively new, unstable, and evolving [4–6]. Hypermobile patients can present with a spectrum of phenotypes, from merely benign joint flexibility, to frequent joint dislocations and subluxations, to more severe bony, tendon, ligament, muscle, and skin injury in response to minor physical trauma, and poor wound healing [3]. Patients even further on the extreme of the hypermobility spectrum can experience systemic manifestations of connective tissue fragility: joint and myofascial pain, gastrointestinal dysfunction, postural orthostatic tachycardia syndrome, mast cell activation disorders, and the psychological distress of living with these limitations [3,5].

A key difference between the other 12 subtypes of EDS and hEDS and HSD lies in their molecular bases. The other 12 subtypes of EDS are linked to known mutations in genes encoding the extracellular matrix (ECM) proteins (i.e., collagen), or enzymes and

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List of Abbreviations

5-methylTHF	5-methyl tetrahydrofolate
ASD	Autism Spectrum Disorder
ECM	Extracellular Matrix
EDS	Ehlers-Danlos Syndrome
FBPs	Folate Binding Proteins
FDHS	Folate-Dependent Hypermobility Syndrome
FRα	Folate Receptor Alpha
hEDS	Hypermobile-type Ehlers-Danlos Syndrome
HSD	Hypermobility Spectrum Disorder
MTHFR	Methylenetetrahydrofolate reductase
MMPs: Matrix Metalloproteinases	
PCFT	Proton-Coupled Folate Transporter
RFC	Reduced Folate Carrier
TGFβ	Transforming Growth Factor β

chaperones that facilitate the processing and assembling of ECM proteins [7,8]. However, the molecular bases for hEDS and HSD remain largely unknown. Two studies of two different families have identified genetic polymorphisms linked to hEDS, and Tenascin-X deficiency has been implicated in hypermobility [9–11]. However, none of these findings appear to be pervasive among sufferers of hEDS or HSD. The uncertainty regarding hypermobility's pathophysiology greatly limits the therapeutic options and support available to patients.

Based on observations made in our clinic, we propose that common polymorphisms in a key folate-metabolizing enzyme, methylenetetrahydrofolate reductase (MTHFR), are tied to the development of hypermobility. We notice a consistent pattern arises upon evaluation of our symptomatic hypermobile patients, showing elevated serum folate levels, normal mean corpuscular volume of red blood cells, normal homocysteine levels, and C677T or A1298C *MTHFR* polymorphisms. These observations raised the possibility that hypermobility symptoms may be dependent on folate status. We propose a folate-dependent hypermobility syndrome (FDHS) model wherein (1) decreased MTHFR activity derepresses the ECM-specific proteinase matrix metalloproteinase 2 (MMP-2), and subsequently, (2) increases MMP-2-mediated cleavage of the proteoglycan decorin. This cleavage destabilizes collagen, leading to laxity and fragility of the ECM. This cleavage also triggers pro-fibrotic pathways downstream of aberrant transforming growth factor β (TGFβ) signaling, resulting in the thickening of fascia and the development of myofascial pain. Based on our FDHS model, we speculate that supplementation with MTHFR's end-product, 5-methyltetrahydrofolate (5-methylTHF), could re-establish methylation of the MMP-2 promoter, preserve decorin-dependent collagen organization in connective tissue, and mitigate the formation of fibrotic adhesions. If this is the case, then 5-methylTHF supplementation could be a viable strategy to lessen impact and progression of hypermobility's manifestations.

2. Folate: diverse and highly regulated

Folates are a family of B9 vitamins necessary for several fundamental and ubiquitous cellular processes such as nucleotide synthesis for cell division and DNA repair, regulation of cellular oxidation and reduction reactions, and epigenetic regulation, among others. Dietary folates exist mostly in their reduced form, 5-methylTHF, but they are also found as dihydrofolate (DHF), tetrahydrofolate (THF), and others, depending on their place in the folate metabolic pathways [12]. Research on the mechanisms of folate absorption through the gut and metabolism in different cellular compartments has revealed a diverse array of folate-binding proteins (FBPs), transporters, and receptors, many of which have different substrate specificities and affinities. Such exhaustive research highlights the importance of regulating when, where, and how folate metabolism proceeds [13].

