ARI Webinar:
Ehlers-Danlos Syndrome & Hypermobility Spectrum Disorders in Families with Autism

Emily L. Casanova, PhD
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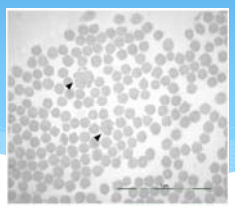
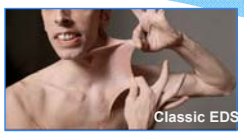
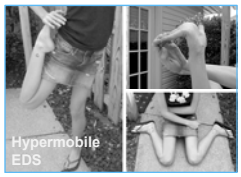


What are the Ehlers-Danlos syndromes (EDS)?





- Usually involves joint hypermobility, skin elasticity, and tissue fragility to varying degrees
- May affect internal organs (uterus, bladder, etc.)
- Often involves chronic musculoskeletal pain/instability
- Has MANY secondary issues (immune, dysautonomia, etc.)

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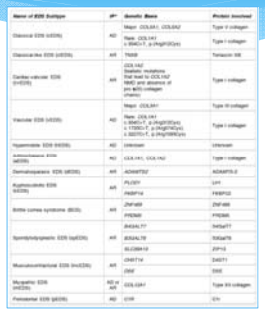
What are the Ehlers-Danlos syndromes (EDS)?

- Currently 13 recognized types of EDS
- Many associated with mutations in **collagen** or collagen pathway-related genes
- Majority of types are very rare
- **Hypermobile EDS (hEDS)** composes approx. 80% of the EDS population
- hEDS is the only type of EDS that has no known associated mutations
- **Classic EDS (cEDS)** makes up approx 20%
- Prevalence overall probably ranges 1-10:5,000 people
- This estimate is probably much higher in certain clinical populations



What is the joint hypermobility spectrum?

The Spectrum of Joint Hypermobility

Type	*Beighton score*	*Musculoskeletal involvement**	*Notes*
Asymptomatic generalized JH	Positive	Absent	
Asymptomatic peripheral JH	Usually negative	Absent	JH typically limited to hands and/or feet
Asymptomatic localized JH	Negative	Absent	JH limited to single joints or body parts
Generalized-HSD	Positive	Present	
Peripheral-HSD	Usually negative	Present	JH typically limited to hands and/or feet
Localized-HSD	Negative	Present	JH limited to single joints or body parts
Historical-HSD	Negative	Present	Historical presence of JH
hEDS	Positive	Possible	

Musculoskeletal involvement includes trauma (micro- and macrotrauma), chronic pain, disturbed proprioception, and other traits (flat feet, misaligned bones in the elbow and big toe, mild-to-moderate scoliosis, kyphosis (outward curvature) of the upper spine, lordosis (inward curvature) of the lower spine.

- JH spectrum has varying degrees of hypermobility (localized or generalized)
- Varying levels of impairment from asymptomatic to severe musculoskeletal impairment
- Can vary over the lifetime

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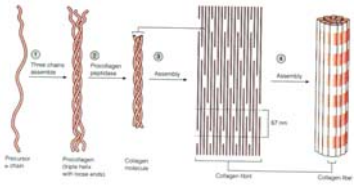
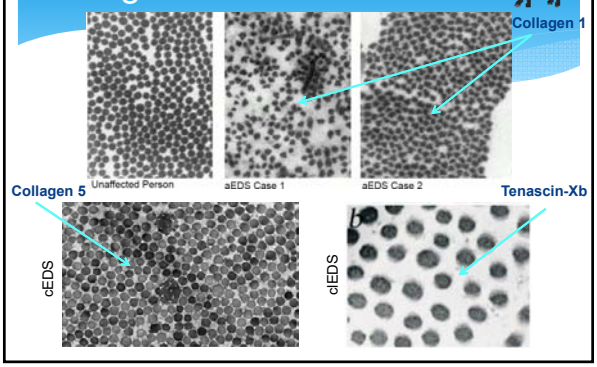
- HSDs have **significant musculoskeletal impairment** in affected joints
- Generalized HSD is essentially subclinical hEDS

Fibrillar collagens

- 28 types of collagen in humans
- 7 are *fibrillar* (I, II, III, V, XI, XXIV, XXVII)



