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The Persistence of Duchenne vs Becker Muscular Dystrophies

Vive la Difference?

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The diagnostic entity of Becker muscular dystrophy owes its name to a German neurologist and geneticist, Peter Emil Becker (1908–2000), who first described "a new type of X-chromosomal muscular dystrophy" in 1955.[1] At that time, Duchenne muscular dystrophy (DMD), another X-chromosomal muscular dystrophy, was already well recognized, but the patients identified by Prof. Becker were considerably less severe than those with DMD and they were capable of reproduction, with all daughters becoming X-linked carriers of the disorder.

With the advent of gene cloning and DNA diagnostics in the late 1980s, it became clear that patients with Becker muscular dystrophy had pathogenic variants in the same gene as patients with DMD.[2] Hence, Duchenne and Becker muscular dystrophies were different clinical severities of the same genetic disorder.

At this historical juncture, it could be appropriate to combine all variants of the *DMD* gene into a single diagnostic group of "dystrophinopathies"; however, the distinct entities have persisted. In the 2024 ICD-11 categorization by the WHO, Becker muscular dystrophy (8C70.0) is listed as the first type of muscular dystrophy and Duchenne muscular dystrophy (8C70.1) as the second. Neither entry references the other.

In this issue of *Neurology® Genetics*, Nakamura et al. in 2024[3] delve into genotype/phenotype correlations in a subset of patients with Becker muscular dystrophy having nondeletion pathogenic variants of the *DMD* gene (microvariants and duplications). There have been previous publications that have aptly described the quite variable natural history of Becker muscular dystrophy,[4-10] including a recent Japan-wide study of 225 patients.[11] All these studies have shown that the 2 most common variants in Becker muscular dystrophy are deletions of exons 45–47 and exons 45–48.

What sets this article by Nakamura et al. apart is the focus on the subset of patients with Becker muscular dystrophy with microvariant variants. The authors draw on their impressive Japanese registry and natural history study to focus on 49 patients; 16 showed duplications of 1 or more exons, and 33 patients showed microvariants defined as missense variants (single amino acid changes), nonsense variants (premature stop codons), and splice site mutations (variable inclusion of neighboring exons in the mRNA).

In focusing on the microvariants, the authors illustrate the inherent challenges of cleanly assigning a Becker vs Duchenne muscular dystrophy diagnosis to specific patients. To give an example, the pathogenic variant in their patient No. 29 (c.265-463A>G) had a splice site variant, and the patient carried the diagnosis of Becker muscular dystrophy based on the results of muscle biopsy (present, but abnormal dystrophin). However, this patient's sibling, who carries the same splice site variant, lost ability to walk at 14 years of age and was diagnosed with Duchenne muscular dystrophy.

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Another "gray" area in the Becker vs Duchenne muscular dystrophy assignments is nonsense variants. In the *DMD* gene, most nonsense variants are considered diagnostic of severe Duchenne muscular dystrophy. The authors included nonsense mutations in their Becker muscular dystrophy cohort because of reports that some nonsense variants in the *DMD* can be skipped over (by naturally occurring splicing or variant-induced exon skipping). Although possible, nonsense mutations with residual dystrophin expression may be the exception rather than the rule. An elegant French study determined the residual dystrophin in 26 patients with stop codon pathogenic variants in exons that could be "skipped" to an in-frame (Becker-like) transcript and found 69% to show 0% dystrophin, 23% to show between 0% and <5% dystrophin, and 8% to show >5% dystrophin.[12] In this article by Nakamura et al., 8 patients with Becker muscular dystrophy with nonsense variants were studied. Two shared the same c.10320T>A (p.T3440*) (exon 72) variant, with one losing ambulation before age 20 and the second also with relatively severe motor, pulmonary, and cardiac involvement (but remaining ambulatory after 20 years).

Key strengths of the article by Nakamura et al. include the impressive ascertainment of Becker muscular dystrophy throughout Japan, enabling the study of less common gene variants and their associated clinical features, based on type of genetic variant and position in the very large *DMD* gene. The authors report that clinical severity best correlates with the gene variant position within the *DMD* gene, where pathogenic variants toward the 3′ end of the gene (carboxyl terminus of the corresponding dystrophin protein) seem to show a more severe clinical phenotype. This fits well with the established model of sequential involvement of an increasing number of dystrophin protein isoforms as the location of the pathogenic variant moves toward the 3′ end.[13] Specifically, variants in the beginning of the *DMD* gene only affect the full-length 427 kDa dystrophin protein (Dp427), whereas variants in the very end of the *DMD* gene affect multiple dystrophin isoforms (Dp427, Dp140, Dp71), leading to more severe motor outcomes in patients with Duchenne muscular dystrophy.

The authors conclude that "currently, treatment for BMD is under investigation, but, to develop effective therapies, clinical data from a large number of patients with BMD with microvariants and duplications are required, as well as analysis of their genotype-phenotype profile." This statement could (and should) be debated. There is extensive allelic heterogeneity and clinical variation in symptoms, so recruitment into clinical trials of Becker muscular dystrophy will unlikely be based on specific pathogenic variants or variant classes (nonsense, splicing, etc.). Instead, one could argue that there is a continuum between Duchenne and Becker muscular dystrophies that can only partly and imperfectly be explained by specific pathogenic variant types or classes. A term currently utilized in some text books, "dystrophinopathies",[14] encompasses the range of clinical symptoms, from severe to mild. The term "Duchenne muscular dystrophy" is here to stay, in part due to the official name of the corresponding gene (*DMD* gene, not 'dystrophin' gene), and the classical clinical presentation and progression that is associated with 'null' (or nearly null) dystrophin protein in muscle. The term "Becker muscular dystrophy" is becoming more difficult to defend. Replacing this with "non-DMD dystrophinopathy" might better reflect the broad range of clinical symptoms, and be inclusive of carrier females showing symptoms as well.

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