EHLERS-**D**ANLOS **S**YNDROMES (EDS) WITH FOCUS ON THE HYPERMOBILE EDS

David Tilstra, Medical Geneticist

Amber Lieser, APRN

INTRODUCTION

The **E**hlers-**D**anlos **s**yndromes (EDS) are a group of 13 heritable connective tissue disorders. The conditions are caused by genetic changes that affect connective tissue. Each type of EDS has its own set of features with distinct diagnostic criteria. Some features are seen across all types of EDS, including joint hypermobility, skin hyperextensibility, and tissue fragility.

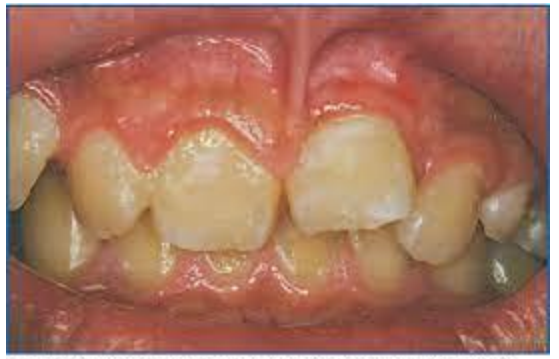
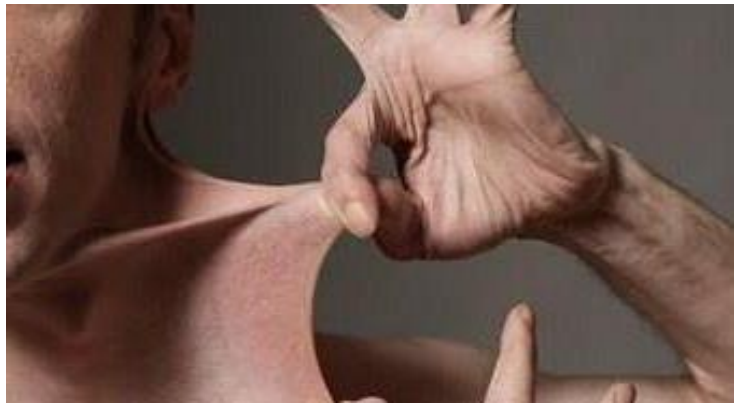
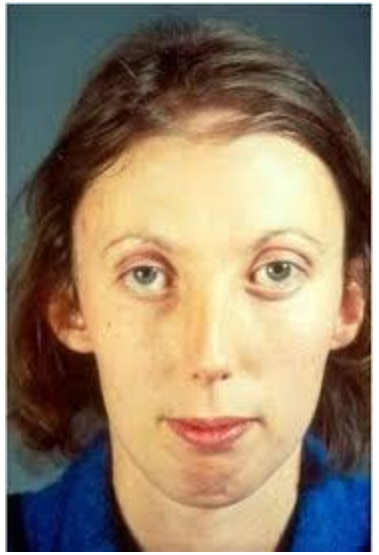


Figure 2 Frontal view of patient AA's dentition showing anterior crowding and a retained





