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CASE REPORT

Comorbid autosomal dominant LDLR- and collagen VI-related disorders

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Objectives. Collagen 6-related Bethlem myopathy and LDLR-related familial hypercholesterolemia are presumed to be quite rare in the general population. Case report. Here, we present the clinical findings from a 65-year-old man with comorbid Bethlem myopathy and familial hypercholesterolemia to highlight some important molecular diagnostic considerations and clinical management implications.

Key words: collagen, *COL6A3*, hyperlipidemia, *LDLR*, phenotype

The heterogeneity of the genotype and phenotype spectrum of collagen 6-related disorders (*COL6*-RD) is an area of growing interests, yet cases of genetic comorbidities that may impact long-term management outcomes are lacking. Here, we present a 65-year-old male who was diagnosed with concurrent autosomal dominant *COL6A3*-RD and *LDLR*- related familial hypercholesterolemia. The patient underwent gene panel testing [comprehensive neuromuscular diseases and comprehensive lipidemia panel at Invitae laboratories (San Francisco CA, USA)] followed by exome sequencing at GeneDx laboratories [Gaithersburg, MD, USA] in the setting of persistently elevated creatine protein kinase levels [ranging from around 600 to > 1000 (IU/L)], muscle weakness, muscle spasm, myalgias, inguinal hernia, diaphragmatic hernia, hyperlipidemia, carotid artery stenosis, abdominal aortic ectasia, renal cyst, transient ischemic attack, chronic liver disease, cardiac conduction disorder, and hypersomnia.

The patient had no known personal history of contractures or gait abnormalities. His family history includes multiple 1st degree relatives with hyperlipidemia, but he has no known family history of muscle diseases (Fig. 1A). The patient's myopathic symptoms began at age 56. The genetic tests demonstrated *COL6A3*-RD [due to a heterozygous pathogenic variant, c.399del (p.Ala134Leufs*14)] and *LDLR*- related familial hypercholesterolemia [due to a heterozygous pathogenic variant, c.781T > A (p.Cys261Ser)]. *COL6A3* [NM_004369.4] c.399del is a novel frameshift variant that creates a premature translational stop signal (p.Ala134Leufs*14), which is predicted to result in an absent or disrupted protein product. Haploinsufficiency of *COL6A3* has been associated with *COL6A3*-RD, Bethlem myopathy [1,2]. *COL6A3* c.399del (p.Ala134Leufs*14) fulfills the PVS1 (very strong), PM2 (moderate, applied at supporting level), pathogenicity criteria of the American College of Medial Genetics (ACMG) and the Association for

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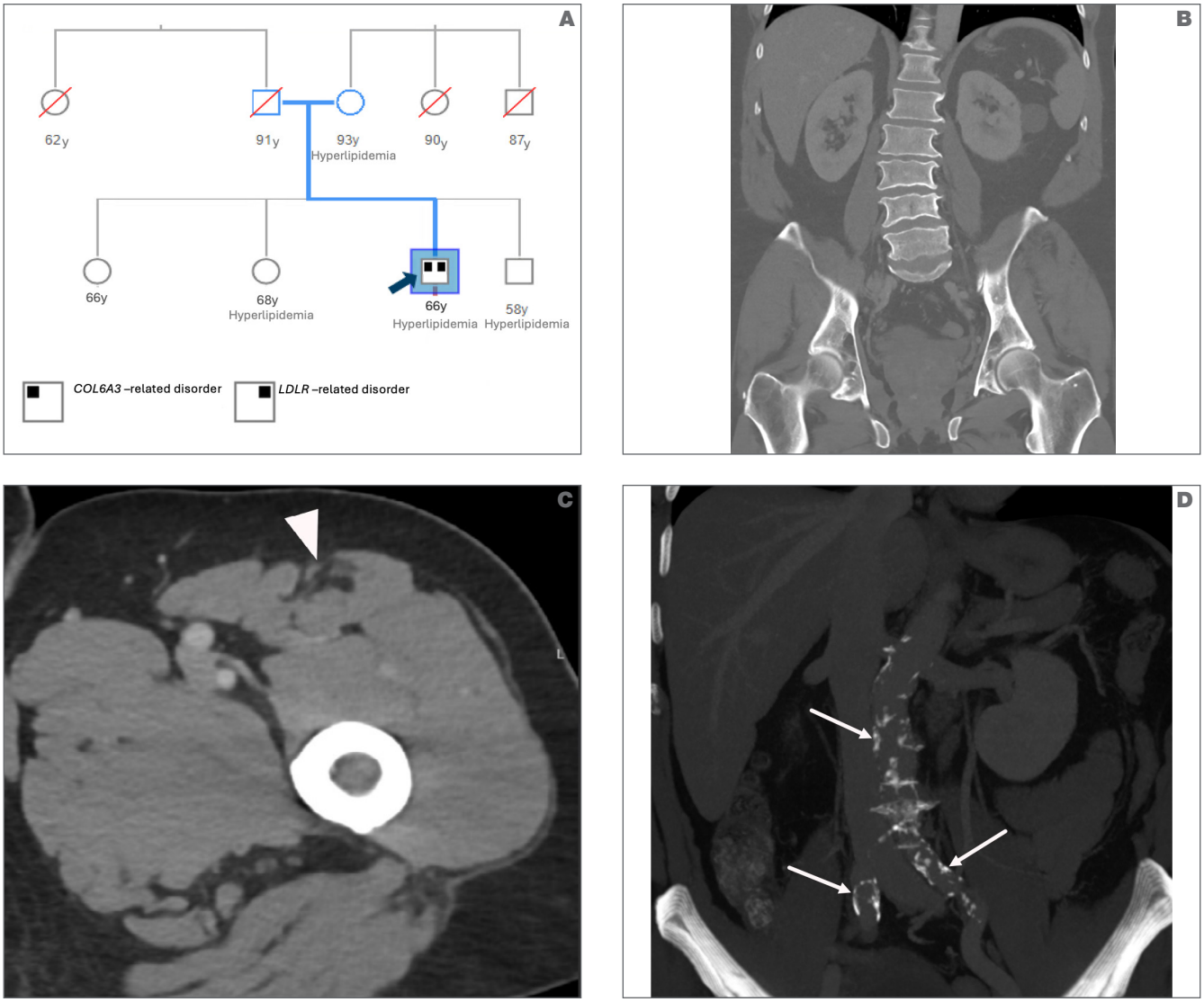

