

Phenotypic expansion of COL12A1-related myopathy

- Insights from a multigenerational family

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1 BACKGROUND

Pathogenic variants in COL12A1 are associated with a congenital connective-tissue and myopathy overlap syndrome, collectively referred to as collagen XII-related myopathy. Clinical severity range from severe Ullrich muscular dystrophy to subtle myopathic presentations and even isolated clubfoot. We present a multigenerational Norwegian family with a mild Bethlem-like myopathy *without* connective-tissue abnormalities.

2 METHODS

Six affected individuals carrying a heterozygous COL12A1 variant of uncertain significance (NM_004370.6: c.4013C>A, p.Ala1338Asp) were evaluated through clinical and neurological examinations, electrophysiology, and spirometry. Variant classification followed American College of Medical Genetics and Genomics (ACMG) criteria. Additional analyses included segregation analysis, *in silico* structural modelling, and immunocytochemical studies with advanced light microscopy of dermal fibroblasts.

3 RESULTS: CLINICAL FEATURES



Figure 1:

Clinical photographs from three family members with collagen XII-related myopathy. Close-up images of hands and feet highlight distal contractures and skeletal characteristics such as short hands and feet, with corresponding nerve entrapments (carpal tunnel on electrophysiological tests). Anterior and lateral standing views demonstrate posture and muscle involvement. Shared features across all family members were congenital clubfeet, distal arthrogryposis, and mild axial muscle weakness. Some individuals also had proximal muscle weakness and restrictive pulmonary dysfunction.

- A:** Joint contractures of the ankles. Congenital clubfoot with progressive equinus contracture. Small feet with short toes.
- B:** Mild interphalangeal contractures. Short hands with short fingers (3rd finger length 7.0 cm).
- C:** Joint contractures of the wrist, with restricted flexion.
- D:** Joint contractures of the wrist, with restricted extension.
- E:** Short stature (height 150 cm; arm span 161 cm). Internally rotated shoulders, proximal muscle wasting around the pectoral girdle. Small feet (EU size 37/JP 23.5 cm).
- F:** Axial weakness with mildly dropped head, protuberant abdomen, lumbar hyperlordosis, and winged scapula. Posture with anterior pelvic tilt and wide-based stance, indicating a waddling gait.

4 RESULTS: FUNCTIONAL STUDIES

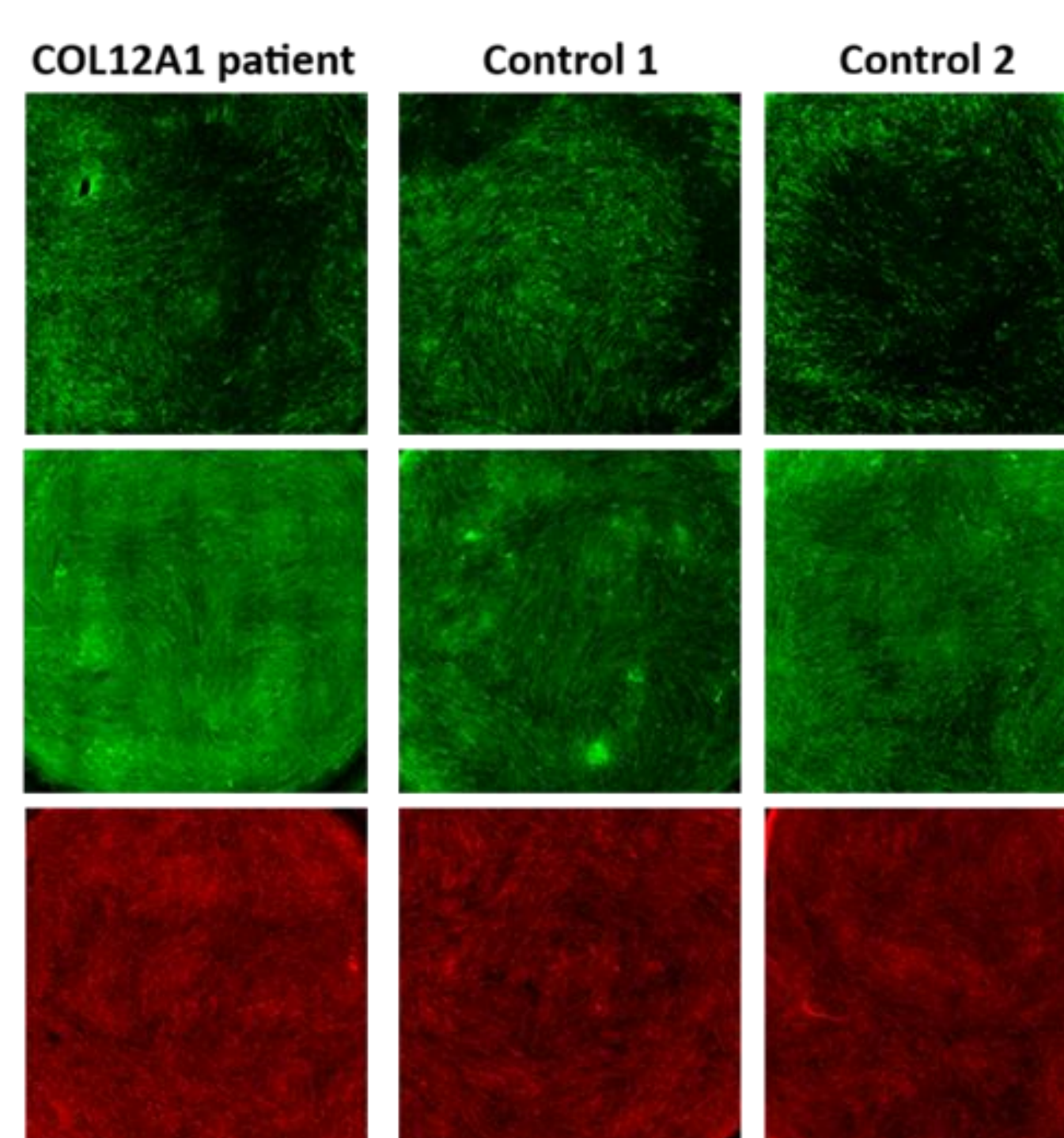


Figure 2: Immunofluorescence analysis showed preserved collagen XII expression, localization, and extracellular matrix fibre organization in fibroblasts from one COL12A1-affected individual, comparable to control samples.
Upper panel: Collagen XII (green) Extracellular fibres
Middle panel: Collagen XII (green) Intracellular fibres
Lower panel: Collagen VI (red) Extracellular fibres

