

A Framework for the Classification of Joint Hypermobility and Related Conditions

MARCO CASTORI,* BRAD TINKLE, HOWARD LEVY, RODNEY GRAHAME, FRANSISKA MALFAIT, AND ALAN HAKIM

In the last decade, growing attention has been placed on joint hypermobility and related disorders. The new nosology for Ehlers–Danlos syndrome (EDS), the best-known and probably the most common of the disorders featuring joint hypermobility, identifies more than 20 different types of EDS, and highlights the need for a single set of criteria to substitute the previous ones for the overlapping EDS hypermobility type and joint hypermobility syndrome. Joint hypermobility is a feature commonly encountered in many other disorders, both genetic and acquired, and this finding is attracting the attention of an increasing number of medical and non-medical disciplines. In this paper, the terminology of joint hypermobility and related disorders is summarized. Different types of joint hypermobility, its secondary musculoskeletal manifestations and a simplified categorization of genetic syndromes featuring joint hypermobility are presented. The concept of a spectrum of pathogenetically related manifestations of joint hypermobility intersecting the categories of pleiotropic syndromes with joint hypermobility is introduced. A group of hypermobility spectrum disorders is proposed as diagnostic labels for patients with symptomatic joint hypermobility but not corresponding to any other syndromes with joint hypermobility. © 2017 Wiley Periodicals, Inc.

KEY WORDS: classification; Ehlers–Danlos syndrome; joint hypermobility; nosology; terminology

How to cite this article: Castori M, Tinkle B, Levy H, Grahame R, Malfait F, Hakim A. 2017. A framework for the classification of joint hypermobility and related conditions. *Am J Med Genet Part C Semin Med Genet* 175C:148–157.

INTRODUCTION

During the first international symposium for the Ehlers–Danlos syndromes (EDS) in 2012 in Ghent, Belgium an initiative to found the International Consortium on Ehlers–Danlos Syndromes was started

by a group of experts in the field. This initiative was then further developed by the Ehlers–Danlos National Foundation and the Ehlers–Danlos Support UK, with other international groups, culminating in 2016 with the foundation of the Ehlers–Danlos Society. Two of the

Society's key objectives, with the support of many experts in the field worldwide, were to sponsor an update of the nosology for EDS, and the development of best practice clinical guidelines. This article is a supplemental product of that program.

Marco Castori is a Clinical Geneticist at the San Camillo-Forlanini Hospital (Rome) with focus on the diagnosis and management of hereditary connective tissue disorders, particularly Ehlers–Danlos syndromes. He is (co-)author of more than 130 papers on International journals and 14 book chapters.

Brad Tinkle is a Clinical Geneticist with interests in connective tissue disorders and is Division Head of Clinical Genetics at the Advocate Children's Hospital.

Howard Levy is an Associate Professor at Johns Hopkins University. He is a primary care internist and a medical geneticist, with particular interest and experience in Ehlers–Danlos syndrome and other hereditary disorders of connective tissue.

Rodney Grahame is a consultant rheumatologist who specializes in the care of patients with connective tissue disorders, in particular, the Ehlers–Danlos syndrome. His first paper on EDS (with Peter Beighton), which dates back to 1969, was on the mechanical properties of skin in EDS *in vivo*. He is currently Honorary Professor in Division of Medicine, University College, London, UK and Affiliate Professor, School of Medicine, University of Washington, Seattle, WA, USA.

Fransiska Malfait, M.D., Ph.D., is a rheumatologist and clinical geneticist. She is an Associate Professor at the Centre for Medical Genetics at the Ghent University Hospital, where she directs the research, clinical service and laboratory facility for diagnosis and genetic testing for the Ehlers–Danlos syndrome and other heritable disorders of connective tissue. She has (co-)authored over 80 papers in international journals, and 6 book chapters, and is the Chair of the medical and scientific board of the Ehlers–Danlos Society.

Alan Hakim is a consultant in Rheumatology and General Medicine with a specialist interest in the diagnosis and management of hereditary connective tissue disorders. He is (co-)author of more than 100 papers in International journals, co-author and editor of 5 books, and numerous book chapters.

Conflicts of interest: None.

*Correspondence to: Marco Castori, M.D., Ph.D., Unit of Clinical Genetics, San Camillo-Forlanini Hospital, Circonvallazione Gianicolense, 87, I-00152 Rome, Italy. E-mail: m.castori@scf.gov.it

DOI 10.1002/ajmg.c.31539

Article first published online 1 February 2017 in Wiley Online Library (wileyonlinelibrary.com).

In the last two decades, the identification of over a dozen novel genes underlying new clinical variants of EDS enhanced our understanding of the molecular backbone of the connective tissue, and added new tools for the diagnosis, management, and prognosis of an increasing number of patients. Many EDS patients, however, still remain without a laboratory confirmation and this lack of knowledge contributes to the patients' burden. This is mostly the case for individuals affected by the two largely overlapping conditions previously termed "Ehlers–Danlos syndrome, hypermobility type (EDS-HT)" and "joint hypermobility syndrome (JHS)." These two disorders were originally recognized by different sets of diagnostic criteria, which share many items [Beighton et al., 1988; Grahame et al., 2000]. In the ensuing years, the inconsistency of such a clinical separation emerged from expert opinion [Tinkle et al., 2009]; a single segregation study formally demonstrating co-segregation of these two disorders in pedigrees with multiple affected members with a significant proportion fitting both criteria (i.e., JHS and EDS-HT) [Castori et al., 2014].

Many EDS patients, however, still remain without a laboratory confirmation and this lack of knowledge contributes to the patients' burden. This is mostly the case for individuals affected by the two largely overlapping conditions previously termed "Ehlers–Danlos syndrome, hypermobility type (EDS-HT)" and "joint hypermobility syndrome (JHS)."

The new nosology for EDS abolishes the dyadic nature of this community of phenotypes (EDS-HT, JHS, and JHS + EDS-HT) and proposes a unified set of criteria for a single entity called hypermobile EDS (hEDS) (see "Hypermobile Ehlers–Danlos Syndrome (a.k.a. Ehlers–Danlos Syndrome Type III and Ehlers–Danlos syndrome hypermobility type): Clinical Description, and Natural History" by Tinkle et al. [2017], *this issue*). However, the delineation of a single entity arising as the full-blown expression of the phenotype in common between EDS-HT and JHS leaves without an "identity" many individuals with symptomatic joint hypermobility (JH) and/or features of hEDS, who do not meet the stricter criteria incorporated in the new EDS nosology. The classification of such cases requires resolution.