Understanding the role of FBPs is particularly important for three reasons. First, soluble FBPs are found in the blood, and their folate-binding properties are the basis of competitive binding assays used by laboratories to assess levels of serum folate (i.e., largely 5-methylTHF) [14]. Second, membrane-bound FBPs regulate the transport of folate species into and out of cells, thus determining the cell's access to this crucial class of B vitamins [13]. Third, cytosolic FBPs are diverse and bind a variety of folate species, thus playing a complex role in orchestrating the activities of different folate-dependent processes, such as the methylation cycle. Therefore, disruption of these enzymes due to *MTHFR* polymorphisms can substantially impact cellular function in many ways, some of which are still not well-understood [15].

3. MTHFR polymorphisms and serum folate levels

MTHFR irreversibly reduces 5,10-methylene-tetrahdyrofolate to 5-methylTHF in preparation for homocysteine recycling and methionine generation (Fig. 1) [16]. *MTHFR* polymorphisms reduce enzyme function by an estimated 8.8–78%, depending on the type of polymorphism and whether the individual is heterozygous or homozygous for one or both polymorphic alleles [17–19]. Two

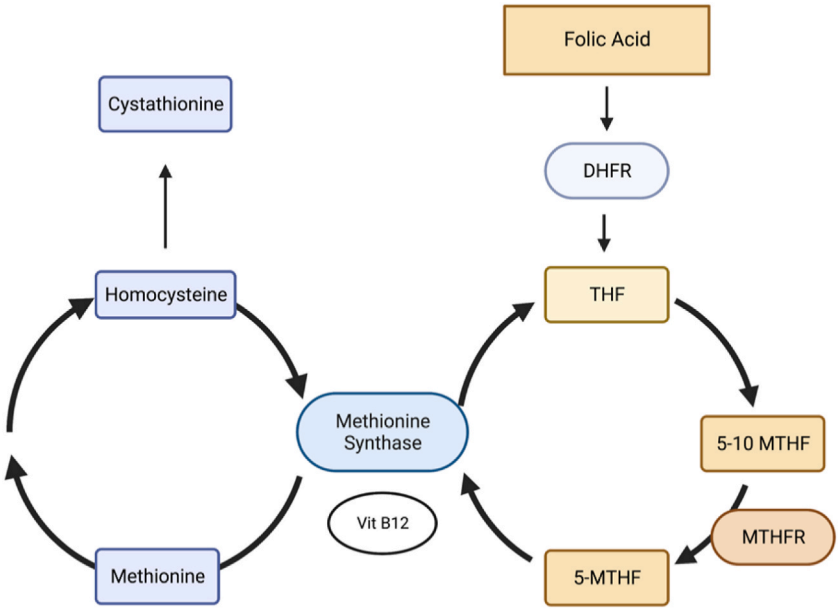

Fig. 1. Metabolism of folate and folic acid through the one-carbon pathway. DHFR: dihydrofolate reductase; THF: tetrahydrofolate; 5–10 MTHF: 5–10 methylene tetrahydrofolate; MTHFR: methylenetetrahydrofolate reductase; 5-MTHF: 5-methyl tetrahydrofolate; Vit B12: Vitamin B12, a cofactor for methionine synthase.

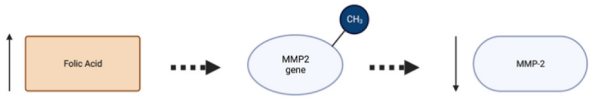

Fig. 2. Increased folic acid was found to modulate MMP2 gene transcription by methylation. Methylation decreases transcription of the MMP2 gene, thus decreasing the amount of available matrix metalloproteinase 2 (MMP-2).

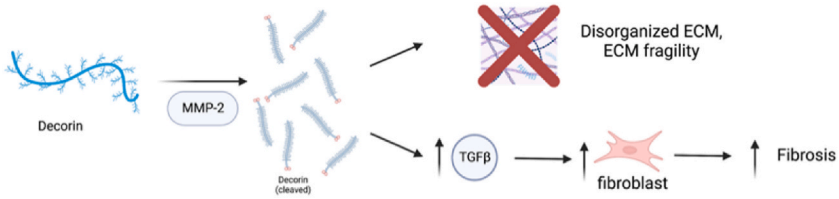

Fig. 3. Decorin, when cleaved by matrix metalloproteinase 2 (MMP-2), leads to extracellular matrix disorganization and fragility as well as increased availability of Transforming Growth Factorβ (TGFβ), increased fibroblast activity, and development of fibrosis.

common polymorphisms described most frequently in the literature are the polymorphisms C677T and A1298C. These polymorphisms arise in as much as 35% of the population, depending on which polymorphism, ethnic group, and geographic location studied [20–23]. The C677T allele results in a more severe decrease in folate metabolism than the A1298C allele, and homozygous polymorphisms result in a further decrease in folate metabolism [17–19]. Polymorphisms in both alleles can be present, but enzymatic activity studies did not report concomitant homozygous alleles [17–19].

