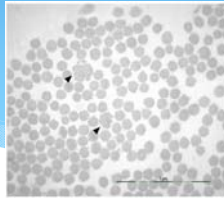


ARI Webinar: Ehlers-Danlos Syndrome & Hypermobility Spectrum Disorders in Families with Autism

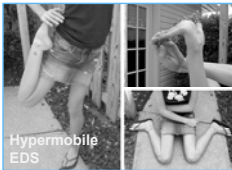
Emily L. Casanova, PhD
Dept. Biomedical Sciences
University of South Carolina
School of Medicine Greenville



What are the Ehlers-Danlos syndromes (EDS)?



Classic EDS



Hypermobile 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.)

What are the Ehlers-Danlos syndromes (EDS)?



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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

Name of EDS Syndrome	EDS Type	Gene(s)	Inheritance	Prevalence (approx)
Classical EDS (cEDS)	1	COL3A1, COL3A2, COL1A1, COL1A2	Autosomal recessive	1:7000
Hypermobility EDS (hEDS)	2	None known	Autosomal recessive	80%
Hypermobile EDS (hEDS)	3	COL5A1	Autosomal recessive	1:2500
Arterio-ectatic EDS (aEDS)	4	SMAD3	Autosomal recessive	1:10000
Atypical classical EDS (atcEDS)	5	COL4A1, COL4A2, COL4A3, COL4A4	Autosomal recessive	1:10000
Periodic paralysis EDS (ppeEDS)	6	PRKG2	Autosomal recessive	1:10000
Atypical hypermobile EDS (ahEDS)	7	COL6A1, COL6A2, COL6A3	Autosomal recessive	1:10000
Atypical classical EDS (atcEDS)	8	COL4A1, COL4A2, COL4A3, COL4A4	Autosomal recessive	1:10000
Atypical hypermobile EDS (ahEDS)	9	COL6A1, COL6A2, COL6A3	Autosomal recessive	1:10000
Atypical classical EDS (atcEDS)	10	COL4A1, COL4A2, COL4A3, COL4A4	Autosomal recessive	1:10000
Atypical hypermobile EDS (ahEDS)	11	COL6A1, COL6A2, COL6A3	Autosomal recessive	1:10000
Atypical classical EDS (atcEDS)	12	COL4A1, COL4A2, COL4A3, COL4A4	Autosomal recessive	1:10000
Atypical hypermobile EDS (ahEDS)	13	COL6A1, COL6A2, COL6A3	Autosomal recessive	1:10000

What is the joint hypermobility spectrum?



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

What is the joint hypermobility spectrum?




Type	Beighton score	Musculoskeletal Involvement*	Notes
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Historical-HSD	Negative	Present	Historical presence of JH
hEDS	Positive	Possible	

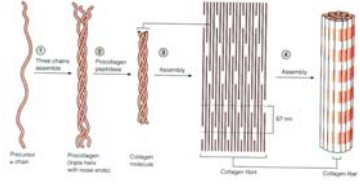
Musculoskeletal involvement includes trauma (micro- and macrotrauma), chronic pain, disturbed proprioception, and other traits (flat feet, misaligned bones in the elbow and big toe, mild to moderate scoliosis, kyphosis (outward curvature) of the upper spine, lordosis (inward curvature) of the lower spine)

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

Fibrillar collagens

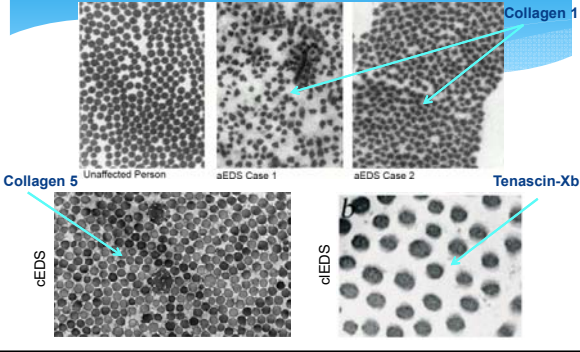



- * 28 types of collagen in humans
- * 7 are *fibrillar* (I, II, III, V, XI, XXIV, XXVII)