Collagen fibers in EDS skin



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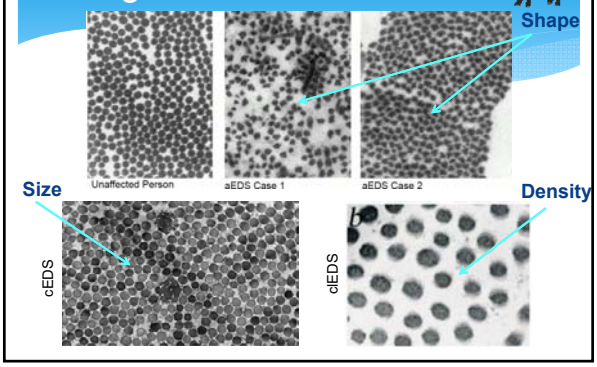


Ultrastructural differences in collagen in “unaffected” family members in hEDS families

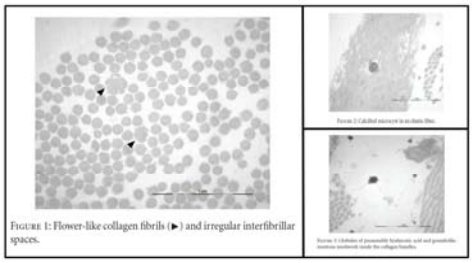
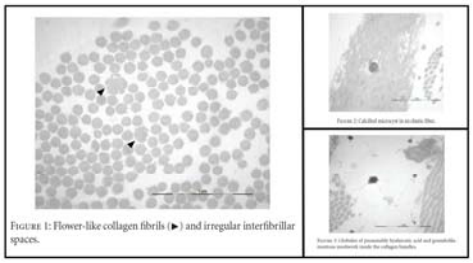


FIGURE 1: Flower-like collagen fibrils (▶) and irregular interfibrillar spaces.

The EDS Spectrum?



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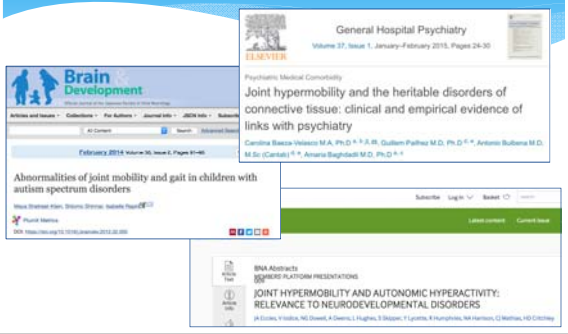
How often does autism co-occur alongside EDS?



How often does autism co-occur alongside EDS?

behavioral sciences

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Behav. Sci. 2018, 8(3), 35; https://doi.org/10.3390/bs8030035

Open Access Article

A Cohort Study Comparing Women with Autism Spectrum Disorder with and without Generalized Joint Hypermobility

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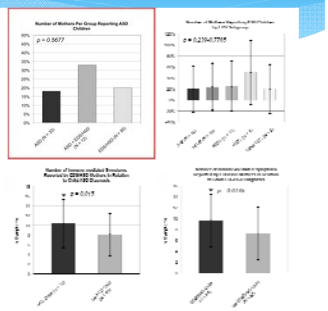
Hereditary relationship between EDS/HSD and autism

- **Mothers with EDS/HSD seem to have increased risk of having autistic children**
- Likelihood appears to be common across different forms of EDS
- EDS mothers with autistic children report more immune symptoms
- EDS mothers with EDS/HSD children also report more immune symptoms



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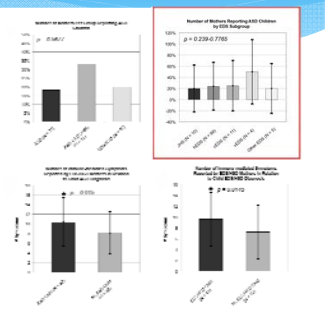

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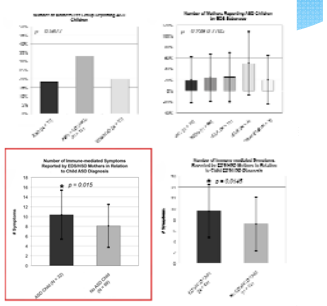

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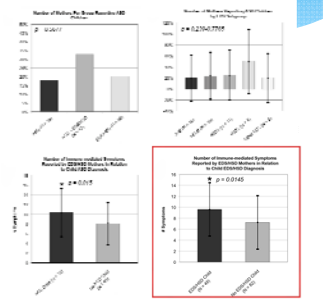
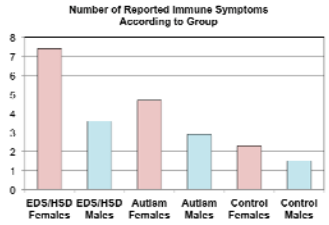


