# Impact of Deletion Screening in Differential Diagnosis of Becker and Limb-Girdle Muscular Dystrophies

Borut Peterlin, Janez Zidar[1] and Neza Zupancic[2]

*Division of Medical Genetics, Department for Obstetrics and Gynecology, University Medical Centre, Ljubljana, (1) University Institute for Clinical Neurophysiology, University Medical Centre, Ljubljana and (2) Department for Paediatrics, University Medical Centre, Ljubljana*

**Abstract**

Three patients (22 %) with Becker muscular dystrophy were found in the group of 14 male patients with clinical diagnosis of limb-girdle muscular dystrophy using PCR screening for deletions in the dystrophin gene. Specific diagnosis of BMD and DMD has an important impact on genetic counselling and epidemiology of progressive muscular dystrophies.

**Key words:** Becker muscular dystrophy, Limb-girdle muscular dystrophy, deletion screening, differential diagnosis.

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Duchenne and Becker muscular dystrophies (DMD, BMD) are severe X-linked recessive myopathies with an incidence of approximatively 1 in 3500 births. Manifestations of DMD are usually apparent before the age of 5 by wasting and weakness of predominantly proximal limb girdle musculature, calf pseudohypertrophy and high serum levels of creatine kinase. By the age of 12 affected boys are usually confined to a wheelchair and about ninety per cent die before the age of 20. BMD differs from DMD by later onset and more benign course of the disease.

Apart from skeletal muscle other tissues can be either directly (brain, heart, smooth muscle) or indirectly (skeletal system) affected by the disease.

While DMD and BMD are allelic and are due to mutations in the dystrophin gene, diagnosis of a limb-girdle muscular dystrophy (LGD) is a descriptive one and may represent a genetically heterogeneous group of disorders (Emery 1989). The term is most often used to delineate patients with muscular dystrophy who show preferential involvment of shoulder and pelvic girdles, or both. There is a considerable overlap in clinical picture and laboratory findings (EMG, muscle histology) between BMD and LGD which usually follows autosomal recessive inheritance pattern. Thus, the differential diagnosis between BMD and LGD is often difficult for neurologist, especially when a patient is male and has no family history.

After finding of a dystrophin gene (Koenig et al. 1987) and its protein product dystrophin (Hoffman et al. 1987) two new specific diagnostic tests emerged.

As a part of the epidemiology study of DMD and BMD in Slovenia we screened for deletion in the dystrophin gene 14 male LGD patients without family history of disease.

## Materials and Methods

*Patients*

Fourteen isolated male patients out of 71 patients with the diagnosis of LGD from Slovene register for neuromuscular diseases were analysed. All patients had proximal muscle weakness on examination, myopathic EMG and muscle histology characteristic of a primary muscular dystrophy.

*Deletion screening*

DNA was extracted from venous blood and multiplex polymerase chain reaction (PCR) performed to screen for deletions in the dystrophin gene as described elsewhere (Chamberlain et al. 1988, Beggs et al. 1990).

## Results and Discussion

Deletions were found in 3 out of 14 (22 %) patients with LGD.

Mutations mapped in the " hot spot" site for deletions in the dystrophin gene with the deletion involving exons 44, 45 and 45-48 in the three patients as detected by multiplex PCR.

Our findings are comparable with results of Norman et

al. (1989) who found deletions in 4 out of 15 (27 %) LGD patients using cDNA dystrophin probes, while Arikawa et al. (1991) reported misclassification in 4 out of 13 (31 %) LGD patients using parallel immunofluorescence and immunoblot to detect dystrophin abnormalities as well as DNA studies.

Deletions represent about 60 % of molecular mechanisms for mutations in the dystrophin gene (Den Dunnen et al. 1987, Koenig et al. 1989, Upadyaya et al. 1990) and 53 % in the panel of 45 slovene DMD/BMD patients (unpublished observations). Higher estimated misclassification rate in the study of Arikawa et al. (1991) could be thus interpreted by the failure of detecting BMD patients without deletions in the dystrophin gene in our study and the study of Norman et al. (1989).

In addition to LGD there are other muscular disorders important for differential diagnosis of BMD and DMD in different age groups. These include congenital muscular dystrophies, congenital myopathies, Emery-Dreifuss muscular dystrophy (Emery 1989), spinal muscular atrophy type III (Kugelberg-Welander)(Clarke et al. 1989) and male patients with autosomal recessive DMD (Vainzof et al. 1991).

Correct diagnosis is not only crucial for appropriate genetic counseling of patients and their families, but has an important impact on the epidemiological estimates of muscular diseases. Our preliminary results show that the proportion of incidence rates for BMD versus DMD is 28 % using deletion screening of the dystrophin gene as an additional diagnostic test. This estimate well correlates to report of Bushby et al. (1991), who used DNA and dystrophin analysis, but contrasts to reports that predate introduction of molecular genetic methods with reported ratio of 6-20% (Monckton et al. 1982, Tangsrud et al. 1988).

In conclusion, finding a significant proportion of BMD patients in the group of LGD implies the need to reinvestigate this group of patients with molecular genetic methods and to introduce these methods in the routine diagnostic procedure in neurology.

**Address correspondence to:**

Dr. Borut Peterlin, Division of Medical Genetics, University Department for Obstetrics and Gynecology, Šlajmerjeva 3, 61000 Ljubljana, SLOVENIA, tel: (38) 61 312 129, fax: (38) 61 101 110.

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