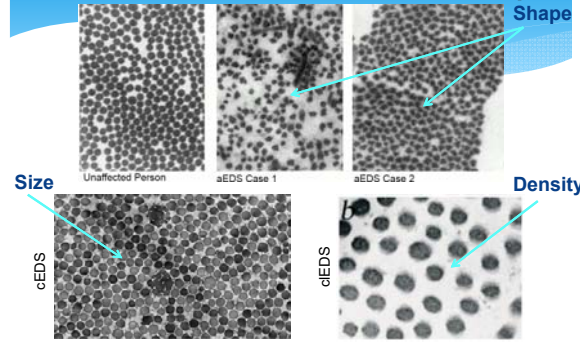

The diagram illustrates the hierarchical assembly of fibrillar collagen. It starts with three alpha chains (1) that assemble into a procollagen molecule (2). This procollagen molecule is then processed into a collagen molecule (3). Multiple collagen molecules assemble into a collagen fibril (4), which is 47 nm in diameter. Finally, collagen fibrils assemble into a collagen fiber (5).

Collagen fibers in EDS skin



This slide shows electron micrographs of collagen fibers. The top row shows three panels: 'Unaffected Person', 'aEDS Case 1', and 'aEDS Case 2'. The bottom row shows two panels: 'cEDS' and another 'cEDS' panel. Labels with arrows point to 'Collagen 1' and 'Tenascin-Xb' in the aEDS Case 2 panel, and 'Collagen 5' in the cEDS panels.

Collagen fibers in EDS skin



This slide shows electron micrographs of collagen fibers, similar to the previous slide. The top row shows three panels: 'Unaffected Person', 'aEDS Case 1', and 'aEDS Case 2'. The bottom row shows two panels: 'cEDS' and another 'cEDS' panel. Labels with arrows point to 'Shape' in the aEDS Case 2 panel, and 'Size' and 'Density' in the cEDS panels.

Ultrastructural differences in collagen in "unaffected" family members in hEDS families

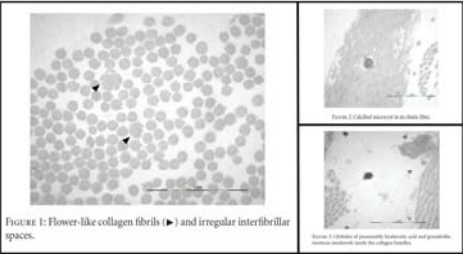


Figure 1: Flower-like collagen fibrils (▶) and irregular interfibrillar spaces.

Figure 2: Collagen fibrils in unaffected skin.

Figure 3: Electron of partially hydrolyzed and partially sodium borohydride treated skin collagen fibrils.

The EDS Spectrum?

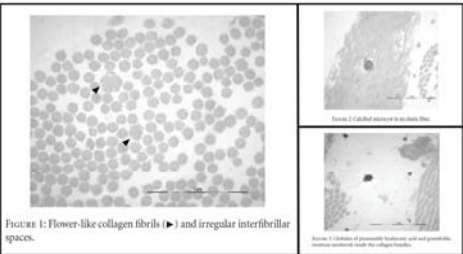



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How often does autism co-occur alongside EDS?



Brain Development

General Hospital Psychiatry
Volume 37, Issue 1, January-February 2015, Pages 24-30

Physicians Medical Community
Joint hypermobility and the heritable disorders of connective tissue: clinical and empirical evidence of links with psychiatry

Carolina Basso Valencio M.A. Ph.D. ¹, F.J.R. Guillem-Palhou M.D. Ph.D. ², Antonio Bulbena M.D. M.Sc. (Genetics) ³, Ana Maria Baghaiati M.D. Ph.D. ⁴

February 2015, Volume 36, Issue 1, Pages 61-66

Abnormalities of joint mobility and gait in children with autism spectrum disorders

Brain Abstracts
RELEVANCE TO NEURODEVELOPMENTAL DISORDERS

How often does autism co-occur alongside EDS?



behavioral sciences

Title / Keyword: Journal: Substantial: Advanced: Search

Author / Affiliation: Article Type:

Volume 8, Issue 3

Views: 2261 Downloads: 5241

No citations found yet

Article Versions: Abstract, Full Text PDF (1114 kb), Full Text HTML, Full Text XML, Full Text ePub, Article Versions Notes, Supplementary material

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

Bridley L. Casanova^{1,2,3}, Julia L. Sharp^{1,3}, Stephen M. Edelson⁴, Deborah P. Kelly^{1,3} and Manuel F. Casanova^{1,3}

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² Department of Pediatrics, Greenville Health System Children's Hospital, Greenville, SC 29605, USA.
³ Department of Statistics, Colorado State University, Fort Collins, CO 80523, USA.
⁴ Autism Research Institute (ARI), San Diego, CA 92116, USA.

* Author to whom correspondence should be addressed.

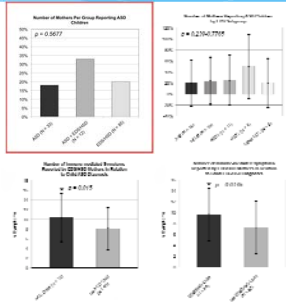
Received: 23 November 2017 / Revised: 26 February 2018 / Accepted: 18 March 2018 / Published: 17 March 2018

[This article belongs to the Special Issue Selected Papers from CUBANNI 2017—"The Fourth International Workshop of Neuroimmunology".]

Hereditary relationship between EDS/HSD and autism



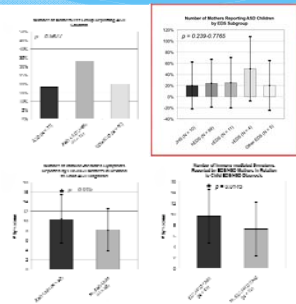
- * Mothers with EDS/HSD seem to have increased risk of having autistic children
- * Likelihood appears to be common across different forms of EDS
- * EDS mothers with autistic children report more immune symptoms
- * EDS mothers with EDS/HSD children also report more immune symptoms



Hereditary relationship between EDS/HSD and autism

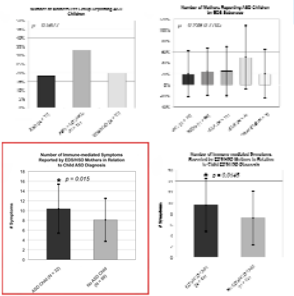


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- * EDS mothers with EDS/HSD children also report more immune symptoms

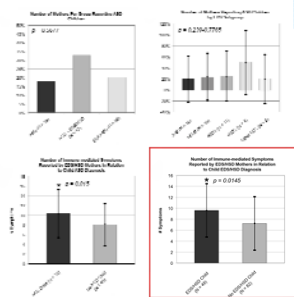


The charts show the following data trends:

- Number of autistic children per EDS mother:**
 - EDS (p = 0.0007): ~1.5
 - EDS/HSD (p = 0.0007): ~2.5
 - EDS/HSD (p = 0.0007): ~1.5
- Number of immune-related symptoms reported by EDS mothers with autistic children:**
 - EDS (p = 0.015): ~10
 - EDS/HSD (p = 0.015): ~8
- Number of immune-related symptoms reported by EDS/HSD mothers with autistic children:**
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 - EDS/HSD (p = 0.014): ~8

Hereditary relationship between EDS/HSD and autism


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 - EDS/HSD (p = 0.014): ~8


EDS, autism, and the maternal immune system


Trends in Molecular Medicine 

Volume 17, Issue 7, July 2011, Pages 389-394

Review
Maternal infection and immune involvement in autism
Paul H. Patterson 
[Show more](#)
<https://doi.org/10.1016/j.molmed.2011.03.001>