AIM

In this paper, the terminology of JH and related disorders is summarized. Different types of JH, its secondary musculoskeletal manifestations and a simplified categorization of genetic syndromes featuring JH are presented. We consider the spectrum of JH-related musculoskeletal manifestations and the range of pleiotropic manifestations of syndromes featuring JH, noting that these are two separate domains that only partially overlap (Fig. 1). We also propose a classification

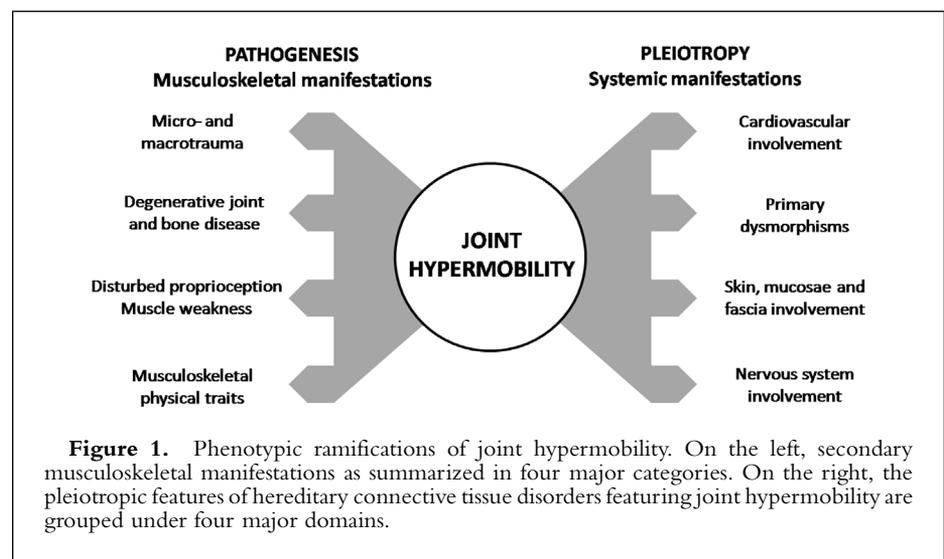
for the spectrum of JH-related disorders (Fig. 2).

The rationale for an evolution in thinking is threefold:

- (1) Nosology: distinguishing pathogenesis and etiology is the background for a classification aimed at identifying more effective scientific, therapeutic, and healthcare strategies.
- (2) Management: JH-related musculoskeletal manifestations likely require homogeneous rehabilitation/treatment issues shared by the different genetic conditions, which in turn diverge for specific extra-articular manifestations.
- (3) Research: a clear separation of the JH secondary musculoskeletal manifestations from the primary pleiotropic manifestations of EDS may help in dissecting the intrafamilial and inter-individual variability of hEDS for studies aimed at deciphering its molecular basis.

DEFINITIONS OF JOINT HYPERMOBILITY

Joint hypermobility (JH) is the term universally accepted to define the capability that a joint (or a group of joints) has to move, passively and/or actively, beyond normal limits along physiological axes. Hence, JH is a descriptor rather than a diagnosis. JH may exist as an isolated diagnostic finding, but is often a feature of a larger syndromic diagnosis.



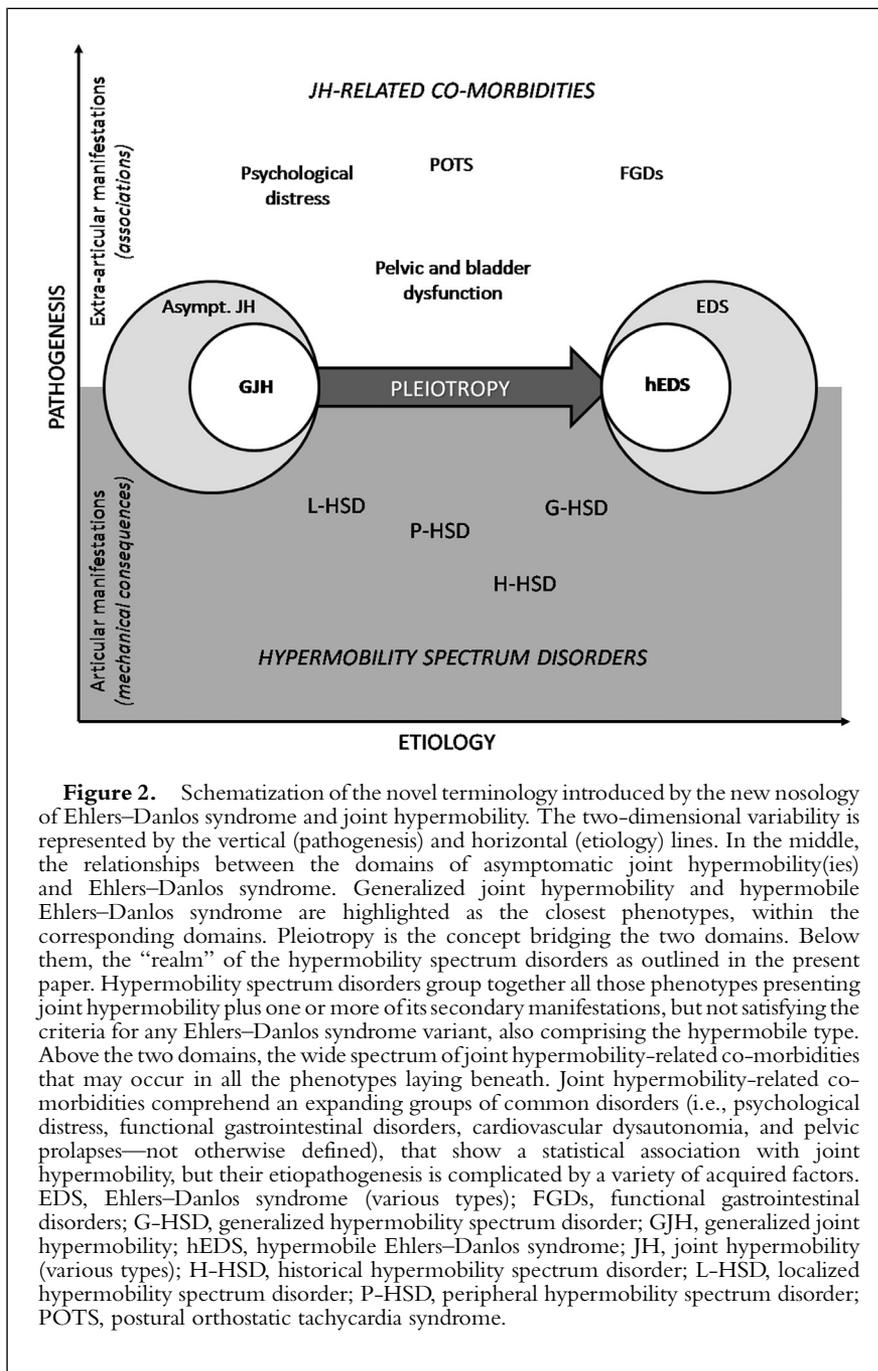


Figure 2. Schematization of the novel terminology introduced by the new nosology of Ehlers–Danlos syndrome and joint hypermobility. The two-dimensional variability is represented by the vertical (pathogenesis) and horizontal (etiology) lines. In the middle, the relationships between the domains of asymptomatic joint hypermobility(ies) and Ehlers–Danlos syndrome. Generalized joint hypermobility and hypermobile Ehlers–Danlos syndrome are highlighted as the closest phenotypes, within the corresponding domains. Pleiotropy is the concept bridging the two domains. Below them, the “realm” of the hypermobility spectrum disorders as outlined in the present paper. Hypermobility spectrum disorders group together all those phenotypes presenting joint hypermobility plus one or more of its secondary manifestations, but not satisfying the criteria for any Ehlers–Danlos syndrome variant, also comprising the hypermobile type. Above the two domains, the wide spectrum of joint hypermobility-related co-morbidities that may occur in all the phenotypes laying beneath. Joint hypermobility-related co-morbidities comprehend an expanding groups of common disorders (i.e., psychological distress, functional gastrointestinal disorders, cardiovascular dysautonomia, and pelvic prolapses—not otherwise defined), that show a statistical association with joint hypermobility, but their etiopathogenesis is complicated by a variety of acquired factors. EDS, Ehlers–Danlos syndrome (various types); FGDs, functional gastrointestinal disorders; G-HSD, generalized hypermobility spectrum disorder; GJH, generalized joint hypermobility; hEDS, hypermobile Ehlers–Danlos syndrome; JH, joint hypermobility (various types); H-HSD, historical hypermobility spectrum disorder; L-HSD, localized hypermobility spectrum disorder; P-HSD, peripheral hypermobility spectrum disorder; POTS, postural orthostatic tachycardia syndrome.

