# A R T I C L E

# Neurodevelopmental Attributes of Joint Hypermobility Syndrome/Ehlers–Danlos Syndrome, Hypermobility Type:
## Update and Perspectives

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In the last decade, increasing attention has been devoted to the extra-articular and extra-cutaneous manifestations of joint hypermobility syndrome, also termed Ehlers–Danlos syndrome, hypermobility type (i.e., JHS/EDS-HT). Despite the fact that the current diagnostic criteria for both disorders remain focused on joint hypermobility, musculoskeletal pain and skin changes, medical practice and research have started investigating a wide spectrum of visceral, neurological and developmental complications, which represent major burdens for affected individuals. In particular, children with generalized joint hypermobility often present with various neurodevelopmental issues and can be referred for neurological consultation. It is common that investigations in these patients yield negative or inconsistent results, eventually leading to the exclusion of any structural neurological or muscle disorder. In the context of specialized clinics for connective tissue disorders, a clear relationship between generalized joint hypermobility and a characteristic neurodevelopmental profile affecting coordination is emerging. The clinical features of these patients tend to overlap with those of developmental coordination disorder and can be associated with learning and other disabilities. Physical and psychological consequences of these additional difficulties add to the chief manifestations of the pre-existing connective tissue disorder, affecting the well-being and development of children and their families. In this review, particular attention is devoted to the nature of the link between joint hypermobility, coordination difficulties and neurodevelopmental issues in children. Presumed pathogenesis and management issues are explored in order to attract more attention on this association and nurture future clinical research. © 2015 Wiley Periodicals, Inc.

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## INTRODUCTION

Joint hypermobility syndrome (JHS) and Ehlers–Danlos syndrome (EDS), hypermobility type (EDS-HT) are clinically overlapping connective tissue disorders chiefly featuring generalized joint hypermobility (gJHM), musculoskeletal pain and minor skin features. Although JHS and EDS-HT are recognized by different sets of diagnostic criteria (i.e., Brighton criteria for JHS and Villefranche criteria for EDS-HT) [Beighton et al., 1998; Grahame et al., 2000], their distinction appears mostly academic and many experts consider the two syndromes the same clinical entity (i.e., JHS/EDS-HT) [Tinkle et al., 2009]. Probably, the reasons for the existence of two sets of criteria lay on the lack of confirmatory molecular test, on the protean natural

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history of JHS/EDS-HT, and on the different background and expertise of the medical specialists originally involved in the characterization of JHS and EDS-HT. In our experience, extended family investigations often reveal affected family members showing an attenuated age-dependent progression from EDS-HT to JHS through a mid-life coexistence of both phenotypes, with other relatives possibly presenting a- or oligo-symptomatic gJHM only [Castori et al., 2014]. This intrafamilial variability from gJHM to JHS and EDS-HT supports the knowledge that JHS/EDS-HT is the most common syndromic form of gJHM in humans.

The clinical variability of JHS/EDS-HT is not simplistically explained by the complementary nature of Villefranche and Brighton criteria. In fact, a wide range of extra-cutaneous and extra-articular features, such as reduced bone mass [Gulbahar et al., 2006], chronic fatigue [Voermans et al., 2010], sleep disturbance [Guilleminault et al., 2013], functional gastrointestinal disorders [Zarate et al., 2010] and cardiovascular dysautonomia [De Wandele et al., 2014], are very common in JHS/EDS-HT, but cannot be used for syndrome recognition due to the lack of updated diagnostic criteria. These ancillary features tend to present in an age-dependent pattern adding complexity to the characterization of these syndromes [Castori et al., 2013a]. Accordingly, age at first ascertainment of JHS/EDS-HT significantly varies with different core manifestations in adults and children. While early literature was mainly focused on adult manifestations of JHS/EDS-HT, Adib et al. [2005] presented data on more than 100 children reportedly affected by JHS/EDS-HT and described an unexpectedly high rate of impaired coordination. JHS/EDS-HT children were described as "clumsy". More explicitly, the works by Kirby et al. define the motor difficulties as typical of "developmental coordination disorder" (DCD) noting a rough overlap between JHS/EDS-HT and DCD in terms of motor attributes [Kirby et al., 2005; Kirby and Davies, 2007].

DCD is one of the commonly accepted definitions of developmental dyspraxia, intended as "the inability to utilize voluntary motor abilities effectively in all aspects of life from play to structured skilled tasks" and, more specifically, as "motor difficulties caused by perceptual problems, especially visual-motor and kinesthetic motor difficulties" [Gibbs et al., 2007]. A diagnosis of DCD is made by exclusion according to recognized criteria (Table I) [American Psychiatric Association, 2000], and included in the DSM-5 chapter of neurodevelopmental disorders. It is relevant that the diagnosis of DCD needs the exclusion of any other "neurologic condition affecting movement (e.g., cerebral palsy, muscular dystrophy or a degenerative disorder)", but does not consider other possible mechanisms leading to impaired coordination. Recent works highlight defective proprioception in children and adults with gJHM especially at lower limbs [Smith et al., 2013], while this feature may be linked to a wide variety of clinical manifestations [Castori et al., 2013a,b]. These findings and clinical practice support a developmental (rather than degenerative) nature of impaired proprioception in gJHM/JHS/EDS-HT and suggest that the relationship with DCD may lie on poor proprioception in hypermobile children. Nevertheless, the body of evidence supporting this presumed pathogenesis is fragmented and not readily available to most practitioners.

