

COL4A1

Tutorial with Parents (May 20, 2019)

The *COL4A1* tutorial took place on the afternoon of May 20, 2019, with both parents present as well as their 4-year old daughter who was held in the mother's lap throughout the tutorial. Dr. Walkley hosted the meeting which occurred in the IDDRC office in Kennedy. The child's pediatrician, Dr. Wasserstein, began with a review of her patient and the general information about the severe clinical consequences evident with mutations in this gene. The parent, particularly the mother, offered additional comments on her daughter's development. This was followed by a lay scientific summary of the gene and its protein and possible explanations for some of the brain clinical signs by Dr. David Spray's lab, with postdoc, Sean McCutcheon providing most of the details. Another postdoc, Antonio Cibelli also attended. The Spray lab is currently funded by a 2019 IDDRD pilot grant to pursue an understanding of how this gene defect could undermine the integrity of the blood brain barrier. The parents, with the mother living in Queens and the father in the Bronx, expressed considerable gratitude for the explanations of their daughter's condition.

Patient Description:

This is a 4-year-old girl with severe failure to thrive (she currently weighs 14 lb, the typical weight of a six month old), microcephaly, global developmental delay, bilateral congenital cataracts (s/p removal at 8 and 9 months of age), glaucoma, seizures and spasticity. She was born at 27 weeks gestation with IUGR (Intrauterine Growth Restriction); the prematurity, however, does not explain her symptoms. At four years of age, she is legally blind, unable to sit alone largely due to spasticity, and has several single words. She continues to have complex medical needs focused on ophthalmologic care, seizure control, addressing spasticity, and her nutritional needs. Of note, an MRI of the brain was performed in December of 2015 with the following results—periventricular leukomalacia, a small right caudate lacunar infarct, a thin corpus callosum, asymmetry, and the suggestion of several “prominent venous structures”.

Patient Specific Genetics:

A heterozygous de novo pathogenic variant in *COL4A1*, c.2987 G>A (p.G996D), was detected in this patient, c.2987 G>A (p.G996D). This variant has not been reported in large populations, nor has it previously been reported to be either pathogenic or benign. The non-conservative amino acid substitution caused by this mutation, based on in-silico analyses, supports the pathogenicity of this mutation (see below Protein/Mechanisms).

Disease/Syndrome Features:

Pathogenic mutations in *COL4A1* are usually highly penetrant and manifest clinically as a spectrum of disorders which have been described in a total of less than 100 families of American, Spanish, Chinese, Japanese, Dutch, Italian, French, and German descent.

Despite usually being inherited in an autosomal dominant fashion, more than twenty seven percent of patients with diseases related to this gene harbor a de novo mutation with variable age of onset within and between families. Dosing defects of this gene are

felt to be lethal since to date no deletions or duplications causative of COL4A1-related disorders have been found.

Manifestations of COL4A1 mutations in individual organs:

Brain--small-vessel brain disease (as periventricular leukomalacia, porencephaly, lacunar infarcts, microhemorrhages, dilated perivascular spaces, deep intracerebral hemorrhages--all presenting either antenatally, neonatally, or recurrently), large-vessel disease (as cerebral aneurysms)

--clinically presenting as infantile hemiparesis, seizures, single/recurrent hemorrhagic stroke, ischemic stroke, isolated migraine with aura, intellectual/developmental delay, dementia.

Eye-- retinal arterial tortuosity, Axenfeld-Reiger anomaly (iris abnormalities, posterior embryotoxon, microcornea, increased ocular pressure/glaucoma), cataracts, micro/anophthalmia —can clinically present as transient visual loss due to retinal hemorrhage

Kidney-- hematuria, unilateral renal atrophy, renal cysts

Muscle-- cramps, elevated creatine kinase

Peripheral vascular--Raynaud phenomenon

Cardiac-- supraventricular arrhythmia, mitral valve prolapse

Erythrocytes--hemolytic anemia

COL4A1-related Syndromes (OMIM 120130):

Porencephaly Type 1/Autosomal dominant familial porencephaly (OMIM 175780):

Porencephaly with varying levels of periventricular leukomalacia, microbleeds, lacunar infarcts, and intracerebral calcifications. Neurologic symptoms include infantile hemiparesis, seizures, intellectual deficits, dystonia, strokes, and migraines. Frequently associated with congenital cataracts and anterior segment abnormalities, rarely with retinal artery tortuosity, occasionally with hematuria or muscle cramping.

Brain small-vessel disease with or without ocular anomalies/ Autosomal dominant brain small vessel disease with hemorrhage (OMIM 607595): Diffuse periventricular leukomalacia, lacunar infarcts, microbleeds, dilated perivascular spaces, deep intracerebral hemorrhages, intracerebral calcifications. Neurologic symptoms—ranges from none to migraine with aura or infantile hemiparesis. Variably associated with retinal artery tortuosity, congenital cataracts, anterior segment anomalies, renal atrophy, and renal cysts. Occasionally associated with hematuria, hemolytic anemia, or muscle cramping.

HANAC (hereditary angiopathy with nephropathy, aneurysms and muscle cramps)(OMIM 611733): Asymptomatic small-vessel brain disease asymptomatic with subcortical, periventricular or pontine leukoencephalopathy, dilated perivascular spaces, lacunar infarcts, microbleeds, and carotid siphon aneurysms. Gross or microhematuria, bilateral cortical or medullary renal cysts. Muscle cramps, elevated creatine kinase levels and bilateral retinal arteriolar tortuosity in all patients. Variably associated with Raynaud's phenomenon, supraventricular arrhythmia and liver cysts.

