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Comprehensive target capture/next-generation sequencing as a second-tier diagnostic approach for congenital muscular dystrophy in Taiwan.

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Abstract

PURPOSE: Congenital muscular dystrophy (CMD) is a heterogeneous disease entity. The detailed clinical manifestation and causative gene for each subgroup of CMD are quite variable. This study aims to analyze the phenotypes and genotypes of Taiwanese patients with CMD as the epidemiology of CMD varies among populations and has been scantly described in Asia.

METHODS: A total of 48 patients suspected to have CMD were screened and categorized by histochemistry and immunohistochemistry studies. Different genetic analyses, including next-generation sequencing (NGS), were selected, based on the clinical and pathological findings.

RESULTS: We identified 17 patients with sarcolemma-specific collagen VI deficiency (SSCD), 6 patients with merosin deficiency, two with reduced alpha-dystroglycan staining, and two with striking lymphocyte infiltration in addition to dystrophic change on muscle pathology. Fourteen in 15 patients with SSCD, were shown to have COL6A1, COL6A2 or COL6A3 mutations by NGS analysis; all showed marked distal hyperlaxity and normal intelligence but the overall severity was less than in previously reported patients from other populations. All six patients with merosin deficiency had mutations in LAMA2. They showed relatively uniform phenotype that were compatible with previous studies, except for higher proportion of mental retardation with epilepsy. With reduced alpha-dystroglycan staining, one patient was found to carry mutations in POMT1 while another patient carried mutations in TRAPPC11. LMNA mutations were found in the two patients with inflammatory change on muscle pathology. They were clinically characterized by neck flexion limitation and early joint contracture, but no cardiac problem had developed yet.

CONCLUSION: Muscle pathology remains helpful in guiding further molecular analyses by direct sequencing of certain genes or by target capture/NGS as a second-tier diagnostic tool, and is crucial for establishing the genotype-phenotype correlation. We also determined the frequencies of the different types of CMD in our cohort which is important for the development of a specific care

system for each disease.

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