EDS, autism, and the maternal immune system

- Maternal immune activation (MIA) has been implicated in autism risk
- Changes in fetal brain gene expression during infection appear to be a protective mechanism but also disrupt normal brain development

Immune symptoms in EDS/HSD



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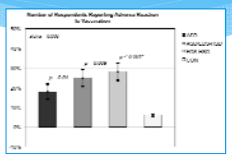
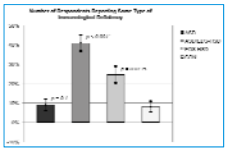
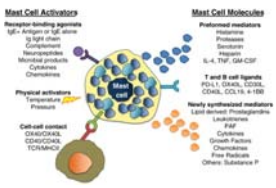




Mast Cell Activation Syndrome (MCAS)

Mast Cell Activation Disorder Symptoms
(Mast Cell Mediator Release Symptoms)

- Anaphylaxis
- Flushing of the face, neck, and chest
- Itching, +/- rash
- Hives, skin rashes
- Angioedema (swelling)
- Nasal itching and congestion
- Wheezing and shortness of breath
- Throat itching and swelling
- Headache and/or brain fog, cognitive dysfunction, anxiety, depression
- Diarrhea, nausea, vomiting, abdominal pain, bloating, gastroesophageal reflux disease (GERD)
- Bone/muscle pain, osteosclerosis, osteopenia, osteoporosis
- Light-headedness, syncope/fainting
- Rapid heart rate, chest pain
- Low blood pressure, high blood pressure at the start of a reaction, blood pressure instability
- Uterine cramps or bleeding



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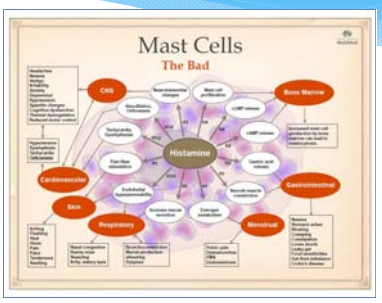
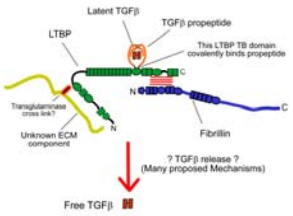


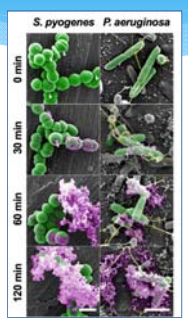
Lessons from Marfan syndrome & TGF-beta



Non-fibrillar collagen as a defense mechanism against bacterial pathogens

Contains Von Willebrand Factor (VWF) Type A domain:

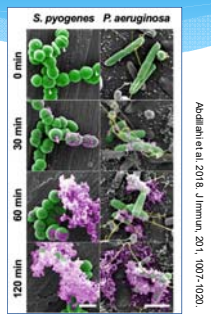
- Collagen VI
- Collagen XXII
- Collagen XXVIII



Abdillahi et al. 2018. J Immun. 201: 1007-1020.

Non-fibrillar collagen as a defense mechanism against bacterial pathogens

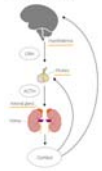
How else is collagen involved in immune system function???

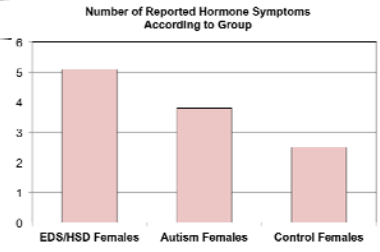


Abdallah et al. 2018. J Immun. 201. 1007-1020.