Isolated retinal vessel tortuosity (OMIM 180000): Manifests as second/third order retinal artery involvement with normal first order retinal arteries/veins. Spontaneous or stress/trauma induced retinal hemorrhage leading to transient visual

Nonsyndromic autosomal dominant congenital cataracts

Schizencephaly (OMIM 269160)

Clinical mimics involving other genes:

COL4A2-related diseases

Autosomal dominant Walker-Warburg syndrome/Muscle-brain-eye disease (Labelle-Dumais et al. 2011)

CARASIL/CADASIL

RVCL/HERNS/HVR

Micro/anophthalmia with coloboma spectrum

Synonyms of COL4A1/A2-Related Disorders: COL4A1/A2 syndrome, Gould syndrome

COL4A1 Gene/Protein :

Type IV collagen is the main component of basement membranes, the other components of which are laminins, proteoglycans and entactin/hidogen. Type IV collagen is made up of three trimers consisting of varying proportions of six variants of type IV alpha chains (alpha 1 alpha 1 alpha 2/alpha 3 alpha 4 alpha 5/alpha 5 alpha 5 alpha 6). Commonalities between the six different alpha chains are 1) the 7S amino-terminal domain and 2) the large collagenous domain formed by Gly-X-Y repeats. Interactions between non-collagenous NC1 carboxy-terminals of these chains (arresten- see below) determine the types and proportions of alpha chains ultimately undergoing assembly in the above configurations. The glycine residues are crucial for the stabilization of the triple helices that form, and the distribution of the three isoforms are tissue and developmentally specifically expressed, with the first of the three being the most ubiquitously expressed.

The gene for the alpha-1 chain of Type IV collagen is located on 13q34, is 158 kilobases long and contains 52 exons. Too few pathogenic variants in this gene to be able to discuss true genotype/phenotype relationships but certain patterns have emerged. Firstly, the most common pathogenic variants involve missense alterations to glycine residues within the collagenous domain (exons 24-51) which most closely correlate with brain disease (Jeanne et al 2016). Similarly, the HANAC form of COL4A1 disease involves variants in exons 24 and 25 exclusively affecting glycines in a specific proximal 30-amino acid region of the protein. Only six pathogenic variants in the arresten domain have been found to date.

Putative molecular mechanisms for COL4A1-related disease:

Sudhakar et al. 2005 found that arresten binds to alpha-1/beta-1 integrins and plays a role in angiogenesis in the context of low oxygen tension environments, specifically inhibiting migration, proliferation and tube formation by endothelial cells. Could mutations in the collagenous domains of the COL4A1 allow for unmitigated arresten activity, perhaps explaining why vascular sequelae follow the malformation of Type 4 alpha 1 chains, particularly in microvascular beds during development?

Certain missense mutations in Col4a1 in animals causes focal detachment of vascular endothelium from its underlying media. Additionally, by reducing intrinsic endothelial-based nitric oxide synthase activity, hypotension and reduced red cell volume was induced in the areas fed by the Col4a1-defective vessels (Van Agtmael et al 2010).

In *Drosophila* embryo and ovary, type IV collagen extracellular matrix proteins were shown to bind Dpp, a bone morphogenetic protein (BMP) signaling molecule, and regulate its signaling by modulating its presence in the extracellular space during development (Wang et al, 2008). The authors predicted that this role of type IV collagens is likely to be conserved. Perhaps an early disruption in BMP gradient formation during early development is an underlying mechanism contributing to the profound growth failure observed in our patient.

Databases used: Online Inheritance in Man

Publications:

Jeanne, M., Gould, D.B. **Genotype-Phenotype Correlations in Pathology Caused by Collagen Type IV alpha 1 and 2 Mutations.** *Matrix Biol.* 2016 Oct 26.

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Plaisier, E., Ronco, P., **COL4A1-Related Disorders.** In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, editors. *GeneReviews®[Internet].* Seattle (WA): University of Washington, Seattle; 1993-2018. 2009 Jun 25 [updated 2016 Jul 7].

Sudhakar, A., Nyberg, P., Keshamouni, V. G., Mannam, A. P., Li, J., Sugimoto, H., Cosgrove, D., Kalluri, R. **Human alpha-1 type IV collagen NC1 domain exhibits distinct antiangiogenic activity mediated by alpha-1-beta-1 integrin.** J. Clin. Invest. 115: 2801-2810, 2005.

Van Agtmael, T., Bailey, M. A., Schlotzer-Schrehardt, U., Craigie, E., Jackson, I. J., Brownstein, D. G., Megson, I. L., Mullins, J. J. **Col4a1 mutation in mice causes defects in vascular function and low blood pressure associated with reduced red blood cell volume.** Hum. Molec. Genet. 19: 1119-1128, 2010.

Wang, X., Harris, R. E., Bayston, L. J., Ashe, H. L. **Type IV collagens regulate BMP signalling in Drosophila.** Nature 455: 72-77, 2008.

Support Groups and Information:

Gould Syndrome Foundation: gouldsyndromefoundation.org

- Nonprofit dedicated to providing hope and help for children and adults with Gould Syndrome, affecting COL4A1 and COL4A2 genes. Mission includes education, advocacy, and forming connections between doctors and researchers to patient global registry to bring research and medical therapeutic options to those affected.

Facebook groups:

- Col4a1/Col4a2 Gould Syndrome Family Support Group (private facebook group, >300 members)
- Col4a1 Gene mutation – GOULD SYNDROME (private facebook group, >180 members)
- Gould Syndrome Foundation Col4a1/Col4a2 Group (private facebook group, family support and advocacy site for Gould Syndrome Foundation, >150 members)

Last updated 5/9/2020, MKR