In this work, we review the literature in order to organize previous data and offer some practical points for the management of the JHS/EDS-HT child with the additional diagnosis of DCD or other developmental disabilities.

## LITERATURE REVIEW

A PubMed search was carried out with the following research string: ["Ehlers–Danlos syndrome" OR EDS OR "joint hypermobility"] AND children AND [balance OR coordination OR development]. In addition, citation lists of the papers retrieved were scrutinized for further references. The pediatric literature over time has accumulated scattered reports on motor and coordination disorders in gJHM and JHS/EDS-HT as reported below. Other co-morbidities (such as speech and language disorders, attention disorders, sensory processing and psychological disorders) often accompany DCD in unselected cohorts and, hence, it is reasonable that they can also affect with a higher frequency patients with gJHM and JHS/EDS-HT. Thirteen studies reported positive correlation [Hunter et al., 1998; Jaffe et al., 1988; Tirosh et al., 1991; Adib et al., 2005; Kirby et al., 2005; Kirby and Davies, 2007; Schubert-Hjalmarsson et al., 2012; Falkerslev et al., 2013; Jelsma et al., 2013; Morrison et al., 2013; Castori et al., 2014; Easton et al., 2014] and three failed to identify an association [Davidovitch et al., 1994; Engelbert et al., 2005; Juul-Kristensen et al., 2009]. Clark and Khattab [2012] reviewed five out of these 16 papers.

In summary, impaired coordination associated with gJHM mostly manifests with delay in attainment of autonomous walking, lack of crawling, clumsiness, and low performances in both fine and gross motor activities. Speech, and language disorders and writing skills can be also affected with an impact on academic performances, which may cause the wrong attribution of cognitive/global delay and learning disabilities by practitioners and educators.

### Positive Studies

The influences of gJHM on development of motor competence were first noted by Benady and Ivanans [1978]; who described nine children (five females and four males) with selective motor delay in combination with gJHM. Shared features included delayed attainment of sitting and walking alone in the absence of clinical signs for any muscle, neurological and overt connective tissue disorder. Additional common findings comprised muscle hypotonia, congenital dislocation of the hip, gJHM in one or more first-degree relative and positive family history for "mother late walker". All

**TABLE I. Definition of Developmental Coordination Disorder (DCD) According to the DSM-5**

Diagnostic criteria for DCD

Acquisition and execution of coordinated motor skills are below what would be expected at a given chronological age and opportunity for skill learning and use; difficulties are manifested as clumsiness (e.g., dropping or bumping into objects) and as slowness and inaccuracy of performance of motor skills (e.g., catching an object, using scissors, handwriting, riding a bike or participating in sports)

The motor skills deficits significantly or persistently interferes with activities of daily living appropriated to the chronologic age (e.g. self-care and self-maintenance) and impacts academic/school productivity, prevocational and vocational activities and play

The onset of symptoms is in the early developmental period

The motor skills deficits cannot be better explained by intellectual disability or visual impairment and are not attributable to a neurologic condition affecting movement (e.g., cerebral palsy, muscular dystrophy or a degenerative disorder)

patients subsequently developed well. The authors identified the following four "criteria" for defining this subset of patients among children referred for suspected developmental delay: (i) gJHM best appreciable on hands; (ii) discrepancy between the delay in attainment of motor competences and roughly normal intellectual development; (iii) increased range of motion of joints with normal muscle power, tendon reflexes and resistance to passive flexion; and (iv) presence of gJHM in a parent, sibling or both.

In 1988, Jaffe et al. studied 717 children (365 boys and 352 girls), aged between 8 and 14 months and recruited from various well baby clinics, for scrutinizing relationships between joint mobility and motor development. They found that odds of developmental motor delay are higher in presence of gJHM and increases with the increasing number of hypermobile joints (mainly, foot dorsiflexion, hip abduction and elbow extension). They also showed that development milestone attainment normalized in over 83% of the children who did not display anymore excessive laxity within a 6-month period, while it normalized only in 54.5% of those who did not improve in gJHM. gJHM of examined children also associated with bottom shuffling at young age in other family members (e.g. parents and siblings). The same group conducted another study on 59 infants aged 18 months subdivided in three groups including 20 individuals with both gJHM and motor delays, 19 with gJHM but normal motor development and 20 normally developing controls

[Tirosh et al., 1991]. gJHM was measured as previously described [Jaffe et al., 1988]. The groups were reassessed at 3.5 and 5 years, and compared for gross and fine motor competence. Children originally presenting with both gJHM and motor delay showed more significant gross motor dysfunctions than the other two groups, while less differences were noted in fine motor skills. The authors concluded that, among toddlers ascertained for motor delay, those showing gJHM had a less favorable motor outcome.