Synonyms of JH include joint laxity and double-jointedness. In general terms, joint hyperlaxity is often considered a further synonym of JH. Establishing whether a joint is hypermobile or not is a relatively easy task and it is carried out by (i) using professional tools, such as the orthopedic goniometer; (ii) following specific procedures (e.g., [Juul-Kristensen et al., 2007]); and (iii) comparing the measured range of motion (ROM) with normal parameters.

When JH is observed at one or a few types of joints (usually fewer than five) it may be defined as localized joint hypermobility (LJH). Typically, LJH affects a single small or large joint and may be bilateral (e.g., bilateral *genu recurvatum* due to knee hyperextensibility). LJH may be inherited, but it may be an acquired trait related to, for example, past trauma, joint disease, surgery, or training (e.g., spine hypermobility). In individuals with JH at multiple sites (usually five

or more), the term generalized joint hypermobility (GJH) is preferred. Theoretically, GJH is the presence of JH appreciable simultaneously at the four limbs and axial skeleton. Given this, it is not necessarily straightforward as to whether an individual has GJH or not. Also, ROM of most joints and the distribution of JH at the different sites is strongly influenced by age, sex, and ethnicity [Remvig et al., 2007]. Therefore, the identification of a standardized procedure applicable in all circumstances is challenging. Over the years, a handful of clinical tools have been used to define GJH, with some validated in different populations. The Beighton score [Beighton et al., 1973] is the most commonly used and, perhaps, the most reliable tool for assessing GJH (see “Measurement Properties of Clinical Assessment Methods for Classifying Generalized Joint Hypermobility—a Systematic Review,” by Juul-Kristensen et al. [2017], this issue). However, all of them have limitations and the attribution of GJH as a feature remains partly influenced by the examiner’s professional experience and recognition of the need to look at all the joints (certainly at least those in the context of the clinical presentation) and not simply those assessed in these tools.

Unlike LJH, GJH is more often a congenital, possibly an inherited trait. Acquired forms of GJH also exist and include widespread inflammatory or degenerative diseases of the joints, musculoskeletal tissues and nerves, and hypothyroidism and other endocrine disorders. Furthermore, malnutrition might also be a source of secondary GJH in children [Hasija et al., 2008].

Further classifications of JH, LJH, and GJH are speculative. However, clinical practice and the literature prompt speculation as to the existence of two additional clinical manifestations of JH. Peripheral joint hypermobility (PJH) is a potentially discrete form of JH that is appreciable at the hands and/or feet only. It is not defined as localized due to involvement of the four limbs, but, at the same time, PJH is distinguished from GJH by the absence of large and axial joint involvement. It is common in infants, toddlers, and children, in whom it is

usually non-pathological or only mild in impact. However, in selected circumstances, PJH may be a clue of vascular EDS, as it is classically associated with JH limited to the small joints (see “*Vascular Ehlers–Danlos Syndrome*,” by Byers et al. [2017], *this issue*).

The effect of age negatively impacting the ROM of many joints has prompted some researchers to hypothesize the possibility of chronic musculoskeletal symptoms (see below) in older adults who have progressively lost their GJH. The five-point questionnaire was introduced as a rapid screening tool to investigate historical joint hypermobility (HJH) in adults who presumably have lost their GJH [Hakim and Grahame, 2003]. Although this hypothesis is reasonable and some cross-sectional studies have tried to support it [Castori et al., 2011], prospective research tracing the natural history of GJH in individuals is lacking.

JOINT INSTABILITY

Joint instability (JI) has in the past been used as a synonym of JH. However, JI by inference is a prelude to detrimental effect on the involved joint(s), while JH is a neutral term often defining a benign trait. Hypermobile joints may also be unstable, but JI is not a mandatory consequence of JH. Also, the reverse is true: not all unstable joints are hypermobile.

Instability arises from a number of pathologies including laxity in the supporting soft tissue structures; congenital or acquired abnormality of the joint articulation; muscle disorders (inherent or acquired weakness, and biomechanical imbalance); and musculoskeletal dysfunction as a result of neurological disorders. The lack of support puts an individual at increased risk of joint dislocations (luxations and subluxations), and articular and soft-tissue injuries. While JH is frequently a consequence of (either congenital or acquired) ligamentous (hyper-) laxity, the pathogenesis of JI is wider, as the propensity to joint dislocations, joint pain, and soft-tissue traumas may arise from a number of hereditary and acquired muscle and bone disorders.

SECONDARY MANIFESTATIONS OF JOINT HYPERMOBILITY

JH is frequently a symptomless trait. However, a relatively robust amount of data supports the existence of a series of musculoskeletal symptoms and complications that may be interpreted as *bona fide* secondary manifestations of JH.

Trauma

The hypermobile joint may be predisposed to an excess of macro- and microtrauma. Macrotrauma (i.e., dislocations, subluxations, and other soft-tissue injuries—that is, any form of damage of muscles, ligaments, tendons, synovium, and cartilage) is most likely the result of isolated or recurrent trauma due to excessive joint movement along non-physiological axes, potentially compounded by joint instability. Macrotrauma typically leads to acute pain, loss of function, and often the need for acute treatment. Microtrauma is subtle/silent injury typically not perceived by the individual or practitioner as it occurs. However, over time it might predispose to recurrent or persistent pain and potentially to early joint degeneration (i.e., early osteoarthritis). While JH is largely accepted as predisposing to recurrent musculoskeletal pain, neither chronic pain nor early osteoarthritis is a uniform obligate complication of JH. Repetitive microtrauma and occasional/recurrent macrotrauma may lead to regional joint disorders, for example, temporomandibular joint dysfunction [De Coster et al., 2005] (see also “*Oral and Mandibular Manifestations in Ehlers–Danlos Syndrome*,” by Mitakides and Tinkle [2017], *this issue*), or labral tear of the hip [Groh and Herrera, 2009].