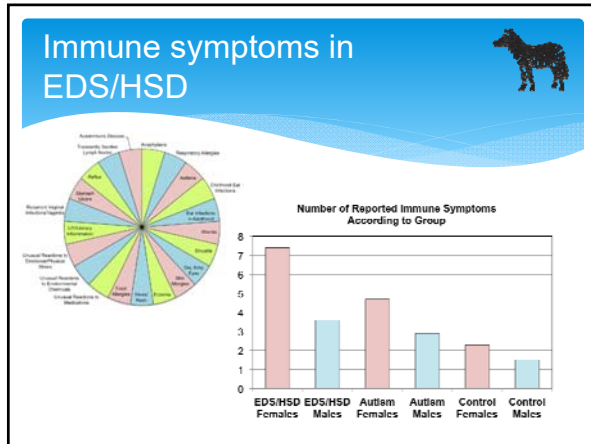
Translational Psychiatry

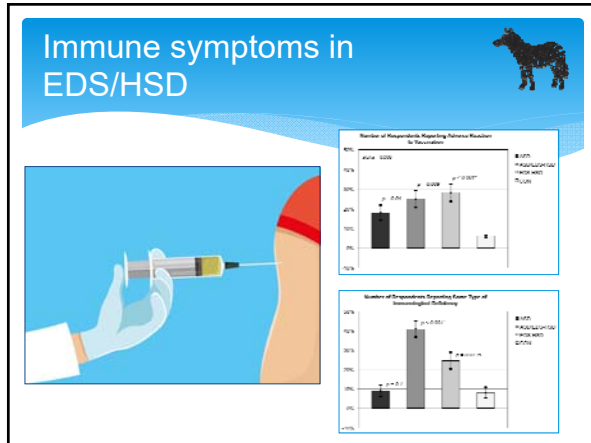
Original Article  Published: 03 April 2012

Effects of maternal immune activation on gene expression patterns in the fetal brain
A. Garbett, E. Y. Honea, S. Kalandi, P. H. Patterson & M. Minou 

Translational Psychiatry 1, 499 (2012) | [Download Citation & More](#)

- * 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





Mast Cell Activation Syndrome (MCAS)

Mast Cell Activation Disorder Symptoms (Mast Cell Activation Syndrome)

- Anaphylaxis
- Flushing of the face, neck, and chest
- Itching, w/ 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)
- Sore/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


Mast Cell Activators

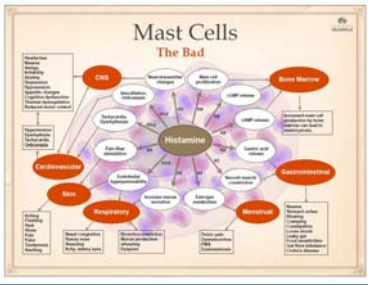
- Receptor-binding agonists
- IGE, Anigen or IgE alone
- 5-HT, histamine
- Complement
- Neurotransmitters
- Microbial products
- Cytokines
- Chemokines

Mast Cell Molecules


- Proteolytic mediators:
 - Proteinase
 - Proteinase 3
 - Serineprotease
 - Heparin
 - IL-4, TNF, GM-CSF
- T and B cell ligands:
 - CD45, CD44, CD44v6, CD44v7, CD44v8, CD44v9, CD44v10, CD44v11, CD44v12, CD44v13, CD44v14, CD44v15, CD44v16, CD44v17, CD44v18, CD44v19, CD44v20, CD44v21, CD44v22, CD44v23, CD44v24, CD44v25, CD44v26, CD44v27, CD44v28, CD44v29, CD44v30, CD44v31, CD44v32, CD44v33, CD44v34, CD44v35, CD44v36, CD44v37, CD44v38, CD44v39, CD44v40, CD44v41, CD44v42, CD44v43, CD44v44, CD44v45, CD44v46, CD44v47, CD44v48, CD44v49, CD44v50, CD44v51, CD44v52, CD44v53, CD44v54, CD44v55, CD44v56, CD44v57, CD44v58, CD44v59, CD44v60, CD44v61, CD44v62, CD44v63, CD44v64, CD44v65, CD44v66, CD44v67, CD44v68, CD44v69, CD44v70, CD44v71, CD44v72, CD44v73, CD44v74, CD44v75, CD44v76, CD44v77, CD44v78, CD44v79, CD44v80, CD44v81, CD44v82, CD44v83, CD44v84, CD44v85, CD44v86, CD44v87, CD44v88, CD44v89, CD44v90, CD44v91, CD44v92, CD44v93, CD44v94, CD44v95, CD44v96, CD44v97, CD44v98, CD44v99, CD44v100
- Nearly symmetrical mediators:
 - Leukotrienes
 - Prostaglandins
 - Leukotrienes
 - PGI2
 - CD44v6
 - CD44v7
 - CD44v8
 - CD44v9
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Mast Cell Activation Syndrome (MCAS)