A questionnaire study administered to 414 members of the UK nationwide EDS support group for hearing, voice, speech and swallowing difficulties in all types of EDS found a 48% rate of speech and language difficulties in pre- and school age children with EDS and specifically language development delays were noted [Hunter et al., 1998]. Adib et al. [2005] carried out a cross-sectional study on 125 children (64 females and 61 males), aged 3–17 years, with JHS [defined as "joint hypermobility diagnosed by a consultant pediatric rheumatologist and adverse symptom(s) related to the hypermobile joint(s)"]. They found an increase for various developmental issues, including clumsiness (48%), poor coordination (36%), learning difficulties (14%), dyspraxia (7%) and dyslexia (2%). Concerning pertinent clinical features on examination, they also found weakness and muscle wasting in 39% and 26% of patients, respectively.

In a couple of questionnaire studies, Kirby and Davies [2007] and Kirby et al. [2005] investigated the clinical overlap

between JHS/EDS-HT (Brighton criteria) and DCD. The first work consisted in an interview of 68 children with JHS/EDS-HT and 58 children with DCD concerning various motor coordination activities. No significant differences were noted between the JHS/EDS-HT and DCD groups, except more severe difficulties in writing, reading and ball skills in the latter group. The authors concluded that the impairment in acquisition of motor competence is roughly comparable between children diagnosed with DCD and JHS/EDS-HT [Kirby et al., 2005]. In another paper, Kirby and Davies [2007] interviewed 27 children with a DCD diagnosis and 27 typically developing children for a range of symptoms related to a possibly underlying JHS/EDS-HT diagnosis (Brighton criteria) including autonomic nervous system symptoms. They found that the rate of JHS/EDS-HT symptoms was 37% in children with DCD compared to 7.4% in typically developing children.

A non-random association between gJHM and DCD has been reinforced by a more recent work, comparing 36 DCD and 352 typically developing children, aged 3–16 years, for degree of JHM (Beighton score) and motor performance (Movement Assessment Battery for Children) [Jelsma et al., 2013]. The mean Beighton score in the DCD group was 5.0 compared to 2.6 in the control group and there was a negative correlation between Beighton score and degree of motor competence. Having observed a high rate of positive Beighton score and gJHM in the pediatric population the authors also

proposed that 7 (out of 9) should be a more appropriate cut-off for defining gJHM in children. The Movement Assessment Battery for Children (second edition) was used by another research group for investigating motor competence in 119 children (5–16 years) with gJHM [Easton et al., 2014]. Motor competence was low (≤15th centile) in 32.8% of patients and very low (≤5th centile) in 18.4%. Motor difficulties were more common in males and in younger subjects.

In recent work exploring intra-familial and interfamilial variability in 23 Italian pedigrees with JHS/EDS-HT, among 20 children with an age comprised between 2 and 16 years, 55% showed the criteria for DCD [Castori et al., 2014]. In the same study, 8 out of 23 (34.8%) JHS/EDS-HT patients also presented with attention deficit (and hyperactivity) disorder [Castori, 2014]. Three additional studies reported marginal data concerning the clinical overlap between gJHM and coordination impairment. Schubert-Hjalmarsson et al. [2012] and Falkerslev et al., [2013] found reduced balance in children compared to healthy controls, while Morrison et al. [2013] described lower limb hypermobility and *pes planus* foot posture in 14 DCD children and considered these features to be major contributors to abnormal gait typical of this condition.

### Negative Studies

Among the studies retrieved during the literature review three reported a lack of correlation between DCD and gJHM or JHS/EDS-HT. Davidovitch et al. [1994] compared a population of 320 primary school children and 110 first-grade children from special education program for presence/absence of gJHM by using six signs and neurodevelopmental attributes by testing sequential processing, word retrieval, coordination and visual-motor integration competences. No significant difference was registered and gJHM appeared less represented in children from a special education program. Engelbert et al. [2005] carried out a research on 72 children (16 aged 1 to

2.5 years, 56 aged 4 to 12 years) and did not find a relationship between the degree of JHM according to the Bulbena score and delay in motor development in both subgroups. Finally, in a cross-sectional study of 524 children from 10 public schools of Denmark, 29% had a Beighton score of ≥4, 19% a score of ≥5, 10% a score of ≥6 and 9% received a diagnosis of JHS/EDS-HT (Brighton criteria). No difference was noted concerning duration of physical activities between children with and without gJHM, while motor competence appeared higher in those with a Beighton score of ≥5 and 6 [Juul-Kristensen et al., 2009].