The C677T polymorphism may result in a lower serum folate level [20]. In contrast, the heterozygous and homozygous A1298C polymorphism may be associated with an elevated blood folate concentration compared to its wild type [24–26].

4. Folate-dependent methylation and the extracellular matrix

Methylation, or the addition of methyl groups to sequences in DNA, is one mechanism by which gene expression can be selectively and reversibly suppressed [27]. Changes in a tissue's methylation can occur under normal circumstances, such as aging, as well as in pathological situations, such as cancer; appropriate methylation plays a critical role in governing tissue function and homeostasis [27]. In an experiment investigating spinal cord recovery in mice, Miranpuri et al. found that folic acid supplementation caused higher levels

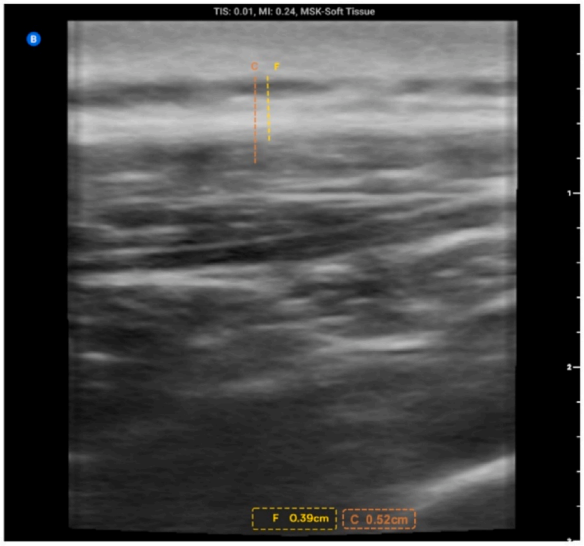

Fig. 4. Lumbar Fascia Ultrasound Image. 31-year-old male with normal lumbar fascia thickness of 0.39 cm. Note the organized fascial layers.

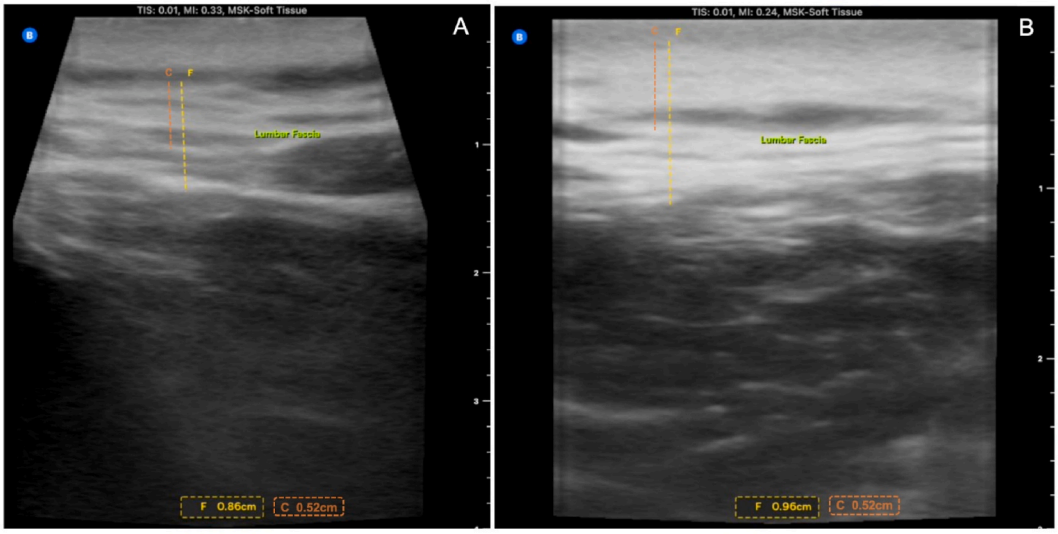

Fig. 5. Lumbar Fascia Ultrasound Image. A 46-year-old male (5A) and a 42-year-old female (5B) with thickened lumbar fascia of 0.86 cm and 0.96 cm, respectively. Note the disorganized fascial layers and increased thickness.

of methylation in the CNS, which decreased the expression of two ECM-targeting proteinases, matrix metalloproteinases 2 and 9 (MMP-2 and MMP-9) in rats with experimental spinal cord injury [28]. Their findings demonstrate a direct connection between the folate cycle and ECM-modifying MMP's (Fig. 2) [28].

