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A multistage sequencing strategy pinpoints novel candidate alleles for Emery-Dreifuss muscular dystrophy and supports gene misregulation as its pathomechanism.

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Abstract

BACKGROUND: As genome-wide approaches prove difficult with genetically heterogeneous orphan diseases, we developed a new approach to identify candidate genes. We applied this to Emery-Dreifuss muscular dystrophy (EDMD), characterised by early onset contractures, slowly progressive muscular wasting, and life-threatening heart conduction disturbances with wide intra- and inter-familial clinical variability. Roughly half of EDMD patients are linked to six genes encoding nuclear envelope proteins, but the disease mechanism remains unclear because the affected proteins function in both cell mechanics and genome regulation.

METHODS: A primer library was generated to test for mutations in 301 genes from four categories: (I) all known EDMD-linked genes; (II) genes mutated in related muscular dystrophies; (III) candidates generated by exome sequencing in five families; (IV) functional candidates - other muscle nuclear envelope proteins functioning in mechanical/genome processes affected in EDMD. This was used to sequence 56 unlinked patients with EDMD-like phenotype.

FINDINGS: Twenty-one patients could be clearly assigned: 18 with mutations in genes of similar muscular dystrophies; 3 with previously missed mutations in EDMD-linked genes. The other categories yielded novel candidate genes, most encoding nuclear envelope proteins with functions in gene regulation.

INTERPRETATION: Our multi-pronged approach identified new disease alleles and many new candidate EDMD genes. Their known functions strongly argue the EDMD pathomechanism is from altered gene regulation and mechanotransduction due to connectivity of candidates from the nuclear envelope to the plasma membrane. This approach highlights the value of testing for related diseases using primer libraries and may be applied for other genetically heterogeneous orphan diseases.

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KEYWORDS: Emery-Dreifuss muscular dystrophy; Nuclear envelope; Nuclear envelope transmembrane protein; Orphan disease; primer library

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