Figure 1. (A) Pedigree showing multiple 1st degree relatives with hyperlipidemia. Coronal CT image of the abdomen (B) shows dextroconvex lumbar scoliosis with associated multilevel degenerative disc disease. Axial CT image of the left thigh (C) shows anterocentral atrophy of the rectus femoris muscle (arrowhead) characteristic of Bethlem myopathy. Coronal CT maximum intensity projection (MIP) image (D) shows extensive atherosclerotic disease (arrows) involving the aorta and bilateral common iliac arteries.

Molecular Pathology (AMP) variant classification system [3], hence was classified as a pathogenic variant. *LDLR* [NM_000527.4] c.781T > A (p.Cys261Ser) variant fulfills the PS4 (strong), PM1, PM2,PM5, and PP3 (supporting) criteria of the ACMG/AMP variant stratification system, hence was classified as a pathogenic variant. The patient's relatives were unavailable for family variant testing for the *COL6A3* and *LDLR* variants. The concurrent germline presence of *COL6A3* c.399del (p.Ala134Leufs*14) and *LDLR* c.781T > A (p.Cys261Ser) resulted in a composite neuromuscular phenotype with cardiometabolic and cerebrovascular consequences. CT of the abdomen showed scoliosis (Fig. 1B), anterocentral rectus femoris muscle atrophy (Fig. 1C) consistent with Bethlem myopathy [4], and atherosclerotic disease of the aorta and iliac arteries (Fig. 1D) in the context of *LDLR*-related hypercholesterolemia.

Although autosomal dominant *COL6A3*- related Bethlem myopathy is a relatively mild neuromuscular disorder, without significant cardiac and respiratory involvement [5], the cerebrovascular and cardiovascular consequences of comorbid *LDLR*-related hypercholesterolemia resulted in a more complex phenotype. Our observations suggest that providers should consider possibilities of comorbid genetic disorders in patients who have *COL6A3*- related disorders in a setting of severe cardiorespiratory and/or cerebrovascular diseases. On their own, *LDLR*- and *COL6A3*- related disorders are presumed to be quite rare in the general population, nevertheless the increasing application of genetic testing technologies in clinical settings may help shed light on the prevalence of the dual diagnosis.

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Conflicts of Interest statement

The authors have no conflicts of interest to declare.

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Authors contribution

Conceptualization: M.A.O. Methodology: M.A.O., B.A.O. D.M., J.B.T., K.I.D., G.B., R.S.P., R.D., F.S. Data Analysis; M.A.O., B.A.O., D.M., J.B.T., K.I.D., G.B., R.S.P., R.D., F.S. Writing (original draft): B.A.O. Writing (reviewing and editing): M.A.O., B.A.O., D.M., J.B.T., K.I.D., G.B., R.S.P., R.D., F.S. Supervision: M.A.O. Guarantor: M.A.O.

Consent to participate

Informed consent was obtained from the patient for the study. Informed consent was obtained from the patient for publication.

References

1 Li M, Huang J, Liu M, Et Al. A Novel Variant Of Col6a3 C.6817-2(Ivs27)A > G Causing Bethlem Myopathy: A Case Report. Front Neurol 2023;14:1063090. Https://doi.org/10.3389/Fneur.2023.1063090.

2 Lamande Sr, Bateman Jf, Hutchison W, Et Al. Reduced Collagen Vi Causes Bethlem Myopathy: A Heterozygous Col6a1 Nonsense Mutation Results In Mrna Decay And Functional Haploinsufficiency. Hum Mol Genet 1998;7(6):981-9. Https://doi.org/10.1093/Hmg/7.6.981.

3 Richards S, Aziz N, Bale S, Et Al. Standards And Guidelines For The Interpretation Of Sequence Variants: A Joint Consensus Recommendation Of The American College Of Medical Genetics And Genomics And The Association For Molecular Pathology. Genet Med 2015;17(5):405-24. Https://doi.org/10.1038/Gim.2015.30.

4 Dede O, Abdel-Hamid Hz, Deeney Vf. Spinal Deformity In Bethlem Myopathy. Spine Deform 2014;2(2):143-151. Https://doi.org/10.1016/J.Jspd.2013.11.003.

5 Van Der Kooi Aj, De Voogt Wg, Bertini E, Et Al. Cardiac And Pulmonary Investigations In Bethlem Myopathy. Arch Neurol 2006;63(11):1617-21. Https://doi.org/10.1001/Archneur.63.11.1617.