Chronic Pain

Occasional and recurrent musculoskeletal pain is a quite common immediate manifestation of JH as the natural consequence of predisposition to trauma. The development of chronic pain is sometimes a long-term complication of

JH [Castori, 2016]. Preliminary studies suggest the existence of hyperalgesia as a possible form of pain sensitization in patients with EDS and chronic pain [Rombaut et al., 2015; Di Stefano et al., 2016] (see also “*Pain Management in Ehlers–Danlos Syndrome*” by Chopra et al. [2017], *this issue*). The recent observation of a high rate of small fiber neuropathy in adults with common EDS subtypes (i.e., classical, hypermobile, and vascular) [Cazzato et al., 2016] may lead one to speculate on a direct relationship between an impaired connective tissue function and abnormal pain processing. An alternative or complementary hypothesis is the existence of a common pathogenesis shared by other forms of chronic musculoskeletal pain (e.g., acquired connective tissue disorders and idiopathic osteoarthritis), that may develop in a way independent from the discrete causes of the primary joint disease [Castori et al., 2013].

Occasional and recurrent musculoskeletal pain is a quite common immediate manifestation of JH as the natural consequence of predisposition to trauma. The development of chronic pain is sometimes a long-term complication of JH. Preliminary studies suggest the existence of hyperalgesia as a possible form of pain sensitization in patients with EDS and chronic pain.

Disturbed Proprioception

In the symptomatic patient, it is not uncommon to find JH coupled with reduced proprioception in selected joints [Smith et al., 2013] and with muscle weakness [Rombaut et al., 2012; Schepers et al., 2016]. Reduced proprioception and

muscle strength significantly influence each other and might generate a vicious circle of increasing limitation of activities of daily living in those with EDS. The mechanisms underlying the relationship between reduced/lack of proprioception, weakness, and JH in adults are incompletely understood, but their co-existence should be considered in rehabilitation plans [Scheper et al., 2016].

In other ways, the combination of JH and its neuromuscular attributes may also influence performance in children. Some evidence suggests a significant association between GJH and developmental coordination disorder [Ghibellini et al., 2015], a more inclusive term also comprising developmental dyspraxia. The pathophysiology is unknown but the interplay between poor proprioception and muscle weakness during the development of motor schema may be one mechanism.

Other Musculoskeletal Traits

Individuals with GJH often present a series of minor musculoskeletal physical traits, which may be the result of the interactions between “softer” musculoskeletal tissues and mechanical forces (e.g., recumbent preferred position, body weight, gravity, lateralization, sport activities) during growth and development. Such traits, commonly encountered in individuals with GJH include: pes planus (of the “flexible” type), valgus deformity of elbows, hindfeet and halluces, scoliosis (not congenital, of mild to moderate degree =>7° using the Bunnel scoliometer [Bunnell, 1993]), accentuated dorsal kyphosis and lumbar lordosis, and deformational plagiocephaly [Tinkle, 2010; Morlino et al., 2016].

Some genetic syndromes that feature GJH are associated with severe reduction in bone mass and the propensity to fractures, and long bone deformities. In these conditions, the pleiotropic effect of the causative gene masks any pathogenic correlation between GJH and a defective bone mass. This may not hold true for milder phenotypes in which GJH associates with a milder reduction of the bone mass and a pleiotropic effect is not

straightforward. In these circumstances, the reduction in bone mass is typically milder, not clearly associated with increased fracture risk, and may be multifactorial [Dolan et al., 2003; Gulbahar et al., 2006] and partly related to the lack of proprioception, muscle weakness, and reduced activity that often characterize GJH independently from the underlying cause.

PATHOGENESIS AND PLEIOTROPY

As previously emphasized, JH does not always rise to the level of a clinical disorder, as it is often asymptomatic. Practitioners usually recognize JH when it runs in association with additional musculoskeletal manifestations. Those musculoskeletal manifestations are likely due to pathogenic effects of the underlying JH (pathogenesis). Accordingly, patterns of presentation of JH-related musculoskeletal features are highly variable and strongly related to modifier factors (e.g., sex, mechanical forces, lifestyle habits, job, accidents), which are causally independent from JH and may manifest at different ages. Thus, they are not directly due to the underlying cause of the JH, but instead are secondary effects mediated by the JH and other factors.

Accordingly, patterns of presentation of JH-related musculoskeletal features are highly variable and strongly related to modifier factors (e.g., sex, mechanical forces, lifestyle habits, job, accidents), which are causally independent from JH and may manifest at different ages. Thus, they are not directly due to the underlying cause of the JH, but instead are

secondary effects mediated by the JH and other factors.

In the recent consensus paper on general terminology in Medical Genetics by Hennekam et al. [2013], a (genetic) syndrome is defined as “a pattern of anomalies, at least one of which is morphologic, known or thought to be causally (etiologically) related.” Therefore, the term “syndrome” should be used to name multiple features that share the same underlying cause (etiology) rather than a common pathogenesis. Pleiotropy is the biological mechanism underlying genetic syndromes, that is, patterns of anomalies each caused directly by a defective gene simultaneously (and independently) affecting the development/functions of different tissues/organs/structures.

For all these reasons, the presence of JH in combination with secondary musculoskeletal anomalies does not suffice for the delineation of a genetic syndrome. The appellation “syndrome with JH” should be restricted to genetic conditions featuring JH together with the primary involvement of at least a second tissue/structure (e.g., skin involvement in classical EDS and hEDS). Intrafamilial phenotypic variability is a feature of most genetic syndromes. Hence, within the same pedigree, the involvement of the various systems may be not straightforward in all affected individuals. However, an objective JH should be a highly penetrant trait within and between families, as also emphasized in the new criteria for hEDS.

GENETIC SYNDROMES WITH JOINT HYPERMOBILITY

Hereditary Disorders of the Soft Connective Tissue

These are well known genetic syndromes featuring JH. In particular, EDS is probably the default diagnosis (or suspected diagnosis) of many patients with multiple manifestations combined with JH (for a full description of the new nosology of

EDS, see the Malfait et al. [2017], this issue). Other hereditary disorders of the soft connective tissue with JH as a major feature include Marfan syndrome and related disorders, Loeys–Dietz syndromes, Beals syndrome, arterial tortuosity syndrome, lateral meningocele syndrome, and various hereditary cutis laxa syndromes [Colombi et al., 2015; Mohamed et al., 2015].

Other Genetic Syndromes

An increasing number of skeletal dysplasias also present with JH and its musculoskeletal consequences, such as joint pain and dislocations [Bonafe et al., 2015]. Examples include Larsen syndrome, Desbuquis syndrome, *CST3*- and *gPAPP*-related chondrodysplasias, spondyloepimetaphyseal dysplasia with joint laxity, spondyloepimetaphyseal dysplasia with leptodactyly, diastrophic dysplasia, and trichorhinophalangeal syndromes.

An increasing number of skeletal dysplasias also present with JH and its musculoskeletal consequences, such as joint pain and dislocations. Examples include Larsen syndrome, Desbuquis syndrome, *CST3*- and *gPAPP*-related chondrodysplasias, spondyloepimetaphyseal dysplasia with joint laxity, spondyloepimetaphyseal dysplasia with leptodactyly, diastrophic dysplasia, and trichorhinophalangeal syndromes.

