New era in genetics of early-onset muscle disease: Breakthroughs and challenges.

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Abstract
Early-onset muscle disease includes three major entities that present generally at or before birth: congenital myopathies, congenital muscular dystrophies and congenital myasthenic syndromes. Almost exclusively there is weakness and hypotonia, although cases manifesting hypertonia are increasingly being recognised. These diseases display a wide phenotypic and genetic heterogeneity, with the uptake of next generation sequencing resulting in an unparalleled extension of the phenotype-genotype correlations and "diagnosis by sequencing" due to unbiased sequencing. Perhaps now more than ever, detailed clinical evaluations are necessary to guide the genetic diagnosis; with arrival at a molecular diagnosis frequently occurring following dialogue between the molecular geneticist, the referring clinician and the pathologist. There is an ever-increasing blurring of the boundaries between the congenital myopathies, dystrophies and myasthenic syndromes. In addition, many novel disease genes have been described and new insights have been gained into skeletal muscle development and function. Despite the advances made, a significant percentage of patients remain without a molecular diagnosis, suggesting that there are many more human disease genes and mechanisms to identify. It is now technically- and clinically-feasible to perform next generation sequencing for severe diseases on a population-wide scale, such that preconception-carrier screening can occur. Newborn screening for selected early-onset muscle diseases is also technically and ethically-achievable, with benefits to the patient and family from early management of these diseases and should also be implemented. The need for world-wide Reference Centres to meticulously curate polymorphisms and mutations within a particular gene is becoming increasingly apparent, particularly for interpretation of variants in the large genes which cause early-onset myopathies: NEB, RYR1 and TTN. Functional validation of candidate disease variants is crucial for accurate interpretation of next generation sequencing and appropriate genetic counseling. Many published "pathogenic" variants are too frequent in control populations and are thus likely rare polymorphisms. Mechanisms need to be put in place to systematically update the classification of variants such that accurate interpretation of variants occurs. In this review, we highlight the recent advances made and the challenges ahead for the molecular diagnosis of early-onset muscle diseases.

KEYWORDS: Congenital muscular dystrophy; Congenital myasthenic syndrome; Congenital myopathy; Genetics; Next generation sequencing
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