## ILLUSTRATIVE CASE

This boy came to our attention for clinical genetic evaluation of his neuro-developmental profile. He was a 12 and 5/12-year-old boy, second of three siblings. Early motor development was characterized by typical timing for attainment of sitting and crawling, but delayed autonomous walking, which was attained at 24 months. He was always considered clumsy with recurrent falls and low performance in most physical and coordination activities. These problems were originally attributed to bilateral hip dislocations which needed cast immobilization and subsequent surgical reduction at the right leg at 5 years. Limping persisted and became painful until a diagnosis of bilateral osteonecrosis of the femoral heads was made at 6 years. However, limitations of motor and coordination skills were not restricted to the lower limbs. Over the years, he underwent many neurological assessments resulting in a series of diagnosis including dyspraxia, dyslexia, dyscalculia, dysgraphia and oculomotor dyspraxia, which significantly affected his academic performance. At 11 years of age, concurrent cognitive impairment was ruled out by IQ assessment (WISCH III scale was normal, i.e., verbal IQ 104, performance IQ 99, total IQ 102). However, additional memory and attention issues transitory in nature affected his academic performances. The patient underwent a number

of pediatric neurological examinations noting gJHM and hypotonia with normal muscle power, normal tendon reflexes and creatin kinase plasma levels. Nevertheless, an electromyography, performed at 7 years of age, revealed mild and unspecific myopathic changes, prompting muscle biopsy. This investigation showed increased variation in fiber diameter with slight preponderance of type I fibers; histochemical and enzyme-histochemical staining and morphometric study were negative for congenital myopathy or dystrophy; collagen VI staining was present in both endo- and perimysium with normal distribution pattern and intensity. Muscle MRI of upper and lower limbs was negative for any significant change, as well as brain MRI. He also reported easy bruising and delayed wound healing, recurrent joint pain at fingers, wrists, knees, hips, neck and lumbar spine, myalgias, headache, fatigue, recurrent abdominal pain and chronic diarrhea.
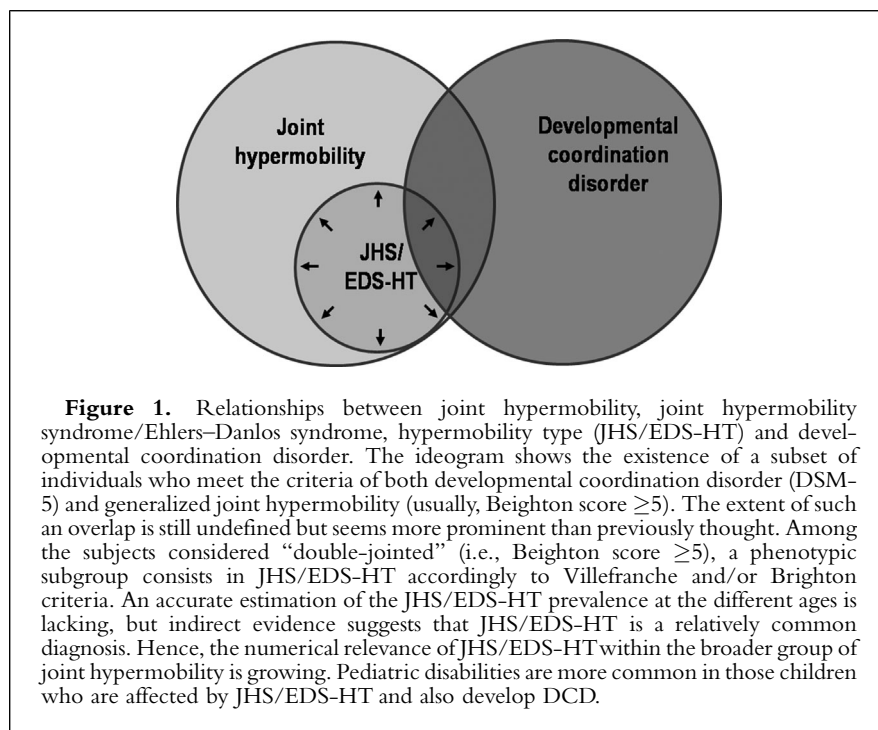
At examination, he showed normal anthropometrics with dolichostenomelia (upper arms span/height ratio 1.051) and relative macrocephaly, Beighton score 5/9, gJHM particularly appreciable at hands and spine, mild scoliosis, right *cubitus valgus*, bilateral *hallux* and *genu valgus*, soft, thin and velvety skin, ecchymoses on the left leg, dystrophic scarring at the site of muscle biopsy with fat herniation, *keratosis pilaris*, leukonychia, blue *sclerae*, hypoplastic lingual *frenulum*, generalized mild hypotonia, shuffling gait and hoarse voice. Contractures or reduced muscle power were absent. Total body radiographs excluded features of bone dysplasia. Heart ultrasound resulted negative. Bone mineral density test showed osteopenia at lumbar spine and femoral head. Fiber laryngoscopy showed incomplete opposition of the vocal cords for nodular deformation of their anterior aspects. Given the presence of the combination of gJHM with bilateral hip dislocation and unspecific myopathic changes, differential diagnosis with EDS, arthrochalasia type [Beighton et al., 1998] and the recently defined myopathy/EDS overlap due to *COL12A1* mutations [Hicks et al.,

2014; Zou et al., 2014] was carried out. Molecular testing excluded pathogenic mutations in *COL1A1*, *COL1A2* and *COL12A1*.