The hereditary myopathies are a third group of genetic conditions which may present with clinically significant JH. A

recent review pointed out the increasing list of hereditary myopathies which typically show JH and, among them Bethlem myopathy, Ullrich congenital myopathy, *COL12A1*-related myopathy (or Ehlers–Danlos syndrome/myopathy overlap), *SEPN1*- and *RYR1*-related myopathies, *MYH7*- and *TTN*-related core myopathies, and limb girdle muscular dystrophy type 2E with joint hyperlaxity and contractures [Donkervoort et al., 2015]. The underlying cause of JH in these conditions is thought to be multifactorial, including the muscle/tendon complex, the joint capsule and other extracellular matrix components [Donkervoort et al., 2015]. JH may also be seen in some forms of mitochondrial myopathy [Sugimoto et al., 2000].

Practice also indicates that some chromosomal and genomic disorders may frequently show JH, a feature that can also impact the overall rehabilitation plan of affected individuals. Down syndrome is a prototype, and in which JH may strongly influence gait performance and may be associated with atlantoaxial instability [Galli et al., 2014; Siemionow and Chou, 2014]. This association extends to other aneuploidies, in particular of the sex chromosomes (47,XXY and 47,XXX), and various microdeletion and microduplication syndromes [e.g., Ciaccio et al., 2016]. However, the impact that JH may have on the management of these conditions remains undetermined, except, perhaps, the link between GJH and coordination troubles commonly observed in children with selected sex chromosome aneuploidies [Tartaglia et al., 2010; Samango-Sprouse et al., 2014].

Finally, JH is also a commonly encountered feature in many multiple congenital anomalies/intellectual disability disorders, such as selected RA-Sopathies (e.g., Noonan, Costello, and cardio–facio–cutaneous syndromes) [Detweiler et al., 2013; Vegunta et al., 2015; Rauen, 2016], Kabuki syndrome [Kawame et al., 1999], and Fragile–X syndrome [Saul and Tarleton, 2012]. The rate and extent of JH in these conditions is probably underestimated due to the relatively small impact that this feature may have on the long-term management of these patients.

An Annotation on hEDS

Molecular discoveries have allowed the identification of an increasing number of uncommon, rare, and ultra-rare syndromes with JH. For patients affected by such conditions, molecular testing is usually the ultimate tool for reaching the correct diagnosis. However, for the hypermobile variant of EDS, there is no known genetic marker. One of the major goals of the revised nosology of EDS was to identify a single term, within the EDS nomenclature, for these patients and the term “hypermobile Ehlers–Danlos syndrome (hEDS)” was elected as the preferred one. The identified new set of clinical criteria for the diagnosis is stricter than the Brighton criteria for JHS and the Villefranche nosology for EDS-HT. The rationale supporting these new criteria reflects (i) the need to place more emphasis on the use of the term “syndrome” and in doing so also highlights the pleiotropic nature of the disorder; and (ii) the opportunity to maintain coherence within the EDS nosology according to the original description of the disease.

Many researchers and practitioners with experience on JH and related conditions perceive that the boundaries separating the continuous spectrum of JH-related musculoskeletal manifestations and the true pleiotropic phenotype (i.e., hEDS) are not always straightforward and sometimes arbitrary. While the identification of stricter criteria for hEDS, which more genuinely reflect the original description of the disease, gives more order to the nosology, it leaves out many “non-syndromic” patients who suffer with the various secondary manifestations of JH. These patients do indeed have real medical needs even if they do not meet criteria for hEDS or another syndrome, and there is need for a logical framework of diagnostic terms to adequately describe their manifestations.

CLASSIFYING JOINT HYPERMOBILITY

We propose that individuals with JH may be classified as follows:

- (1) Subjects with asymptomatic, non-syndromic/isolated LJH, PJH, or

GJH. Asymptomatic JH may occur in multiple individuals from the same pedigree (i.e., familial asymptomatic JH) and, theoretically, might also occur as an isolated trait in healthy relatives of patients with a full-blown hEDS.

- (2) Individuals with a well-defined syndrome with JH, also comprising hEDS (i.e., new diagnostic criteria met).
- (3) In individuals with symptomatic JH but not satisfying the criteria/diagnosis for a syndrome, the term hypermobility spectrum disorder(s) (HSDs) is proposed.

HYPERMOBILITY SPECTRUM DISORDERS

HSDs are a group of clinically relevant conditions related to JH and are intended as descriptive and exclusion diagnoses. They are distinguishable from hEDS and the other syndromes with JH because the phenotypic domains of HSDs are usually limited to the musculoskeletal system. The involvement of the musculoskeletal system is intended as the presence of one or more of the secondary manifestations of JH as reported above (i.e., trauma, pain, degenerative joint and bone disease, neurodevelopmental manifestations, orthopedic traits) (Fig. 1). In these patients' category, a limited extension to other organs and tissues, particularly in form of JH-related co-morbidities (see below), is possible, but the overall clinical picture does not fit the criteria for one of the various EDS types. Therefore, HSDs are mostly intended as alternative labels for patients with symptomatic JH *who do not have any rare type of EDS and do not meet the criteria for hEDS in terms of severity/pattern of musculoskeletal involvement and/or due to the absence of the other necessary criteria (as reported in the new EDS nosology—this issue)*. In many circumstances, the HSDs will become the updated diagnosis for all those individuals who met the previous criteria for EDS-HT or JHS but do not match the new hEDS criteria. However, HSDs are not limited solely to substituting the “old” Brighton criteria, that should not yet be considered for modern

patients' classification. HSDs are also intended to identify discrete subtypes filling the full gap between asymptomatic JH and hEDS.

There might be a scenario where the diagnosis of HSD is given to an individual with a family history of hEDS (i.e., relatives with an independent diagnosis of hEDS). Such a presentation might suggest the same underlying genetic trait with variable expression. However, from a classification perspective, the diagnosis of hEDS is established by the presence of a positive Beighton score (i.e., GJH) plus two or more among musculoskeletal criteria, systemic involvement, and positive family history (as specifically defined in the new nosology). Hence, the addition of a family history alone should not be sufficient to change a diagnosis from HSD to hEDS according to the new criteria. One recognizes this in other areas of musculoskeletal medicine where the same principle applies. For example, there may be a family history of rheumatoid arthritis (RA) (as defined by accepted international criteria), but the individual presents with some clinical features to suggest an autoimmune rheumatic disease but has insufficient clinical and biological markers to define RA. The term “sero-negative inflammatory arthropathy” might apply. This individual would be managed on the basis of their presenting complaint and followed to determine whether their condition changed in any way that might then lead to a diagnosis of RA. HSD should be considered in the same way, including the possibility of clinical evolution and transition to another diagnosis (e.g., hEDS).

Although HSDs share JH with the other conditions and, in particular with EDS, at present it is premature to a priori define HSDs as Mendelian disorders of the soft connective tissue. In fact, their molecular basis remains unknown and they may occur sporadically, may segregate within families as Mendelian traits (dominant, recessive or X-linked) or they may aggregate in families as multifactorial or polygenic traits. In selected cases and, particularly, in some children and in individuals

from families with other relatives with a previous diagnosis of hEDS (according to the new criteria), a “relaxed” follow-up in clinical genetics services may be scheduled due to a potential future revision of the diagnosis to hEDS or potentially another JH-related syndrome.