MMP-2 is relevant to the FDHS model as it cleaves the proteoglycan decorin, which is responsible for tissue integrity of tendons, skin, and in the eye [29–32]. Decorin is considered the glue that holds collagen fibers together [33,34]. Without this protein, collagen becomes more loosely associated, resulting in a lack of adhesion between collagen and the ECM (Fig. 3) [33]. Decorin-deficient mice have more loosely packed and disorganized collagen fibers of variable diameter, increased skin fragility, and a higher risk of Achilles tendon rupture, all of which is consistent with symptoms reported by patients with HSD [7,35–38].

Additionally, the cleavage of decorin leads to the release of growth factors, cytokines, and chemokines, effectively turning the deconstruction of the ECM into a tissue remodeling signal with downstream consequences [29,31]. It has been shown that cleavage of decorin by MMP-2 releases TGFβ [30]. When free to signal, TGFβ stimulates fibroblast migration and proliferation, facilitates the fibroblast-to-myofibroblast phenoconversion, and results in expression of ECM proteins and the development of fibrosis (Fig. 3) [39–41].

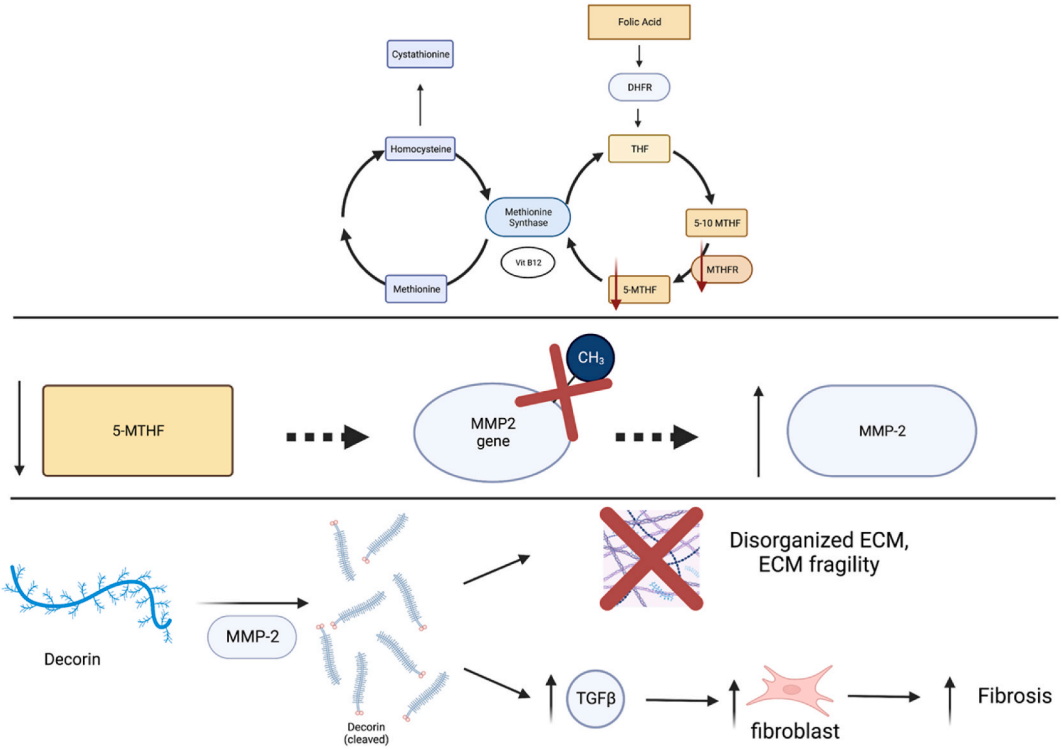

Fig. 6. Decreased efficacy of MTHFR leads to decreased methylation of the MMP2 gene. Loss of epigenetic control leads to increased cleavage of the proteoglycan decorin. Such cleavage ultimately leads to loss of organization of the ECM, in addition to increased fibrosis from aberrant TGFβ signaling.