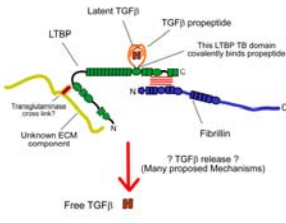





Lessons from Marfan syndrome & TGF-beta





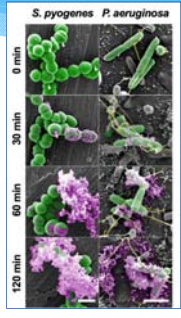


Non-fibrillar collagen as a defense mechanism against bacterial pathogens



Contains Von Willebrand Factor (VWF) Type A domain:

- * Collagen VI
- * Collagen XXII
- * Collagen XXVIII




S. pyogenes P. aeruginosa

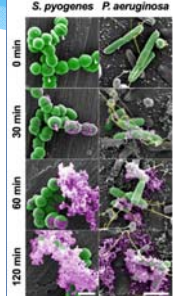
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30 min
60 min
120 min

Ardalane et al., 2016, J Immunol, 201, 1007-1020.

Non-fibrillar collagen as a defense mechanism against bacterial pathogens

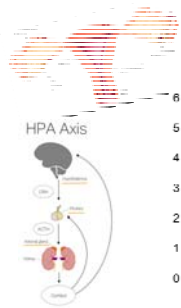



How else is collagen involved in immune system function???

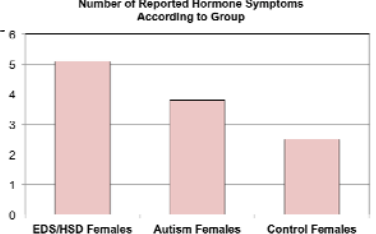


S. pyogenes P. aeruginosa
0 min
30 min
60 min
120 min
Asakura et al., 2018, J Immunol, 201, 1007-1020.

Hormonal symptoms in EDS/HSD





Number of Reported Hormone Symptoms According to Group




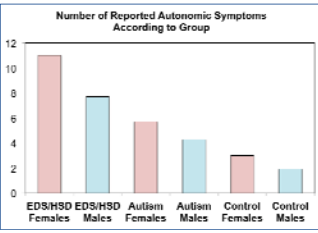
Group	Number of Reported Hormone Symptoms
EDS/HSD Females	5
Autism Females	4
Control Females	3

Hormonal symptoms in EDS/HSD



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


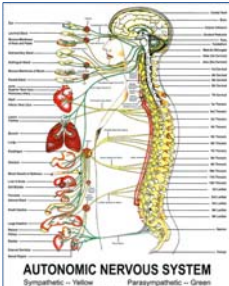

Autonomic symptoms in EDS/HSD

Group	Number of Symptoms
EDS/HSD Females	11
EDS/HSD Males	8
Autism Females	6
Autism Males	5
Control Females	4
Control Males	3

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

Postural Orthostatic Tachycardia Syndrome (POTS)

AUTONOMIC NERVOUS SYSTEM
Sympathetic – Yellow
Parasympathetic – Green

POSTURAL ORTHOSTATIC TACHYCARDIA SYNDROME & HOW TO TREAT IT


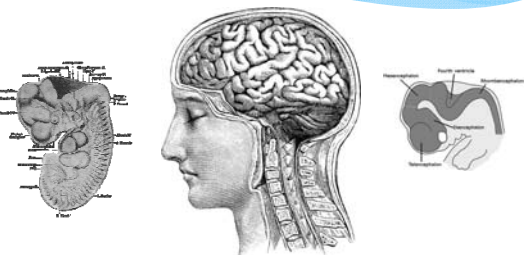
SYMPTOMS

- DIZZINESS
- HEART PALPITATIONS
- CHEST PAIN
- FATIGUE
- SHORTNESS OF BREATH
- SWEATING


HOW TO TREAT IT

- Hydration
- Salt Intake
- Avoid Caffeine
- Avoid Exercise
- Compression Stockings

What about connective tissue in the brain?