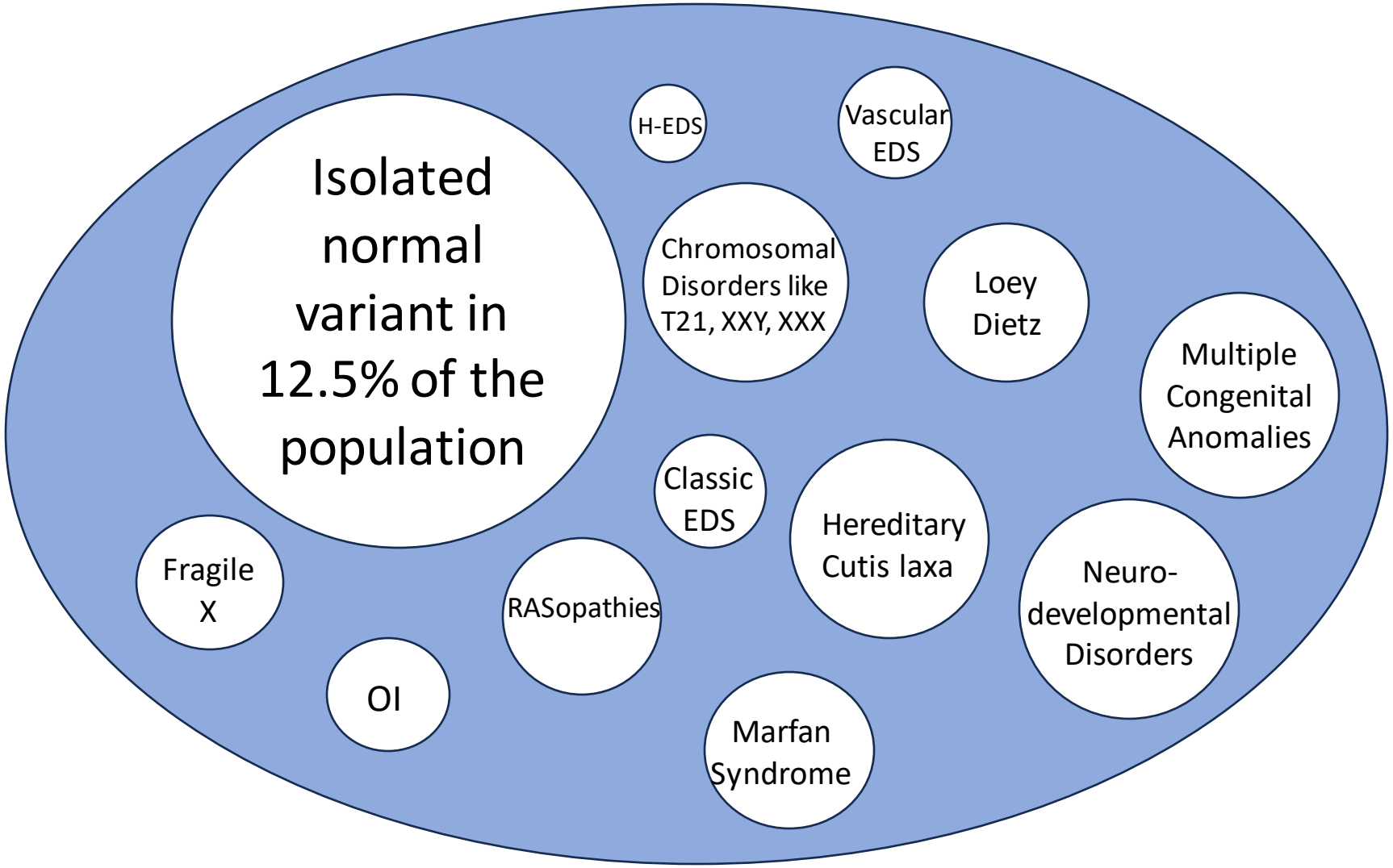
Name of EDS Subtype	***IP****	***Genetic Basis***	***Protein Involved***
Classical EDS (cEDS)	AD	Major: *COL5A1, COL5A2*	Type V collagen
		Rare: *COL1A1* c.934C>T, p.(Arg312Cys)	Type I collagen
Classical-like EDS (clEDS)	AR	*TNXB*	Tenascin XB
Cardiac-valvular EDS (cvEDS)	AR	*COL1A2* (biallelic mutations that lead to *COL1A2* NMD and absence of pro α2(I) collagen chains)	Type I collagen
Vascular EDS (vEDS)	AD	Major: *COL3A1*	Type III collagen
		Rare: *COL1A1* c.934C>T, p.(Arg312Cys) c.1720C>T, p.(Arg574Cys) c.3277C>T, p.(Arg1093Cys)	Type I collagen
Hypermobile EDS (hEDS)	AD	Unknown	Unknown
Arthrochalasia EDS (aEDS)	AD	*COL1A1, COL1A2*	Type I collagen
Dermatosparaxis EDS (dEDS)	AR	*ADAMTS2*	ADAMTS-2
Kyphoscoliotic EDS (kEDS)	AR	*PLOD1*	LH1
		FKBP14	FKBP22
Brittle cornea syndrome (BCS)	AR	*ZNF469*	ZNF469
		PRDM5	PRDM5
Spondylodysplastic EDS (spEDS)	AR	*B4GALT7*	ß4GalT7
		B3GALT6	ß3GalT6
		SLC39A13	ZIP13
Musculocontractural EDS (mcEDS)	AR	*CHST14*	D4ST1
		DSE	DSE
Myopathic EDS (mEDS)	AD or AR	*COL12A1*	Type XII collagen
Periodontal EDS (pEDS)	AD	*C1R*	C1r

