Accumulating data suggest CM-1 with connective tissue diseases (CTD+) may have a different patho-mechanism and different genetics than CM-1 without CTDs (CTD-). To identify CM-1 genetic risk variants, Urbizu et al. performed whole exome sequencing on a single large, multiplex family from Spain and targeted sequencing on a cohort of 186 unrelated adult, Caucasian females with CM-1. Targeted sequencing captured the coding regions of 21 CM-1 and EDS candidate genes, including two genes identified in the Spanish family. Using genetic burden analysis, they compared the frequency of rare, functional variants detected in CM-1 cases versus publically available ethnically-matched controls from gnomAD. A secondary analysis compared the presence of rare variants in these genes between CTD+ and CTD- CM-1 cases. In the Spanish family, rare variants co-segregated with CM-1 in COL6A5, ADGRB3 and DST. A variant in COL7A1 was present in affected and unaffected family members. In the targeted sequencing analysis, rare variants in six genes (COL7A1, COL5A2, COL6A5, COL1A2, VEGFB, FLT1) were significantly more frequent in CM-1 cases compared to public controls. In total, 47% of CM-1 cases presented with rare variants in at least one of the four significant collagen genes and 10% of cases harbored variants in multiple significant collagen genes. Moreover, 26% of CM-1 cases presented with rare variants in the COL6A5 gene. We also identified two genes (COL7A1, COL3A1) for which the burden of rare variants differed significantly between CTD+ and CTD- CM-1 cases. A higher percentage of CTD+ patients had variants in COL7A1 compared to CTD+ patients, while CTD+ patients had fewer rare variants in COL3A1 than did CTD- patients.

In summary, rare variants in several collagen genes are particularly frequent in CM-1 cases and those in COL6A5 co-segregated with CM-1 in a Spanish multiplex family. COL6A5 has been previously associated with musculoskeletal phenotypes, but this is the first association with CM-1. This findings underscore the contribution of rare genetic variants in collagen genes to CM-1, and suggest that CM-1 in the presence and absence of CTD symptoms is driven by different genes [1)]

1)
Urbizu A, Garrett ME, Soldano K, Drechsel O, Loth D, Marcé-Grau A, Mestres I Soler O, Poca MA, Ossowski S, Macaya A, Loth F, Labuda R, Ashley-Koch A. Rare functional genetic variants in COL7A1, COL6A5, COL1A2 and COL5A2 frequently occur in Chiari Malformation Type 1. PLoS One. 2021 May 11;16(5):e0251289. doi: 10.1371/journal.pone.0251289. PMID: 33974636.