What about connective tissue in the brain?



Collagen 1 Protein Expression:

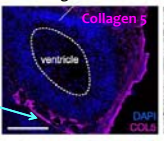
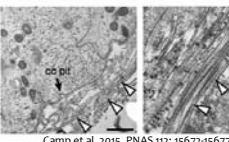
Estimated protein expression log₁₀ (ppm)

Brain	~1
Brain, fetal	~1
Frontal cortex	~1
Cerebral cortex	~1
Cerebrospinal fluid	~1
Spinal cord	~1
Retina	~1

Brain Organoid:


EMAGE 2018

Pseudo-meninges

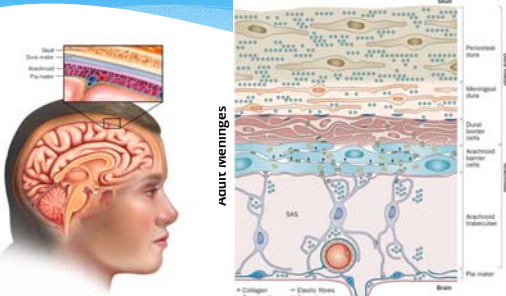



Camp et al. 2015, PNAS 112: 15672-15677.

What about connective tissue in the brain?



Adult meninges




Legend:

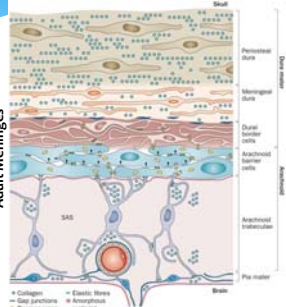
- Collagen → Elastic fibers
- Gap junctions → Desmosomes
- Tight junctions → Basement membrane

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

What about connective tissue in the brain?

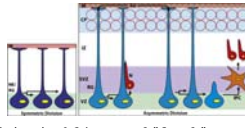


Adult Meninges



Meninges are involved:

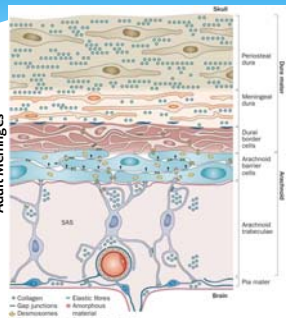
- in maintaining the stem cell pool
- orchestrating cell migration



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

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

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Adult Meninges

- Skull
- Dura Mater
- Arachnoid Mater
- Pia Mater
- Brain

Legend:

- Collagen
- Elastic fibers
- Cell junctions
- Anchorage
- Desmosomes
- Intermediate filaments
- Tight junctions
- Basement membrane

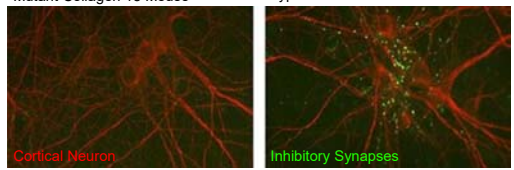
Questions:

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

References:

- Kollas et al. 2014. Nat Rev Neurol 10, 570-578.
- Sockanathan & Galano. 2009. Cell Stem Cell 5, 455-456.

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Mutant Collagen 18 Mouse

Typical Mouse

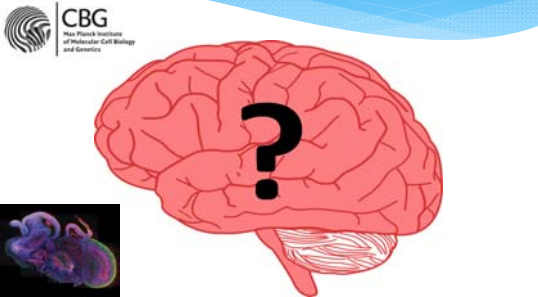
Cortical Neuron

Inhibitory Synapses

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

* Collagen 18 is non-fibrillar

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Brain with question mark