The extended family study, demonstrated that the mother of the patient showed a similar myopathic pattern at electromyography. At 40 years of age, she also showed Beighton score 5/9, recurrent arthralgias at most joints and entire spine, myalgias, temporomandibular joint dysfunction with recurrent blocks, thoracic hyperlordosis, lumbar hyperkyphosis, mild scoliosis, bilateral *cubitus*, *genu* and *hallux valgus*, a history of congenital hip dislocation and recurrent strains of the heels, broad base gait, osteopenia at bone mineral density test, soft skin, *keratosis pilaris*, hypoplastic lingual *frenulum*, blue *sclerae*, and trivial tricuspidal and mitral insufficiency at heart ultrasound. The older and younger sisters of the proband were reportedly affected by gJHM and congenital hip dislocation. Once excluded any other muscle, bone and (soft) connective tissue disorder, the default diagnosis of JHS/EDS-HT was established in this family according to combination of Villefranche (proband, mother) and Brighton (mother) criteria.

## DISCUSSION

Collectively, the sparse literature available suggests a non-casual association between gJHM and impaired motor coordination, which corresponds to the criteria for DCD in children. The reason(s) for such an overlap still remain(s) undetermined. It is now known that most children with DCD are also hypermobile according to the Beighton score and that a proportion of hypermobile children suffer of dyspraxia and other coordination impairments. JHS/EDS-HT is probably the most common syndromic diagnosis for children with symptomatic gJHM [Tofts et al., 2009]. Therefore, among hypermobile children with DCD, there is a subgroup also matiching the JHS/EDS-HT criteria (Fig. 1), although the phenotypic overall still needs to be defined in details. Furthermore, the clinical manifestations of JHS/EDS-



**Figure 1.** Relationships between joint hypermobility, joint hypermobility syndrome/Ehlers–Danlos syndrome, hypermobility type (JHS/EDS-HT) and developmental coordination disorder. The ideogram shows the existence of a subset of individuals who meet the criteria of both developmental coordination disorder (DSM-5) and generalized joint hypermobility (usually, Beighton score ≥5). The extent of such an overlap is still undefined but seems more prominent than previously thought. Among the subjects considered "double-jointed" (i.e., Beighton score ≥5), a phenotypic subgroup consists in JHS/EDS-HT accordingly to Villefranche and/or Brighton criteria. An accurate estimation of the JHS/EDS-HT prevalence at the different ages is lacking, but indirect evidence suggests that JHS/EDS-HT is a relatively common diagnosis. Hence, the numerical relevance of JHS/EDS-HT within the broader group of joint hypermobility is growing. Pediatric disabilities are more common in those children who are affected by JHS/EDS-HT and also develop DCD.

HT are growing and actually blur with those of gJHM, especially among children who typically present more joint laxity than adults. Then, DCD may be a possible independent outcome of gJHM regardless of the background syndromic/non-syndromic diagnosis, or rather it may predict the onset of other JHS/EDS-HT manifestations.

In Figure 1, JHS/EDS-HT is depicted as the only phenotypic subgroup of gJHM. However, practice tells us that the same neurodevelopmental characteristics can manifest in hereditary connective tissue disorders presenting with gJHM, such as classic EDS, Marfan syndrome and related disorders. Hence, the epidemiological and clinical relevance of the link between gJHM and DCD may extend beyond the commonly encountered clumsy child with gJHM (with or without JHS/EDS-HT) to the many other rare hereditary connective tissue disorders for which JHS/EDS-HT likely represents a biopathological model [Castori et al., 2013a]. As DCD can often associate with various learning deficits, understanding the link between gJHM and these pediatric disabilities could help in better evaluating and, hopefully, treating the neurodevelopmental manifestations

of hereditary connective tissue disorders.

## Limitations of Reviewed Articles

Besides the epidemiological relationship between impaired coordination and gJHM, it is difficult to compare the reported published studies because of an overt methodological heterogeneity, especially concerning the evaluation of joint motion. A similar conclusion was reached by the authors of a previous review [Clarks and Khattab, 2012]. In particular, four studies used non-standardized methods [Benady and Ivanans, 1978; Jaffe et al., 1988; Tirosh et al., 1991; Davidovitch et al., 1994], seven applied the Beighton score [Adib et al., 2005; Kirby et al., 2005; Kirby and Davies, 2007; Juul-Kristensen et al., 2009; Falkerslev et al., 2013; Jelsma et al., 2013; Castori et al., 2014], one the Bulbena score or Del Mar criteria [Engelbert et al., 2005; Schubert-Hjalmasson et al., 2012] and one the Lower Limb Assessment score [Morrison et al., 2013]. In the remaining two, no detail was provided concerning the assessment of gJHM [Hunter et al., 1998; Easton et al., 2014]. Among the eight works investigating subjects with syndromic

gJHM, the terms benign joint hyper-mobility syndrome, JHS, hypermobility syndrome and EDS-HT were used presumably as synonyms, with the exception of the work by Hunter et al. [1998] in which patients with different clinical subtypes of EDS were included. Concerning the diagnosis of JHS/EDS-HT (and synonyms) the application of the Brighton and/or Villefranche criteria were declared in two [Juul-Kristensen et al., 2009; Castori et al., 2014], presumed in one [Adib et al., 2005], and not specified in two [Schubert-Hjalmasson et al., 2012; Easton et al., 2014]. The three remaining papers consisted of questionnaires sent to members of national patients' associations related to JHS and EDS; therefore, presumably, the children were diagnosed with one of these syndromes [Hunter et al., 1998; Kirby et al., 2005; Kirby and Davies, 2007].