4.1. Fibrosis and myofascial pain

In our clinic, hypermobile patients present with symptomatic complaints of myofascial pain. Myofascial pain may be secondary to densification of superficial and deep fascia [42–44]. We have observed that hypermobile patients have increased symptomatic fascial fibrosis noted on ultrasound imaging. In a cadaveric study, Barker and Briggs report a normal lumbar fascial thickness of 0.52–0.55 cm [45]. We present an image of a patient's lumbar fascia with organized layers and a fascial thickness of 0.39 cm [Fig. 4]. Frequently, hypermobile patients have fascia that is thicker [Fig. 5A and B].

Clinically, a patient will identify an area of pain, and the ultrasound correlate will demonstrate thickened and disorganized fascia. We propose that MMP-2-mediated cleavage of decorin plays a role in developing adhesions, fibrosis, and hypertrophic scarring in these patients via aberrant TGFβ signaling, and that this is ultimately due to impaired folate metabolism.

4.2. 5-methylTHF supplementation as a potential treatment

Folate insufficiency is linked to neural tube defects, congenital heart defects, pregnancy complications, mental health disorders, and cancer [46]. Beginning in 1998, the FDA required manufacturers to supplement grain products including rice, cereal, breads, pasta and flour with folic acid, which is a synthetic and oxidized form of folate, requiring additional enzymatic alterations prior to becoming 5-methylTHF [47,48].

5-methylTHF supplementation should be explored as a possible management option for hypermobile patients with an *MTHFR* polymorphism. Supplementation would bypass the decreased efficacy of the MTHFR enzyme in those with a polymorphism [49]. It has also been shown that 5-methylTHF stabilizes polymorphic MTHFR, thus improving the apo-to-holoenzyme transition and mitigating the polymorphism's impact on enzymatic activity [50]. We have anecdotally observed the benefits of 5-methylTHF supplementation in our hypermobile patients, but additional studies will be needed to empirically determine the efficacy of supplementation in improving folate availability and in clinical endpoints such as decreasing fascial adhesions and fibrosis development.

5. Discussion

In summary, based on pre-existing literature, we propose a model in which altered MTHFR activity, via loss of epigenetic control of ECM-modifying enzymes, results in excessive ECM turnover leading to increasingly disorganized and unstable connective tissue (Fig. 6). Furthermore, we posit that if this model and mechanism are supported by future research using *in vivo* and *in vitro* studies, then

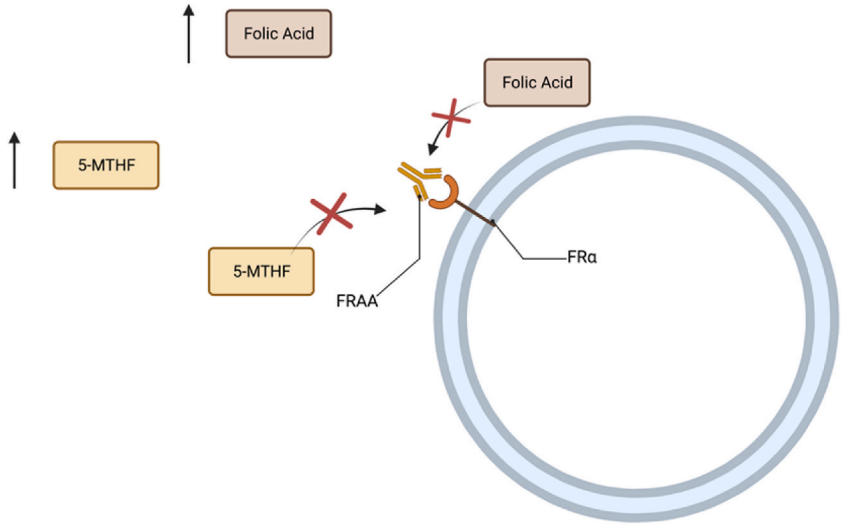

Fig. 7. Blockage or binding of Folate Receptor α auto antibodies (FRAA) would increase serum folate levels by preventing folate and folic acid transportation into cells. 5-MTHF: 5-methyl tetrahydrofolate; FRα: Folate Receptor α

it raises the possibility that hypermobility symptoms could be mitigated by supplementation with 5-methylTHF, the endogenous product of MTHFR activity.

