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FROM ADHALINOPATHIES TO ALPHA-SARCOGLYCANOPATHIES: AN OVERVIEW

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INTRODUCTION

Dystrophin, the defective protein in Duchenne and Becker muscular dystrophy, is associated with a complex of sarcolemmal glycoproteins linking the cytoskeleton of muscle fibres to laminin, a major component of the extracellular matrix [reviewed in 1 and 2].

It has been suggested that deficiencies in any component of the transmembrane linker may disrupt the link between the cytoskeleton and the extracellular matrix and lead to muscle necrosis [3].

The large oligomeric complex with dystrophin is comprised of three sub-complexes [2]:

1. Dystroglycan complex
 - α -dystroglycan (156DAG or A0)
 - β -dystroglycan (43DAG or A3a)
2. Sarcoglycan complex
 - α -sarcoglycan (adhalin or 50DAG or A2)
 - β -sarcoglycan (43DAG or A3b)
 - γ -sarcoglycan (35DAG or A4)
3. Syntrophin complex
 - α -syntrophin (59DAP or A1)
 - β 1-syntrophin (59DAP or A1)
 - β 2-syntrophin (59DAP or A1)

An additional sarcolemmal non-glycosylated protein (25DAP or A5) has been shown to co-purify with these complexes but has not been extensively studied.

Unlike the dystroglycan complex which is ubiquitously distributed, the three components of the sarcoglycan complex are muscle specific [4, 5].

A dramatic reduction of α -sarcoglycan (adhalin or 50DAG) was observed in patients affected with severe childhood autosomal recessive muscular dystrophy (SCARMD) [6, 7], with some reduction of the other members of the sarcoglycan complex. SCARMD was initially described in Tunisia [8] and further reported in patients from other North-African and Middle-Eastern countries [9-11], and in Western Europe [7]. SCARMD is now considered to be the most severe form of a continuum rather than a discrete entity [12]. In addition to this phenotypic heterogeneity the disease is also genotypically heterogeneous [13, 14], because in some cases the α -sarcoglycan (adhalin) gene itself is mutated (LGMD2D at 17q21.2) [15, 16], whereas in other cases the adhalinopathy is secondary to a primary defect involving another gene. Recently two such genes have been shown to be involved in SCARMD with adhalin deficiency: (i) the β -sarcoglycan gene at the LGMD2E locus (4q12) [17, 18], and (ii) the γ -sarcoglycan gene [19, 20] at the LGMD2C locus (13q12) [10, 21].

ALPHA-SARCOGLYCANOPATHIES

Using the powerful DGGE (denaturing gradient gel electrophoresis) method to screen the α -sarcoglycan gene in 50 unrelated patients with proximal muscle dystrophy and adhalin deficiency, we found mutations in 29 unrelated patients (Carrié *et al.*, in preparation). In this series 58 per cent of the patients explored belonged to the category of "primary adhalinopathies". We found 22 different mutations (two non-sense, three frameshift insertions or dele-

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tions, four splice mutations and 13 mis-sense). All the mis-sense mutations were in the extracellular domain, and were found in two-thirds of the mutated chromosomes. Five mis-sense mutations (four of which involved a CpG dinucleotide) were found more than once, with a striking prevalence of the Arg(77)Cys mutation (33 per cent of the mutated chromosomes), and of the Arg(284)Cys mutation (16 per cent of the mutated chromosomes). The recurrent mutations are carried by unrelated subjects on different haplotype backgrounds [16]. The Arg(77)Cys mutation has also been described in Japan [22] and Brazil [23]. The Arg(98)His has also been identified in an Afro-American girl with childhood-onset muscular dystrophy [24].

The severity of the phenotype varies greatly [16]. Patients with null mutations are more severely affected. A broad range of severity is observed in mis-sense mutations. Homozygous patients for the Arg(284)Cys mutations exhibit a milder disease than those with the Arg(77)Cys mutation. Very mild limb-girdle muscular dystrophies (LGMDs) could be underdiagnosed because some patients may simply complain of exercise intolerance, without symptoms of muscle wasting despite constantly elevated levels (30–50-fold) of serum creatine kinase. In these mild cases, muscle biopsies are not routinely performed and sarcoglycan deficiencies are not diagnosed. The actual frequency of α - and γ -sarcoglycan mutations could thus be higher than estimated from investigation of cases with the most severe form of SCARMD.

The widespread geographical origin of the 29 patients of this series (19 from Western Europe, six from North Africa, four from North America) suggests that α -sarcoglycanopathies are produced by world-wide independent mutations. In North Africa, where SCARMD had been primarily described, this severe phenotype is caused either by α - or by γ -sarcoglycanopathies.

QUESTIONS PENDING

After the initial discovery of adhalin deficiency in SCARMD, it became evident that the condition is not rare, that it is widely distributed, and that it is genetically and clinically heterogeneous. With the cloning of the three sarcoglycan genes, each on a different chromo-

some, and the finding that mutations in any of them produce muscular dystrophy, our understanding of the heterogeneous group of SCARMD/LGMD has greatly improved. Many questions are, however, still pending.

The first question regards the actual incidence of sarcoglycanopathies among the group of autosomal recessive muscular dystrophies. At present the data are still scarce and the figures vary from 2 to 12 per cent [25, 26]. This variation could be explained by sample bias or could mirror actual population differences.

Do the three categories of sarcoglycanopathies coexist in the same populations, and what is their respective incidence? We have evidence that both α - and γ -sarcoglycanopathies coexist in North Africa, whereas in Western Europe α -sarcoglycanopathies seem to be largely predominant. In α -sarcoglycanopathies, the clinical course is strikingly variable, ranging from childhood onset with Duchenne-like presentation to adult onset with minimal disability. The spectrum of different mutations is also striking, and we are currently trying to correlate them to the phenotype, essentially in case of mis-sense mutations, because null mutations invariably lead to severe forms of muscular dystrophy. It will be interesting to understand the impact of the different mis-sense mutations on the interactions of α -sarcoglycan with the other member of the sarcoglycan complex.

Another important issue is how to discriminate between the three sarcoglycanopathies? In the absence of a specific phenotype it is not possible to rely only on the clinical presentation. In familial cases linkage analysis with intragenic markers of each of the four cloned LGMD gene loci: α -, β - and γ -sarcoglycan (on chromosomes 17, 4 and 13, respectively) and calpain-3 (chromosome 15), and with markers of the still unknown gene at LGMD2B locus (chromosome 2) should be systematically performed, but this is not always feasible. In sporadic cases or in non-informative pedigrees the amount of residual protein seen on Western blots of muscle extracts seems to be a useful clue, the most defective signal corresponding to the gene harbouring the primary defect (unpublished data). In many cases the only method is to screen the different genes systematically. Practical integrated strategies are urgently needed for this purpose

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