The spectrum of coordination impairments in gJHM or JHS/EDS-HT was grouped under the term DCD in six papers [Kirby et al., 2005; Kirby and Davies, 2007; Morrison et al., 2013; Jelsma et al., 2013; Castori et al., 2014; Easton et al., 2014]. In the remaining eight, neurodevelopmental attributes were selectively investigated as follows: two works collected historical data only [Hunter et al., 1998; Abid et al., 2005]; two checked for developmental milestones attainment, muscle tone and power, and tendon reflexes [Benady and Ivanans, 1978; Jaffe et al., 1988]; one included a dedicated neurologic examination and the administration of specific neuropsychologic tests [Davidovitch et al., 1994]; two investigated gross and fine motor competences with specific performance tests [Tirosh et al., 1991; Juul-Kristensen et al., 2009]; one tested balance with the Bruininks-Oseretsky test [Schubert-Hjalmasson et al., 2012], and another one with gait analysis [Falkerslev et al., 2013].

The extreme heterogeneity in the definition of the two partially overlapping clinical categories in Figure 1 hampers the possible generalization of the data presented; howeve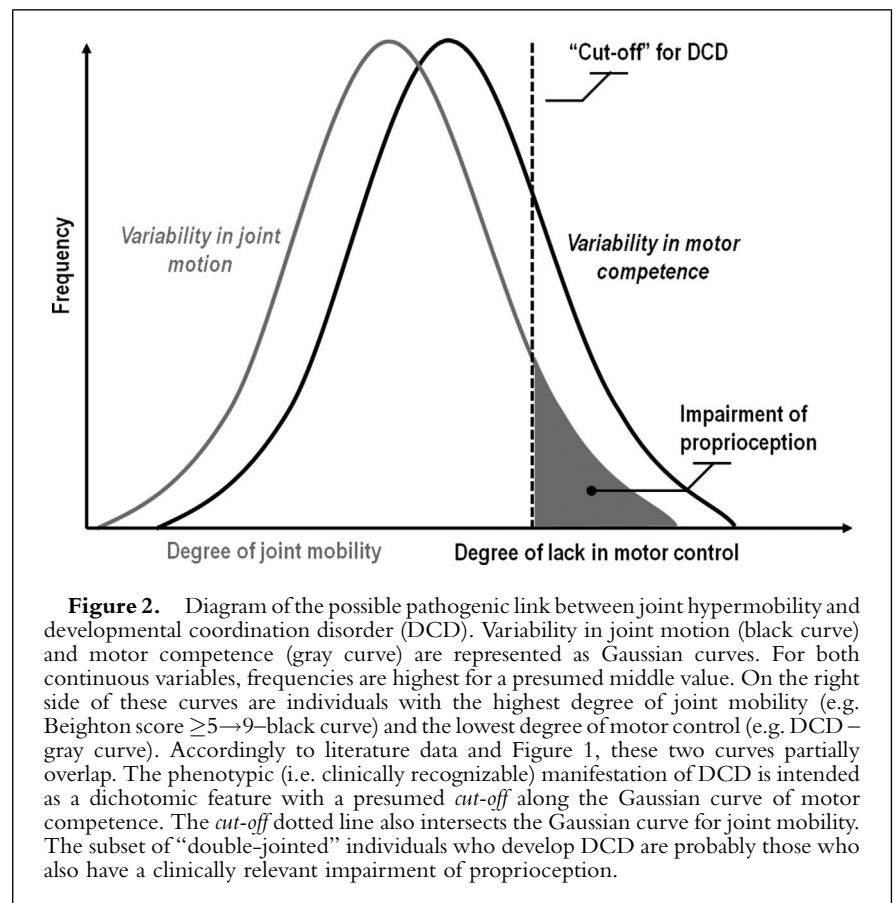r, the dyadic combination of gJHM and DCD is unlikely explained by selection biases or indirect association between relatively common phenomena. While pleiotropy may still explain the coexistence of different features affecting interconnected systems within the same genetic condition, actually, the existence of a pathogenic link between gJHM and DCD seems more reasonable in JHS/EDS-HT.