Despite the immense number of studies on folate metabolism, there are still many aspects of folate metabolism, or folate status, more aptly put, that remain unclear. These uncertainties arise from several places, including complex interactions that likely exist between environment or lifestyle choices and polymorphisms at one or more junctures in one-carbon metabolism pathways, and from limitations of measuring folate metabolites in a clinical setting.

Elevated serum folate levels, like those seen in our patients, could also reflect changes in transport of folate in and out of cells. There are three main types of folate transporters: reduced folate carrier (RFC), proton-coupled folate transporter (PCFT), and folate receptors. Folate receptors have four isoforms: FRα, FRβ, FRγ, and FRδ [51,52]. RFC primarily acts on dietary folate, while PCFT requires acidic conditions and is a main transporter for folate absorption in the gastrointestinal tract [51,52]. FRα has a high affinity for and transports 5-methylTHF and folic acid [53]. The blockage and binding of FRα with autoantibodies has been studied in Cerebral Folate Deficiency and Autism Spectrum Disorder (ASD) [51,54,55]. Such autoantibodies would prevent transportation of 5-methylTHF and folic acid between intracellular and extracellular compartments (Fig. 7). Although there are no studies evaluating FRα in the hypermobile population, there is an association between hypermobility and ASD [56]. Genetic mutations of F*OLR1*, which codes for FRα, and of *PCFT* have been studied and described [55]. However, *FOLR1* mutations are rare, and *PCFT* mutations are described in more severe clinical presentations compared to the typical hypermobile patient [55,57].

To our knowledge, there are no studies that have explored linkage disequilibrium between *MTHFR* polymorphisms and mutations in these transporters and receptors. With the growing body of genetic sequencing data and increased awareness of the prevalence and impact of *MTHFR* polymorphisms, it may soon be possible to perform these analyses.

Regarding potential treatment options for changes in folate transportation, 5-methylTHF and folinic acid are transported by RFC [58]. For those with FRα autoantibodies, supplementation would ensure intracellular folate transport by RFC. 5-MethylTHF's high affinity for FRα may facilitate displacement of autoantibodies and allow transportation of 5-methylTHF via FRα; folic acid cannot displace these autoantibodies as effectively [58].

Based on the proposed model that altered folate status impacts methylation of MMP promoters, then it is possible that serum folate levels could appear elevated due to increased conversion of membrane-bound FBPs to serum FBPs. It has been suggested that membrane-bound FBPs can be cleaved by MMPs and ADAMs ('a disintegrin and metalloproteinase'), releasing them as soluble FBPs [13]. Elevated serum folate levels might mask low intracellular folate levels, leading to findings such as those described in our proposed mechanism.

Further studies should investigate folate transportation and *MTHFR* polymorphism prevalence, MMP levels, and decorin activity and structure in the ECM of hypermobile patients. Evaluation of folate transportation and metabolism would likely require liquid chromatography/mass spectrometry and genetic testing to analyze serum folate metabolites and mutations of folate transportation and metabolism. Folate receptor autoantibodies should be studied in the context of hypermobile patients, as well, as this has already been implicated in Autism Spectrum Disorder [51,54]. If folic acid is the specific metabolite elevated in hypermobile patients, dietary studies decreasing folic acid supplementation may prove useful. MMP-2 expression and decorin activity should be evaluated, potentially in tissue studies of hypermobile animal models or hypermobile human subjects. Additional studies would need to determine the efficacy of supplementation with 5-methylTHF.

Patients with hEDS and HSD and their medical providers have faced many challenges, from arriving at a diagnosis to implementing effective treatment plans. However, based on clinical observations and review of the existing literature, hope prevails in providing

patients and medical professionals a potential answer to facing the challenges. Further studies are needed to better understand this proposed mechanism, but this proposal gives optimism to identifying a metabolic etiology to a complex patient presentation.

Author contribution statement

Jacques Courseault, Catherine Kingry, Christiania Edstrom, Greg Bix: Performed the experiments; Analyzed and interpreted the data; Wrote the paper. Vivianne Morrison, Kelli Morrell, Lisa Jaubert, Victoria Elia: Analyzed and interpreted the data; Wrote the paper.

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Data availability statement

No data was used for the research described in the article.

Declaration of competing interest

The authors declare that they have no competing interests.

Ethics approval and consent to participate

Not applicable.

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