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Contiguous Xp21 Deletion Syndrome with Atypical Phenotype Requires Further Clarification Using WES

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LETTER TO THE EDITOR

We read with interest the article by Blackstone, W.Z. *et al*., 2025 about a man with a contiguous Xp21 deletion syndrome that manifested phenotypically as Duchenne muscular dystrophy (DMD), McLeod syndrome, autism spectrum disorder (ASD), obstructive sleep apnoea syndrome (OSAS), and speech delay (Blackstone, W.Z. *et al*., 2025). Cardiac involvement manifested earlier and progressed faster than in DMD due to point mutations or single exon deletions in the dystrophin gene (Blackstone, W.Z. *et al*., 2025). The patient died suddenly at the age of 12 years with maximal treatment for heart failure, but without having received an implantable cardioverter defibrillator (ICD) (Blackstone, W.Z. *et al*., 2025). The study is remarkable, but some points should be discussed.

The first issue is that whole-exome sequencing (WES) was not performed in the patient to determine whether point mutations in genes other than dystrophin or XK were mutated in the index patient and contributed to the phenotype. This is important given the unusual clinical presentation of obstructive sleep apnoea, expressive language delay, and ASD, which have not previously been reported in DMD patients or patients with McLeod syndrome (Blackstone, W.Z. *et al*., 2025). At the very least, a panel for genetic causes of ASD should have been conducted. The most commonly mutated genes associated with ASD include the SH3, neuroligin (NLGN), multiple ankyrin repeat domains (SHANK)), contactin-associated protein-like 2 (CNTNAP2) and neurexin (NRXN) families (Apte, M. *et al*., 2023).

The second point is that no cardiac MRI image was reported (Blackstone, W.Z. *et al*., 2025). Cardiac MRI could show whether myocardial fibrosis is present and whether it has progressed over time and was the cause of progressive heart failure in the index patient. Of particular interest would be an image with contrast to assess whether or not late gadolinium enhancement (LGE) is present. LGE could be an indicator of myocardial fibrosis, which usually progresses in DMD patients with dilated cardiomyopathy and can be used as a prognostic factor (James, L. *et al*., 2023).

The third point is that DMD is associated with non-compaction, also known as left ventricular hypertrabeculation (Finsterer, J. *et al*., 2006). Has noncompaction been documented in the index patient or another first-degree family member carrying the causative deletion? It is crucial to know whether the patient had non-compaction or not, as it can be complicated by cardioembolism, heart failure, ventricular arrhythmias and sudden cardiac death. The latter was described in the index patient.

The fourth point is that it is not comprehensible why the index patient did not receive an ICD. The concerns about the need for a blood transfusion could have been addressed by autologous blood donation.

In summary, this interesting study has limitations that affect the results and their interpretation. Addressing these limitations could strengthen the conclusions and support the message of the study. All unanswered questions need to be addressed before readers uncritically accept the study's conclusions. If DMD has an unusual phenotype, additional investigation by WES is recommended. DMD patients with severe dilated cardiomyopathy and McLeod syndrome should receive an ICD after provision of autologous blood.

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