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Commentary

Novel candidate alleles associated with gene regulation for Emery–Dreifuss muscular dystrophy

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Since *EMD*, the first gene responsible for Emery–Dreifuss muscular dystrophy (EDMD) was mapped by Thomas and colleagues in 1986 [1], six genes have been found to be associated with EDMD. However, EDMD shows clinical variability and only nearly half of EDMD patients can be genetically diagnosed. This suggests that there should be more genes linked to EDMD or genes that could modify EDMD phenotype. Therefore, it is important to identify novel candidate alleles for EDMD. At present, the known genes associated with EDMD encode the proteins of nuclear envelope maintaining mechanical stability of nucleus and genome stability. Two main pathogenesis hypotheses of EDMD are mechanical instability and abnormal gene expression [2]. This suggests that genes having an influence on mechanical stability of nucleus and genome stability are expected to become the candidate alleles for EDMD.

Typical EDMD is clinically characterized by joint contractures with onset in early childhood, slowly progressive scapulo-humero-peroneal muscle weakness and atrophy, and cardiac involvement with conduction defects [3]. EDMD1 presenting typical clinical triad is mainly caused by small out of frame deletions or splice site mutations in *EMD*. EDMD2 and EDMD3 caused by mutations in *LMNA* show typical skeletal muscle symptoms, as well as high risk of life-threatening ventricular arrhythmia [4]. EDMD4, EDMD5, EDMD6 and EDMD7 with different degrees of clinical severities are caused by mutations in *SYNE1*, *SYNE2*, *FHL1*and *TMEM43*, respectively. Nearly 40% patients of EDMD are associated with mutations in *EMD* and *LMNA*, EDMD3-7 is reported with fewer cases, and many cases with EDMD-like phenotype cannot be diagnosed genetically. Besides genetic heterogeneity, clinical variability is shown in EDMD. Additionally, LMNA gene is associated with a wide range of disease phenotypes called laminopathies [5]. However, the pathogenetic mechanisms remain not well understood.

In the past few years, nuclear morphology defect, abnormal expression or subcellular localization of nuclear envelope related proteins, impairment of the distribution of chromatin, changes of cellular signaling pathways have been reported to support the structural hypothesis and the related gene expression pathways for EDMD [6]. However, the pathogenic pathway leading to EDMD is still not very clear and there is an ongoing debate about which mechanism plays a crucial role.

These facts prompted a basic and clinical research to identify candidate alleles for EDMD conducted by Meinke and colleagues and presented in this article of *EBioMedicine* [7]. Results from this study provide interesting and convincing evidence for the novel candidate alleles and modifying alleles for EDMD, and the EDMD pathogentic mechanism. A total of 252 candidates from five families were identified by the combined exome, genome and RNA sequencing. Mutations in a primer library containing 301 genes from four gene categories including 8 known EDMD-linked genes, 25 genes related muscular dystrophies, 252 candidates from five families and 16 functional candidates were tested in 56 additional unlinked clinically diagnosed EDMD patients. The authors showed that 21 of 56 unlinked but clinically diagnosed EDMD patients are genetically diagnosed with 3 mutations in *LMNA* and 18 mutations in genes related to muscular dystrophies including *CAPN3*, *GBE1*, *VCP*, *TTN*, *DMD*, *COL6A1*, *CAV3*, *ANO5*, *POMT1* and *DYSF*. The top category III candidates were *INIS1*, *ANK2*, *XIRP1* and *USP34*, eight category IV candidate genes were identified with mutations in *WFS1*, *TMEM201*, *TMEM38A*, *PLPP7*, *TMEM214*, *LPCAT3*, *KLHL31* and *BVES*, and most of them encoded nuclear proteins with their functions related to gene regulation. The authors went on to confirm their being EDMD candidate genes by studying the function of 8 functional NET candidates in myogenic gene regulation. The study suggested that the mutant genes could affect other gene positioning and their expressions. However, only *TMEM38A* p.N260D had a slight increase in numbers of abnormal nucleus.

Even though further studies with a larger cohort of EDMD patients and functional studies are needed for confirmation of novel EDMD candidates, the value of this study is that it provides new clues for genetic diagnosis for patients with EDMD or EDMD-like phenotype. It also identified modifying alleles affecting the phenotype with clinical variability and overlaps, and evidence for the EDMD pathogenetic mechanism. The findings should be helpful for the diagnosis of EDMD in more patients and better understanding of the pathogenetic mechanism.

Several questions remain. It is exciting, at first thought, to imagine that all the EDMD patients can be genetically diagnosed. However, the study is not sufficient to exclude the existence of other candidate genes. For instance, the mutations in *XIRP1* and *USP34* were both detected in the same family, and that some other candidates such as *WFS1*, *TMEM38A* and *TMEM201*worked as modifying alleles. This

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makes the diagnosis of EDMD more difficult. It appears that candidate alleles encode proteins from the extracellular matrix and plasma membrane of the nuclear envelope, indicating that both abnormal mechanotransduction and gene regulation are involved in the pathogenetic mechanisms. The different contribution of the two main pathogenesis hypotheses is still unclear even though they have been thought to be not very different [8]. Furthermore, large deletions have been reported in EDMD [9], even though they only accounted for a small portion of mutations in EDMD, these cases with large deletion in *EMD* may be missing by exome sequencing.

At present, there are no specific treatments for EDMD, multidisciplinary management including respiratory support, orthopedic procedure and cardiac treatment is routinely provided. The treatment strategies including targeting MAPK signaling pathway, inducing autophagy, inhibiting apoptosis and gene therapy have been studied [10]. Further recognition of the pathogenetic mechanism is helpful for researching the treatment of EDMD.

In summary, this study provides valuable evidence for candidate alleles and modifying alleles for EDMD. It shows a primer library that could genetically diagnose nearly 50% genetically unsolved EDMD patients. Notably, nine of those genes are related to muscular dystrophies. The fact that the other new candidates are essential for nuclear/cellular mechanical stability and genome regulation supports the two main EDMD pathogenetic mechanisms with a better understanding of genetic heterogeneity and clinical variability in EDMD. In any case, further researches are certain to be done to find out more pathogenic genes for genetic diagnosis of EDMD, and to understand more clearly about the pathogenetic mechanism for treatment strategies.

Declaration of competing interest

The author declares no conflict of interest and no received funding for this work.

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