## Pathogenesis of DCD and Other Developmental Disorders in gJHM and JHS/EDS-HT

To date, deciphering the cause-effect progression underlying the link between gJHM and DCD is a difficult task. On a clinical perspective, it is undoubtedly more common to encounter "double-jointed" toddlers who progressively manifest features of DCD, than a child requiring special education who develops gJHM subsequently to the diagnosis of DCD. Hence, it is likely that gJHM pre-exists the development of DCD in most cases. As no more than 2/3 of DCD patients also show gJHM [Jelsma et al., 2013] and 55% only of JHS/EDS-HT children meet the criteria for DCD [Castori et al., 2014], ligamentous laxity should be considered a possible predisposing trait for a selected subset of DCD patients.

As many (or, perhaps, most) individuals with objective or historical gJHM are thought to develop throughout childhood without obvious signs of DCD or learning deficits, it seems likely that gJHM is not sufficient *per se* to "cause" DCD. Hence, the link between the two should be an intermediate, not obligatory phenotype, which may be represented by impaired proprioception (Fig. 2). Defective kinesthesia is a common feature in children with DCD [Clark and Khattab, 2012]. This evidence may relate to the existence of different neuropsychological subtypes in DCD [Vaivre-Douret et al., 2011], which could result from distinct, but phenotypically convergent neurophy-



**Figure 2.** Diagram of the possible pathogenic link between joint hypermobility and developmental coordination disorder (DCD). Variability in joint motion (black curve) and motor competence (gray curve) are represented as Gaussian curves. For both continuous variables, frequencies are highest for a presumed middle value. On the right side of these curves are individuals with the highest degree of joint mobility (e.g. Beighton score ≥5→9–black curve) and the lowest degree of motor control (e.g. DCD – gray curve). Accordingly to literature data and Figure 1, these two curves partially overlap. The phenotypic (i.e. clinically recognizable) manifestation of DCD is intended as a dichotomic feature with a presumed *cut-off* along the Gaussian curve of motor competence. The *cut-off* dotted line also intersects the Gaussian curve for joint mobility. The subset of "double-jointed" individuals who develop DCD are probably those who also have a clinically relevant impairment of proprioception.

siopathologic pathways, one of which being poor proprioception.

Interestingly, impaired proprioception is also common in gJHM and JHS/EDS-HT, as demonstrated by various research groups showing reduced proprioceptive performance of the knees in adults and children with these conditions [Hall et al., 1995; Sahin et al., 2008; Fatoye et al., 2009; Rombaut et al., 2010; Pacey et al., 2014]. While Rombaut et al. [2010] failed to replicate this observation at the shoulders; Mallik et al. [1994] found impaired position sense at the proximal interphalangeal joints of the fingers. Poor position sense at the hands can affect fine motor skills and handwriting, and could result in poor manipulation competences and dysgraphia in the developing child. On the other hand, poor proprioception at the knee joints may trigger a different pattern of muscle activation of the lower limbs [Greenwood et al., 2011] and significantly affect balance and lateral trunk stability [Rombaut et al., 2011; Celletti et al., 2011a; Falkerslev et al., 2013], which are also jeopardized by low tone of the axial muscles and hypermobility of the spine. Balance is also affected at rest under challenge of the vestibular system, and this may be explained by vestibular deficiency and/ or insufficient proprioceptive capabilities of the neck [Iatridou et al., 2014]. The effects of an impaired vestibular system in JHS/EDS-HT could also extend to visual competences with visual tracking issues and reading disorders, as well as directly to hearing with influences on the auditory processing. Both motor and cognitive competences may be further hampered by the need of concentrating more attention on maintaining posture due to poor balance control [Rigoldi et al., 2013], with significant consequences on the capability of attending classroom tasks. Lack of attention is now considered a common feature in children with gJHM and JHS/EDS-HT, as documented by the high rate of attention deficit (and hyperactivity) disorder in these conditions [Harris, 1998; Kolda□ Doǧan et al., 2011; Shiari et al., 2013; Castori et al., 2014].

Similarly to DCD which commonly features oral apraxia, expressive and mixed expressive and receptive language disorders, speech and language development can also be affected in EDS [Arverdson and Heintskill, 2009]. Details on the pattern of language development in JHS/EDS-HT are scarce, but include language delays as well as speech disorders such as imprecise articulation, deletion of final consonants and fading of ends of phrases [Hunter et al., 1998; Adib et al., 2005; Arverdson and Heintskill, 2009]. These features can be related to hypermobility of the oral structures as well as low muscle tone and lack of muscle coordination. Voice may be equally involved, as depicted in the illustrative case. Possible contributors to speech problems comprise temporomandibular joint hypermobility/dysfunction [De Coster et al., 2005], hypoplastic lingual frenulum [Celletti et al., 2011b] leading to posterior tongue tie, laxity and hypotonia of the oral and laryngeal structures (also comprising vocal cords), and reduced proprioception feedback of oral movements [Arverdson and Heintskill, 2009]. The finding of Adib et al. [2005] that school children diagnosed JHS/EDS-HT also can present language-based learning disabilities such as dyslexia could fit processing disorders possibly linked to vestibular dysfunction [Shumway-Cook et al., 1987].