In line with the previously delineated types of JH, four different HSDs may be identified:

- (1) Generalized (joint) HSD (G-HSD): GJH objectively assessed (e.g., by the Beighton score) plus one or more secondary musculoskeletal manifestations as previously identified. In these patients, the pattern and severity of the involvement of the musculoskeletal system should be carefully assessed in order to explore the possibility of a full-blown hEDS. In this category usually fall most patients with GJH and additional musculoskeletal manifestations but do not meet the full diagnostic criteria for hEDS.
- (2) Peripheral (joint) HSD (P-HSD): JH limited to hands and feet plus one or more secondary musculoskeletal manifestations as previously identified.
- (3) Localized (joint) HSD (L-HSD): JH at single joints or group of joints plus one or more secondary musculoskeletal manifestations regionally related to the hypermobile joint(s).
- (4) Historical (joint) HSD (H-HSD): self-reported (historical) GJH (e.g., by the five-point questionnaire) with negative Beighton score plus one or more secondary musculoskeletal manifestations as previously identified; in these cases, physical examination aimed at excluding the alternative diagnoses of G-HSD, P-HSD, and L-HSD as well as other rheumatologic conditions is mandatory.

The literature is full of case-control studies showing a significant association between GJH (usually assessed by the Beighton score) and specific extra-articular disorders. To date, the strongest associations are with anxiety disorders [Sinibaldi et al., 2015], orthostatic tachycardia [Mathias et al., 2011], a variety of functional gastrointestinal disorders [Zarate et al., 2010], and pelvic and

bladder dysfunction [de Kort et al., 2003; Veit-Rubin et al., 2016]. These associations are often real (i.e., easily confirmed by clinical practice) and clinically relevant as these additional manifestations may be commonly encountered in conditions with JH, in particular hEDS, and might impact seriously on the quality of life and management of affected individuals. Hence, their prompt recognition is useful and the concurrence with GJH should be emphasized also for therapeutic issues (see the many additional papers in this issue).

The literature is full of case-control studies showing a significant association between GJH (usually assessed by the Beighton score) and specific extra-articular disorders. To date, the strongest associations

are with anxiety disorders, orthostatic tachycardia, a variety of functional gastrointestinal disorders, and pelvic and bladder dysfunction.

However, at the moment, it does not seem prudent to consider the combination of GJH and anxiety (or any other strongly associated extra-articular disorders) a syndrome per se, at least from the Medical Genetics perspective. In fact, these satellite manifestations may complicate a variety of phenotypes, including isolated JH, syndromes with JH and HSDs, and the burden may be strongly influenced by acquired factors (e.g., psychological distress). According to such an assumption, it is too premature to consider such manifestations primary (i.e., pleiotropic) clinical expressions of the underlying etiological factor (i.e.,

genetic mutation). Therefore, these complications, when encountered in patients belonging to one of the above-mentioned categories of JH, should be defined as JH-related co-morbidities. The concurrence of JH and one or more of its co-morbidities does not exclude an accurate differential diagnosis for the other causes underlying such co-morbidities. From this perspective, the presence of one or more JH-related co-morbidities aggravates the overall phenotype and usually indicates the need of a multidisciplinary therapeutic approach. Whether the development of chronic pain is a late consequence of JH or rather it should be considered a JH-related co-morbidity is still a matter of debate and further research is needed to clarify this point.

THE SPECTRUM

While Mendelian syndromes with JH can be clearly separated by molecular testing from the other JH-related phenotypes, this is not the case for asymptomatic JH,

TABLE I. Phenotypes Belonging to “the spectrum”

Phenotype	Beighton score	Musculoskeletal involvement	Notes
Asymptomatic GJH	Positive	Absent	–
Asymptomatic PJH	Usually negative ^a	Absent	–
Asymptomatic LJH	Negative ^b	Absent	–
G-HSD	Positive	Present	–
P-HSD	Usually negative ^a	Present	–
L-HSD	Negative ^b	Present	–
H-HSD	Negative	Present	Historical presence of joint hypermobility (e.g., positive 5-point questionnaire)
hEDS	Positive ^c	Possible	Plus positive family history (first-degree relatives) and/or specific systemic manifestations (see new criteria)

GHD, generalized hypermobility disorder; G-HSD, generalized hypermobility spectrum disorder; hEDS, hypermobile Ehlers–Danlos syndrome; L-HSD, localized hypermobility spectrum disorder; LJH, localized joint hypermobility; P-HSD, peripheral hypermobility spectrum disorder; PJH, peripheral joint hypermobility.

All these phenotypes request accurate exclusion of the other acquired and hereditary, partially overlapping disorders.

^aPeripheral joint hypermobility is typically limited to hands and/or feet; Beighton score is usually negative.

^bLocalized joint hypermobility is limited to single joints or body parts; Beighton score is negative.

^cSee the new criteria for the operational definition of “generalized joint hypermobility” as mandatory feature/criterion of hypermobile Ehlers–Danlos syndrome.

hEDS, and HSDs. In fact, their clinical manifestations are variable, but largely overlapping, as seen in extended pedigree study and the identification of family members belonging to all three phenotypes with variable degree of disability.

Therefore, from a clinical perspective, asymptomatic JH, HSDs, and hEDS can be brought back to a single continuous spectrum ranging from isolated JH to full-blown hEDS passing through the various HSDs. The nosologic distinction among them is summarized in Table I. The existence of this spectrum is the rationale supporting the dynamic nature of such a classification and the possibility of phenotype transition due to the changing pattern of JH-associated manifestations. The follow-up of these patients may be relevant also for diagnostic accuracy, especially for patients at risk of developing a phenotype consistent with the new criteria for hEDS, but also for those with HSD whose musculoskeletal conditions are resolved by treatment and who therefore in effect revert to having asymptomatic JH.

The new terminology within this spectrum updates and substitutes all previous terms used to define patients with JH but without a molecularly proved syndromic condition. Among these terms there are: Ehlers–Danlos syndrome type III, Ehlers–Danlos syndrome hypermobility type, hypermobility syndrome, joint hypermobility syndrome, and benign joint hypermobility syndrome. All these names are considered outdated and their use should be discouraged.

CONCLUSIONS AND FUTURE PERSPECTIVES

Putting order to the field of JH is challenging and much more work is needed for reaching a full picture of what JH represents for human health and disease. The nosologic restyling of JH and related conditions is summarized in Figure 2. It is not intended as a rigid guideline for medical and non-medical professionals, but as an updated framework structured on a wider perspective and on the most recently available data for nurturing more clinical and basic research. Dissecting the molecular basis of hEDS, HSDs, and

isolated JH could be one of the future goals of the scientific community, especially in the fields of Human and Medical Genetics. This knowledge will surely ease patients' classification and prognostication, and, perhaps, will better rationalize medical and economic resources. At the same time, exploring the pathogenetic links connecting JH and its secondary musculoskeletal manifestations, as well as the mechanisms underlying the JH-related comorbidities is the greatest challenge for the various disciplines involved in the daily management of patients with JH.

Dissecting the molecular basis of hEDS, HSDs, and isolated JH could be one of the future goals of the scientific community, especially in the fields of Human and Medical Genetics. This knowledge will surely ease patients' classification and prognostication, and, perhaps, will better rationalize medical and economic resources.

ACKNOWLEDGMENTS

The authors would acknowledge Christina Schwarting, as patients' representative, for her inputs and supports during the writing of this manuscript.