Joint hypermobility- when joints have a greater range of motion than is expected or usual. The prevalence of generalized joint hypermobility in a university-aged population can be estimated at 12.5% and is not a rare finding**. A large number of people have joint hypermobility that do not result in a connective tissue disorder.** However, some people with joint hypermobility also have joint instability. Joint instability occurs when the bones of a joint aren't held in place securely. This can lead to joint subluxations, dislocations, sprains, and other injuries. Joint instability can cause both acute and chronic pain and interfere with daily life.

Joint hypermobility is observed throughout the body in most types of EDS, but hypermobility may be limited to the hands and feet in some types. Although joint hypermobility is observed across all types of EDS, not everyone with a type of EDS has joint hypermobility.

Cause of Hypermobility

A feature of more than 450 known disorders



HYPERMOBILE EHLERS-DANLOS SYNDROME (HEDS) OR TYPE 3

- hEDS is a heritable connective tissue disorder that causes generalized joint hypermobility, joint instability, and chronic pain. hEDS is also associated with a variety of other symptoms and related conditions that affect many different areas of the body.
- hEDS is the most common type of EDS, accounting for about 90% of EDS cases. hEDS is currently classified as a rare disorder and is thought to affect at least 1 in 3,100 – 5,000 people. However, the true prevalence of hEDS is not known and may be underestimated. It is thought to be the most common genetic connective tissue disorder.
- Though the cause(s) of hEDS have not been identified, the condition appears to follow an autosomal dominant inheritance pattern.
- The cause(s) of hEDS have not been identified, so there is currently no laboratory test available to diagnose hEDS. The diagnosis of hEDS is given to those who meet the **clinical diagnostic criteria** for hEDS.

CLINICAL MANIFESTATIONS OF H-EDS:

hEDS may be suspected if a person has <u>Joint hypermobility/Joint instability AND</u>:

- Mild skin hyperextensibility
- Abnormal scarring
- Connective tissue findings, examples: Bilateral piezogenic papules of the heel, Recurrent or multiple abdominal hernia, Pelvic floor, rectal, and/or uterine prolapse in children, men or nulliparous women without a history of morbid obesity or other known predisposing medical condition, Mitral valve prolapse (MVP) mild or greater based on strict echocardiographic criteria, Aortic root dilatation with Z-score >+2

<u>People with hEDS may also have- please note these isolated without above findings themselves DO NOT warrant a genetics work up:</u>

- Chronic fatigue
- Gastrointestinal issues
- Dysautonomia
- Headaches
- Mast cell activation diseases
- Chronic pain

Please note, Many people have joint hypermobility that do not have a connective tissue disorder. Isolated hypermobility, isolated pain, and isolated dysautonomia are not a reason for a genetics referral.

CLINICAL DIAGNOSTIC CRITERIA OF HEDS- MUST MEET THREE CRITERIA:

- **Criterion 1: Generalized joint hypermobility. This is completed by using the Beighton scale**
- **Criterion 2: Two or more of the following features (A, B, and C) must be present**

Feature A: at least 5 Manifestations of a connective tissue disorder

Feature B: Positive family history (one or more first-degree relatives independently meet the current diagnostic criteria for hEDS)

Feature C: Musculoskeletal complications (pain, recurrent joint dislocations, frank joint instability)

- **Criterion 3:**

*Exclusion of other heritable and acquired connective tissue disorders, including autoimmune rheumatologic conditions. This is completed by completing genetic testing to eliminate other connective tissue disorders. We also work toward eliminating rheumatic causes if not yet done.