## Management Strategies

Children presenting signs of DCD or other neurodevelopmental disabilities are currently treated with highly personalized rehabilitation plans according to the presentation of the deficits, often regardless of the primary medical diagnosis. At the moment, knowledge is too sparse to support that children with DCD and gJHM or JHS/EDS-HT need a different treatment plan to improve function and neurodevelopment than those with non-syndromic DCD. Suggestions regarding the management of DCD [such as Gibbs et al., 2007], can therefore be extended to children presenting JHS/EDS-HT. Nevertheless, children with a double diagnosis of JHS/

EDS-HT and DCD need specific supports and it is reasonable that selected interventions could have beneficial effects on both disorders and treat the possible root causes of the deficits, such as improve proprioception, vestibular function, core stability and counterbalance ligament laxity and poor posture.

Treatment of chronic symptoms of JHS/EDS-HT is mostly based on anecdotal observations and expert's opinion [Castori et al., 2012]. In a 15-year-old woman, repetitive muscle vibration resulted effective for improving static balance measured by video measurement of displacements of the center of pressure [Celletti et al., 2011a]. In a small study, 15 JHS/EDS-HT adults who underwent 8-week treatment schedule of proprioception exercises were compared with 25 treatment-free patients. Proprioception exercises proved efficacious in reducing pain perception and improving occupational activities [Sahin et al., 2008]. In another pilot study on 12 JHS/EDS-HT women, a multidisciplinary rehabilitation approach consisting in both educational training (physical training, group discussion and lectures) and physical activity (home exercises for three months) improved perceived performance of daily activities, muscle strength and endurance, and reduced kinesiophobia [Bathen et al., 2013]. Although in this study, the effects of exercises to improve proprioception and adequate education regarding the management of their condition were not specifically evaluated, a similar approach could improve developmental features of impaired coordination in children with gJHM or JHS/EDS-HT.

The multisystem nature of JHS/EDS-HT should not be ignored in the treatment approach of any of its "sectional" manifestations, also including DCD and other related delays and disabilities. For example, therapy should aim in preventing the summative effect that impaired coordination and related compensatory strategies could have on the evolution of disabling symptoms, such as musculoskeletal pain and fatigue. Because of the heterogeneity of

**TABLE II. Summary of Management Issues in Families With Generalized Joint Hypermobility or Joint Hypermobility Syndrome/Ehlers–Danlos Syndrome Hypermobility Type and Developmental Coordination Disorder and/or Other Developmental Delays/Learning Disabilities**

Key points

Patients' and parents' education and counseling
    Explain prognosis
    Summarize pathophysiology of coordination disorders related to joint hypermobility
    Help locating therapeutic or academic support for proper diagnosis and treatment plan
    Illustrate common compensatory strategies for both patient(s) and relatives
Promote regular physical activity
    Consider patient's inclinations and desires
    Promote activities with beneficial effects on proprioception (e.g., horse riding and playground activities)
    Discourage contact sports and activities with high risk of joint traumas; trampoline, swings and martial arts are not *a priori* contraindicated but should be executed with caution, especially by those children with extreme joint instability (e.g., positive history for joint dislocations)
    Consider physiatric/orthopedic consultation
Improve awareness among caregivers, educators and community
    Sensitize professionals involved in patient's education through direct (e.g., meetings) and/or indirect (e.g., letters) interventions
    Collaborate with patients' associations for disseminating knowledge to other healthcare professionals and lay people
Promote integrated and pathogenesis-driven therapeutic support
    Emphasize communication between child neurologist, speech and language pathologist, optometrist, physiotherapist and occupational therapist
    Prefer sensory-integration approaches (all ages)
Consider to refer patient and/or parents to the clinical psychologist, especially in case of:
    Low self-esteem
    Lack of coping strategies
    Low compliance to or documented inefficacy of previously illustrated compensatory strategies/self-administered exercises

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symptoms and deficits and their relationship with the chronological age of the child, these children are typically evaluated by many specialists and accumulate multiple "sectorial" diagnoses during their childhood. This can have a confusing effect for families, therapists and educators and delay the establishment and prioritization of adequate support. For this reason it is important to identify the underlying medical condition (i.e., JHS/EDS-HT) that can predispose the children to develop neurodevelopmental delays/disorders and treat holistically the clinical picture. For example, as Kirby et al. [2007] suggests, while handwriting practice might be effective in other children, the extra practice could cause pain and stiffness in patients with hypermobile fingers. The same may apply for adaptation of physical activities to account for risk of injuries.

An approach for DCD treatment in children with JHS/EDS-HT is proposed in Table II. Educational interventions have a prominent role in ensuring active and informed participation of patients and families in the treatment program and in building awareness regarding the needs of affected individuals within the community and academic setting. Psychological support to enable children understanding their limitations is crucial and should not be underevaluated. Development of coping skills and self-esteem are paramount in overcoming the challenges and support these individuals to become a vibrant member of the society. Finally, active treatment should be always discussed in a multidisciplinary setting with a foresighted attention to the long-term symptomatic outcomes of impaired coordination both in daily living activities and academic environment.

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