REFERENCES

- Beighton P, de Paepe A, Danks D, Finidori G, Gedde-Dahl T, Goodman R, Hall JG, Hollister DW, Horton W, McKusick VA, Opitz JM, Pope FM, Peyerit RE, Rimoin DL, Sillence D, Spranger JW, Thompson E, Tsiouras D, Viljoen D, Winship I, Young I, Reynolds JF. 1988. International Nosology of Heritable Disorders of Connective Tissue, Berlin, 1986. *Am J Med Genet* 29:581–594.
- Beighton P, Solomon L, Soskolne CL. 1973. Articular mobility in an African population. *Ann Rheum Dis* 32:413–418.
- Bonafe L, Cormier-Daire V, Hall C, Lachman R, Mortier G, Mundlos S, Nishimura G,

- Sangiorgi L, Savarirayan R, Sillence D, Spranger J, Superti-Furga A, Warman M, Unger S. 2015. Nosology and classification of genetic skeletal disorders: 2015 revision. *Am J Med Genet Part A* 167A:2869–2892.
- Bunnell WP. 1993. Outcome of spinal screening. *Spine (Phila Pa 1976)* 18:1572–1580.
- Byers P, Belmont J, Black J, De Backer J, Frank M, Jeunemaitre X, Johnson D, Pepin M, Robert L, Sanders L, Wheeldon N. 2017. Diagnosis, natural history, and management in vascular Ehlers Danlos syndrome. *Am J Med Genet Part C Semin Med Genet* (in press).
- Castori M, Dordoni C, Valiante M, Sperduti I, Ritelli M, Morlino S, Chiarelli N, Celletti C, Venturini M, Camerota F, Calzavara-Pinton P, Grammatico P, Colombi M. 2014. Nosology and inheritance pattern(s) of joint hypermobility syndrome and Ehlers–Danlos syndrome, hypermobility type: A study of intrafamilial and interfamilial variability in 23 Italian pedigrees. *Am J Med Genet Part A* 164A:3010–3020.
- Castori M, Morlino S, Celletti C, Ghibellini G, Bruschini M, Grammatico P, Blundo C, Camerota F. 2013. Re-writing the natural history of pain and related symptoms in the joint hypermobility syndrome/Ehlers–Danlos syndrome, hypermobility type. *Am J Med Genet Part A* 161A:2989–3004.
- Castori M, Sperduti I, Celletti C, Camerota F, Grammatico P. 2011. Symptom and joint mobility progression in the joint hypermobility syndrome (Ehlers–Danlos syndrome, hypermobility type). *Clin Exp Rheumatol* 29:998–1005.
- Castori M. 2016. Pain in Ehlers–Danlos syndromes: Manifestations, therapeutic strategies and future perspectives. *Expert Opin Orphan Drugs* 4:1145–1158.
- Cazzato D, Castori M, Lombardi R, Caravello F, Dalla Bella E, Petrucci A, Grammatico P, Dordoni C, Colombi M, Lauria G. 2016. Small fiber neuropathy is a common feature of Ehlers–Danlos Syndromes. *Neurology* 87:155–159.
- Chopra P, Hamonet C, Brock I, Gompel A, Bulbena A, Francomano C. 2017. Pain management in Ehlers Danlos syndrome. *Am J Med Genet Part C Semin Med Genet* (in press).
- Ciaccio C, Dordoni C, Ritelli M, Colombi M. 2016. Koolen-de Vries syndrome: Clinical report of an adult and literature review. *Cytogenet Genome Res* 150:40–45.
- Colombi M, Dordoni C, Chiarelli N, Ritelli M. 2015. Differential diagnosis and diagnostic flow chart of joint hypermobility syndrome/Ehlers–Danlos syndrome hypermobility type compared to other heritable connective tissue disorders. *Am J Med Genet C Semin Med Genet Part C* 169C:6–22.
- De Coster PJ, Van den Berghe LI, Martens LC. 2005. Generalized joint hypermobility and temporomandibular disorders: Inherited connective tissue disease as a model with maximum expression. *J Orofac Pain* 19:47–57.
- de Kort LM, Verhulst JA, Engelbert RH, Uiterwaal CS, de Jong TP. 2003. Lower urinary tract dysfunction in children with generalized hypermobility of joints. *J Urol* 170:1971–1974.
- Detweiler S, Thacker MM, Hopkins E, Conway L, Gripp KW. 2013. Orthopedic manifestations