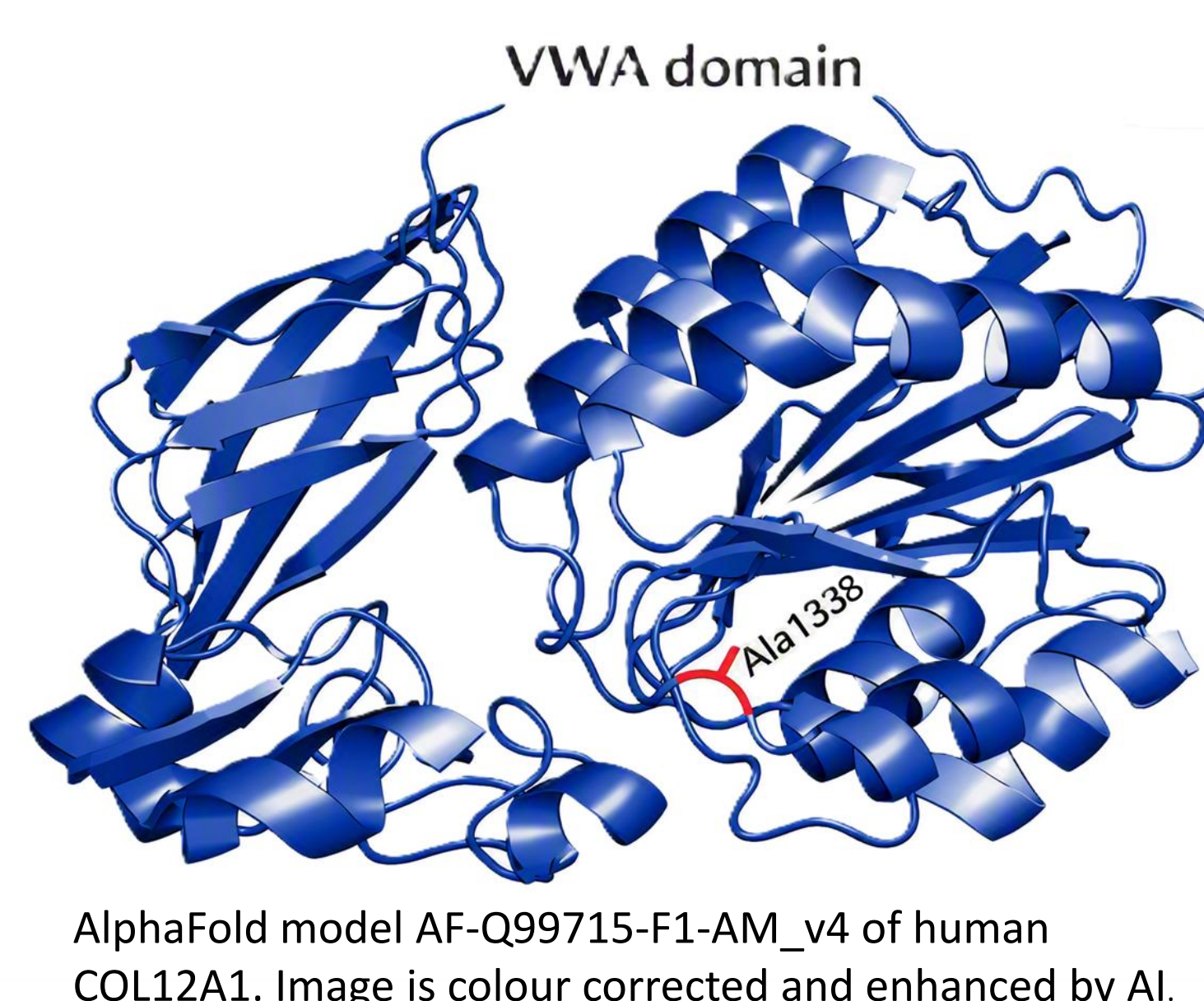


Figure 3: The COL12A1 variant replaces a neutral alanine with a larger and negatively charged aspartate within the triple-helix region adjacent to a von Willebrand factor A (VWA)-like domain (position 1338). Introducing an aspartate at this position may cause instability and affect collagen XII function in the extracellular matrix. Conclusions still remain non-definitive due to the *in silico* nature of the analysis.

5 CONCLUSION

This family represents one of the largest COL12A1 cohorts reported to date. The variant co-segregated with the phenotype across five meioses, and no alternative genetic diagnosis was identified through additional genome sequencing and arthrogryposis gene panels. Although still classified as a variant of uncertain significance (VUS) under American College of Medical Genetics and Genomics (ACMG) criteria, the strong segregation and consistent clinical features support its pathogenic relevance. These findings expand the phenotypic spectrum of collagen XII-related myopathy to include:

- Mild Bethlem type 2-like myopathy
- Short stature, small hands and feet
- Absence of clinical connective-tissue abnormalities