

Muscular dystrophies: molecular genetic testing¹

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1. Muscular dystrophies are a group of diseases which are clinically and, even more so, genetically heterogeneous. This is best illustrated by the group of limb-girdle muscular dystrophies, for which 21 different types are known to date, all caused by mutations in different genes, including some which have yet to be identified [1]. Due to the low prevalence of most types of muscular dystrophies in Switzerland, genetic testing is only offered for a limited number of them. Currently, this is mainly for the most frequent types and those with a good mutation detection rate. Before genetic testing is initiated for a muscular dystrophy patient, it is essential to establish the diagnosis as precisely as possible by thorough clinical examination as well as biochemical, histological and immunohistochemical analyses. Only then molecular genetic testing can be performed in an efficient and economical way. In cases where the number of candidate genes can not be sufficiently limited, a haplotype analysis may be useful.
2. During the past two decades, the field of molecular genetic analysis has been rapidly evolving and this development is still continuing. On the one hand, there is the quantitative aspect of an ever increasing number of genes being identified and being integrated into molecular diagnostics. On the other hand, molecular genetic methods are being developed and/or improved for better performance, be it higher quality of results or increased speed and throughput. From the point of view of the molecular geneticist, the different types of muscular dystrophies could be subdivided according to the type of diagnostic approach they necessitate for detection of the pathogenic change. For Duchenne muscular dystrophy (DMD), the difficulties are twofold: firstly, while large deletions, as present in approximately 65% of patients, can be detected rather easily, the identification of duplications (5–10%) and heterozygous large deletions (for carrier detection) used to be quite demanding. Lately technical improvements, namely the introduction of multiplex ligation-dependent probe amplification [2], have greatly facilitated diagnostics of DMD deletions and duplications. Secondly, scanning

for point mutations, as present in approximately 30% of DMD/BMD patients, is tedious because of the size of the DMD-gene (79 exons, >2.4 Mb). Similarly molecular genetic analysis for LGMD is challenging due to the number of different genes involved, often necessitating time consuming sequential analyses of multiple genes. New methods such as high-resolution melting analysis [3] among others have greatly increased the speed and ease of mutation scanning. Only the last category of mutations, the triplet repeat expansions as present for example in myotonic dystrophy, is technically still quite difficult to perform. Despite attempts to find more convenient methods, to date these analyses are still best performed by Southern blotting.

3. New techniques, such as those mentioned above, have been rapidly spreading, while the next step forward is already in preparation. Currently in use mainly for research and/or in countries with large numbers of patients, it is expected that in the near future “Next generation sequencing” [4] will also become available for molecular genetic diagnostics in Switzerland. While “Next generation sequencing” (NGS) is currently still too costly and not yet suitable in a diagnostic setting for rare diseases, this is likely to change rapidly as NGS technology is spreading and their applications are multiplied. It can be anticipated that diagnostic testing will soon be possible either by means of “muscular dystrophy” arrays (limited versions are already available), or by whole exome or whole genome sequencing. This will substantially improve the diagnostic possibilities for many patients including those with rare forms of muscular dystrophies.

Key words: genetic heterogeneity; muscular dystrophies; genetic analyses; next generation sequencing.

References

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- 1 Lecture at the 1st congress Swiss Federation of Clinical Neurosocieties (SFCNS), June 2–4, 2010.

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