- and implications for individuals with Costello syndrome. *Am J Med Genet Part A* 161A:1940–1949.
- Di Stefano G, Celletti C, Baron R, Castori M, Di Franco M, La Cesa S, Leone C, Pepe A, Cruccu G, Truini A, Camerota F. 2016. Central sensitization as the mechanism underlying pain in joint hypermobility syndrome/Ehlers–Danlos syndrome, hypermobility type. *Eur J Pain* 20:1319–1325.
- Dolan AL, Hart DJ, Doyle DV, Grahame R, Spector TD. 2003. The relationship of joint hypermobility, bone mineral density, and osteoarthritis in the general population: The Chingford study. *J Rheumatol* 30:799–803.
- Donkervoort S, Bonnemann CG, Loeys B, Jungbluth H, Voermans NC. 2015. The neuromuscular differential diagnosis of joint hypermobility. *Am J Med Genet C Semin Med Genet Part C* 169C:23–42.
- Galli M, Cimolin V, Rigoldi C, Pau M, Costici P, Albertini G. 2014. The effects of low arched feet on foot rotation during gait in children with Down syndrome. *J Intellect Disabil Res* 58:758–764.
- Ghibellini G, Brancati F, Castori M. 2015. Neurodevelopmental attributes of joint hypermobility syndrome/Ehlers–Danlos syndrome, hypermobility type: Update and perspectives. *Am J Med Genet C Semin Med Genet* 169:107–116.
- Grahame R, Bird HA, Child A. 2000. The revised (Brighton 1998) criteria for the diagnosis of benign joint hypermobility syndrome (BJHS). *J Rheumatol* 27:1777–1779.
- Groh MM, Herrera J. 2009. A comprehensive review of hip labral tears. *Curr Rev Musculoskelet Med* 2:105–117.
- Gulbahar S, Sahin E, Baydar M, Bircan C, Kizil R, Manisali M, Akalin E, Peker O. 2006. Hypermobility syndrome increases the risk for low bone mass. *Clin Rheumatol* 25:511–514.
- Hakim AJ, Grahame R. 2003. A simple questionnaire to detect hypermobility: An adjunct to the assessment of patients with diffuse musculoskeletal pain. *Int J Clin Pract* 57:163–166.
- Hasija RP, Khubchandani RP, Shenoi S. 2008. Joint hypermobility in Indian children. *Clin Exp Rheumatol* 26:146–150.
- Hennekam RC, Biesecker LG, Allanson JE, Hall JG, Opitz JM, Temple IK, Carey JC, Elements of Morphology Consortium. 2013. Elements of morphology: General terms for congenital anomalies. *Am J Med Genet Part A* 161A:2726–2733.
- Juul-Kristensen B, Røgind H, Jensen DV, Remvig L. 2007. Inter-examiner reproducibility of tests and criteria for generalized joint hypermobility and benign joint hypermobility syndrome. *Rheumatology* 46:1835–1841.
- Juul-Kristensen B, Schmedling K, Rombaut L, Lund H, Engelbert RH. 2017. Measurement properties of clinical assessment methods for classifying generalized joint hypermobility—A systematic review. *Am J Med Genet Part C Semin Med Genet* (in press).
- Kawame H, Hannibal MC, Hudgins L, Pagon RA. 1999. Phenotypic spectrum and management issues in Kabuki syndrome. *J Pediatr* 134:480–485.
- Malfait F, Belmont J, Berglund B, Black J, Bloom L, Bowen JM, Brady A, Burrows NP, Byers P, Castori M, Cohen H, Colombo M, Demirdas S, De Backer J, De Paepe A, Fournel-Gigleux S, Frank M, Francomano C, Ghali N, Giunta C, Grahame R, Hakim A, Jeunemaitre X, Johnson D, Juul-Kristensen B, Kazkaz H, Kosho T, Lavalley ME, Levy H, Mendoza-Londono R, Kapferer-Seebacher, Pepin M, Pope M, Reinstein E, Robert L, Rohrbach M, Sanders L, Sobey GJ, Van Damme T, Vandersteen A, van Mourik C, Voermans N, Wheelton N, Zschocke J, Tinkle B. 2017. The 2017 international classification of the Ehlers–Danlos syndromes. *Am J Med Genet Part C Semin Med Genet* (in press).
- Mathias CJ, Low DA, Iodice V, Owens AP, Kirbis M, Grahame R. 2011. Postural tachycardia syndrome—current experience and concepts. *Nat Rev Neurol* 8:22–34.
- Mitakides J, Tinkle B. 2017. Oral and mandibular manifestations in the Ehlers–Danlos syndromes. *Am J Med Genet Part C Semin Med Genet* (in press).
- Mohamed M, Voet M, Gardeitchik T, Morava E. 2015. *Cutis laxa*. *Adv Exp Med Biol* 802:161–184.
- Morlino S, Dordoni C, Sperduti I, Venturini M, Celletti C, Camerota F, Colombi M, Castori M. 2016. Refining patterns of joint hypermobility, habitus and orthopedic traits in joint hypermobility syndrome and Ehlers–Danlos syndrome, hypermobility type. *Am J Med Genet A* in press.
- Remvig L, Jensen DV, Ward RC. 2007. Epidemiology of general joint hypermobility and basis for the proposed criteria for benign joint hypermobility syndrome: Review of the literature. *J Rheumatol* 34:804–809.
- Rombaut L, Malfait F, De Wandele I, Taes Y, Thijs Y, De Paepe A, Calders P. 2012. Muscle mass, muscle strength, functional performance, and physical impairment in women with the hypermobility type of Ehlers–Danlos syndrome. *Arthritis Care Res* 64:1584–1592.
- Rombaut L, Scheper M, De Wandele I, De Vries J, Meeus M, Malfait F, Engelbert R, Calders P. 2015. Chronic pain in patients with the hypermobility type of Ehlers–Danlos syndrome: Evidence for generalized hyperalgesia. *Clin Rheumatol* 34:1121–1129.
- Rauen KA. 2016. Cardiofaciocutaneous syndrome. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, Bird TD, Fong CT, Mefford HC, Smith RJH, Stephens K, editors *GeneReviews*[®] [Internet]. Seattle, WA: University of Washington, Seattle.
- Samango-Sprouse CA, Stapleton EJ, Mitchell FL, Sadeghin T, Donahue TP, Gropman AL. 2014. Expanding the phenotypic profile of boys with 47,XXY: The impact of familial learning disabilities. *Am J Med Genet Part A* 164A:1464–1469.
- Saul RA, Tarleton JC. 2012. FMR1-related disorders. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, Bird TD, Ledbetter N, Mefford HC, Smith RJH, Stephens K, editors *GeneReviews*[®] [Internet]. Seattle, WA: University of Washington, Seattle. pp 1993–2016.
- Scheper MC, Juul-Kristensen B, Rombaut L, Rameckers EA, Verbunt J, Engelbert RH. 2016. Disability in adolescents and adults diagnosed with hypermobility-related disorders: A meta-analysis. *Arch Phys Med Rehabil* 97:2174–2187.
- Siemionow K, Chou D. 2014. To the occiput or not? C1–c2 ligamentous laxity in children with down syndrome. *Evid Based Spine Care J* 5:112–118.
- Sinibaldi L, Ursini G, Castori M. 2015. Psychopathological manifestations of joint hypermobility and joint hypermobility syndrome/Ehlers–Danlos syndrome, hypermobility type: The link between connective tissue and psychological distress revised. *Am J Med Genet C Semin Med Genet Part C* 169C:97–106.
- Smith TO, Jerman E, Easton V, Bacon H, Armon K, Poland F, Macgregor AJ. 2013. Do people with benign joint hypermobility syndrome (BJHS) have reduced joint proprioception? A systematic review and meta-analysis. *Rheumatol Int* 33:2709–2716.
- Sugimoto J, Shimohira M, Osawa Y, Matsubara M, Yamamoto H, Goto Y, Nonaka I. 2000. A patient with mitochondrial myopathy associated with isolated succinate dehydrogenase deficiency. *Brain Dev* 22:158–162.
- Tartaglia NR, Howell S, Sutherland A, Wilson R, Wilson L. 2010. A review of trisomy X (47,XXX). *Orphanet J Rare Dis* 5:8.
- Tinkle BT, Bird HA, Grahame R, Lavalley M, Levy HP, Silience D. 2009. The lack of clinical distinction between the hypermobility type of Ehlers–Danlos syndrome and the joint hypermobility syndrome (a.k.a. hypermobility syndrome). *Am J Med Genet Part A* 149A:2368–2370.
- Tinkle BT. 2010. Joint hypermobility handbook—A guide for the issues & management of Ehlers–Danlos syndrome hypermobility type and the hypermobility syndrome. Greens Fork, Indiana: Left Paw Press.
- Tinkle B, Castori M, Berglund B, Cohen H, Grahame R, Kazkaz H, Levy H. 2017. Hypermobile Ehlers–Danlos syndrome (a.k.a. Ehlers–Danlos syndrome type III and Ehlers–Danlos syndrome hypermobility type): Clinical description, and natural history. *Am J Med Genet Part C Semin Med Genet* (in press).
- Vegunta S, Cotugno R, Williamson A, Grebe TA. 2015. Chronic pain in Noonan Syndrome: A previously unreported but common symptom. *Am J Med Genet Part A* 167A:2998–3005.
- Veit-Rubin N, Cartwright R, Singh AU, Digesu GA, Fernando R, Khullar V. 2016. Association between joint hypermobility and pelvic organ prolapse in women: A systematic review and meta-analysis. *Int Urogynecol J* 27:1469–1478.
- Zarate N, Farmer AD, Grahame R, Mohammed SD, Knowles CH, Scott SM, Aziz Q. 2010. Unexplained gastrointestinal symptoms and joint hypermobility: Is connective tissue the missing link? *Neurogastroenterol Motil* 22:252–e78.