Hormonal symptoms in EDS/HSD

HPA Axis





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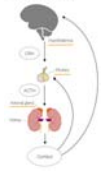
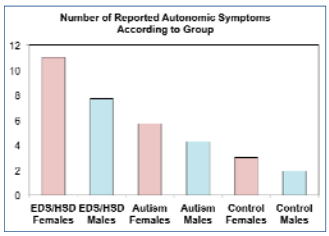


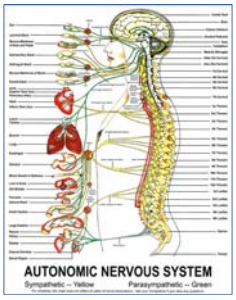
- Hirsutism
- Unusually heavy/prolonged menstruation
- Unusually painful menstruation
- Endometriosis
- Polycystic Ovary Syndrome (PCOS)

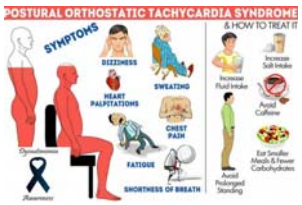
Autonomic symptoms in EDS/HSD



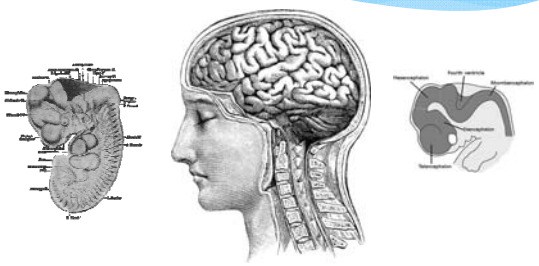
- Dizziness, vertigo, fainting
- Fatigue
- Headaches
- Gastrointestinal distress
- Shortness of breath

Postural Orthostatic Tachycardia Syndrome (POTS)





What about connective tissue in the brain?



What about connective tissue in the brain?

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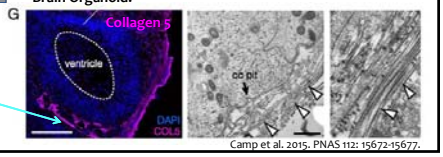
Collagen 1 Protein Expression:

Brain Organoid:



Pseudo-meninges

Camp et al. 2015. PNAS 112: 15672-15677.

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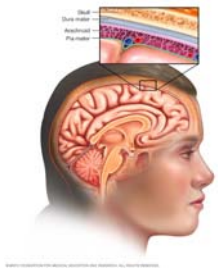

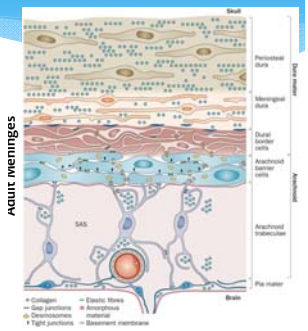

Kolias et al. 2014. Nat Rev Neurol 10, 570-578.

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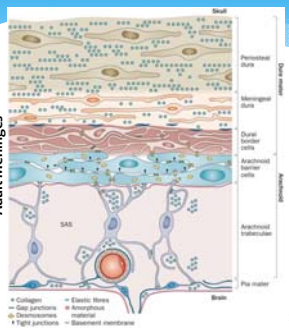
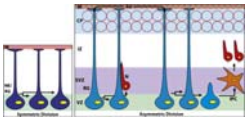


Kolias et al. 2014. Nat Rev Neurol 10, 570-578.

- **Meninges are involved:**
  - in maintaining the stem cell pool
  - orchestrating cell migration



Sockanathan & Gaiano. 2009. Cell Stem Cell 5, 455-456.

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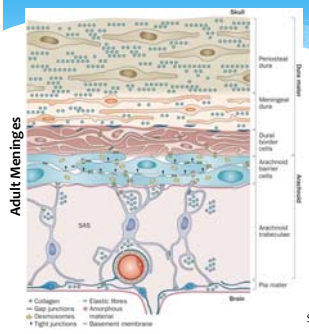
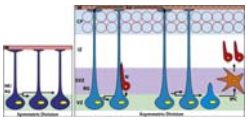


Kollas et al. 2014. Nat Rev Neurol 10, 570-578.

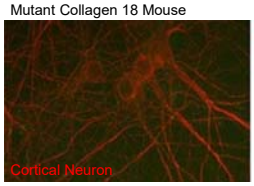
- Do **collagens** play roles in these processes?
- If so, how?



Sockanathan & Gaiano. 2009. Cell Stem Cell 5, 455-456.

What about connective tissue in the brain?

Mutant Collagen 18 Mouse



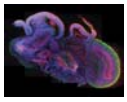
Typical Mouse

Su et al. 2016. J Cell Biol 212, 721.

** Collagen 18 is non-fibrillar*

What about connective tissue in the brain?

CBG
Max Planck Institute of Molecular Cell Biology and Genetics



Thank you!! Any questions?