Of note, Exclusion of alternative diagnoses that may also include joint hypermobility by means of hypotonia and/or connective tissue laxity. Alternative diagnoses and diagnostic categories include, but are not limited to:

- Neuromuscular disorders (such as myopathic EDS and Bethlem myopathy)
- Other heritable connective tissue disorders (such as other types of EDS, Loeys–Dietz syndrome, Marfan syndrome)
- Skeletal dysplasias (such as osteogenesis imperfecta)

HOW IS HEDS MANAGED?

- hEDS is managed by addressing the symptoms a person is experiencing. hEDS can cause a variety of symptoms in many different areas of the body, so people with hEDS may require multiple providers in different specialties to manage their care. Key aspects of care include physical therapy and pain management. Everyone with hEDS is different, so each person should work with their care team to develop a care plan that meets their individual needs.

•**Order to physical therapy**
Centracare Plaza has a PT Program for those with hypermobility.

•**GI issues**- Place order for GI consult if not yet working with one.
GI will treat the s/s that the patient is having according to their clinical presentation

•**Headaches**-
*Place order for headache specialty if not yet working with one
*Chiari type I manifestations may also present with headaches at times. Consider MRI of the head if headache symptoms originating in the posterior neck are persistent for patient prior to appointment with genetics
CentraCare Headache in the neurology department is aware of patients with connective tissue concerns and headaches.

•**Chronic Pain**- Referral to the pain clinic to discuss pain options
CentraCare pain clinic has providers aware of hypermobility and pain management options.

OTHER CONSIDERATIONS

- Hypermobility is a feature of more than 450 known disorders, and it is common for it to occur as an isolated normal variant. Do not label the patient with Ehlers-Danlos syndrome simply because of hypermobility.
- Neurodevelopmental disorders (NDD) frequently have hypotonia or joint hypermobility. If the patient has autism or developmental delays, Ehlers-Danlos syndrome is NOT an appropriate diagnosis. Refer for evaluation of the NDD.
- Muscle weakness, falling, movement disorders and ataxia are symptoms of other disorders and are not part of EDS; some are genetic in origin.

OTHER INDICATIONS FOR GENETIC TESTING:

- Failure to thrive or growth problems.
- Decreased or excessive muscle tone
- Birth defects/ Congenital anomalies
- Delay in developmental milestones or loss of milestones such as grasping objects, rolling over, walking, and babbling/talking
- Seizures/epilepsy
- Intellectual disability
- Autism Spectrum disorder
- Cerebral Palsy
- Significant hearing or vision problems-
- ALL congenital hearing problems
- Significant muscle or movement differences
- Child seen by multiple specialists for complex care needs.
- Cardiovascular disorder- including congenital heart defects, infantile heart failure, cardiomyopathy, channelopathies, arterial tortuosity
- Immune deficiency- recurrent severe infections
- Disorder of blood and coagulation
- Early/late puberty
- Onset of obesity before the age of 2

- If questions, comments, or concerns arise. Please call our department at 320-654-3654. If you have a case you need reviewed prior to referral call the number above and hit extension 2 to speak with our nurse. Or reach out to Amber Lieser, APRN CNP via in basket on epic.

THANK YOU

Phone: 320-645-3654

Fax: 320-654-3696

Website: https://www.centracare.com/locations/centracare-plaza-clinic-genetics/

David Tilstra, Medical Geneticist

Amber Lieser, APRN

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- Scan QR Code or click on the link below-

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https://survey.alchemer.com/s3/7645302/CME-Clinical-Updates-ENDURING-MATERIAL

- Contact carla.griffin@centracare.com with questions or for a CME transcript.