

Linkage analysis of families with severe childhood autosomal recessive muscular dystrophy in Morocco indicates genetic homogeneity of the disease in North Africa

F El Kerch, A Sefiani, K Azibi, N Boutaleb, M Yahyaoui, A Bentahila, M-C Vinet, F Leturcq, L Bachner, J Beckmann, K P Campbell, F M S Tomé, M Fardeau, J-C Kaplan

Abstract

It has been previously shown in Tunisian and Algerian families that the locus for SCARMMD maps to the proximal part of 13q, and in Algerian families that the disease is associated with deficiency of the 50 kDa dystrophin associated glycoprotein (50DAG). We have tested this linkage in six families from Morocco where this disease is also prevalent. In one family the 50DAG was tested and found to be negative in a muscle biopsy. Our results showed similar linkage in this country, with statistical tests indicating genetic homogeneity between the three Maghreb countries.

(J Med Genet 1994;31:342-343)

Severe childhood muscular dystrophy (SCARMMD) is a Duchenne-like form of progressive muscular dystrophy affecting both sexes, first described by Ben Hamida and Fardeau in Tunisia.^{1,2} This autosomal recessive disease (MIM 253700) is prevalent in Tunisia and Algeria^{3,4} where it may be as frequent as Duchenne/Becker myopathies. The gene responsible has not yet been identified, but it was recently shown that: (1) in muscle specimens from Algerian patients the sarcolemmal 50 kDa dystrophin associated glycoprotein (50DAG) is absent whereas dystrophin and the other dystrophin associated proteins are normally present⁵; (2) the SCARMMD locus maps to 13q12 by linkage analysis, as shown first in three Tunisian families³ and confirmed in 13 Algerian families.⁶

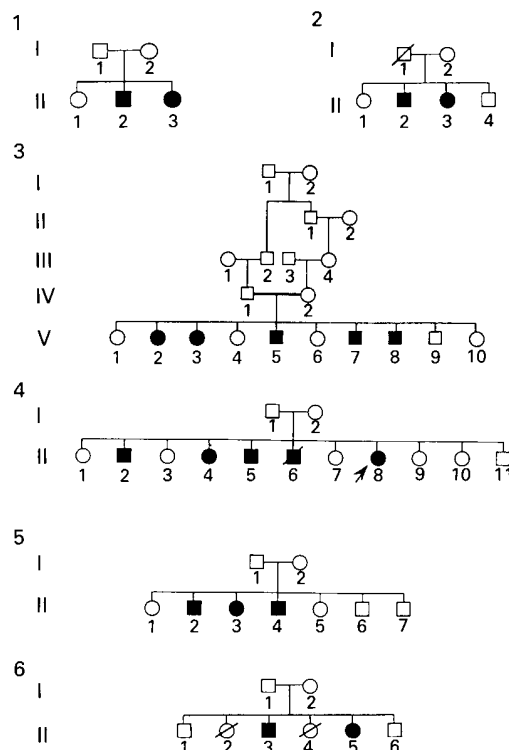
Like Tunisia and Algeria, Morocco belongs to the Maghreb, a geographical region of north west Africa characterised by a common Arabo-Berberic population with a high frequency of inbreeding. Therefore SCARMMD would also be expected to be prevalent in Morocco. Indeed, Duchenne-like families with affected girls are quite frequent in this country (M Yahyaoui, personal communication).

In the present study we have selected for linkage analysis six well characterised families from Morocco, comprising 18 patients (10 males and eight females) (figure). They were selected on the following obligate criteria: (1) a clinical and pathological pattern typical of SCARMMD^{1,2}; (2) multiplex families with at

least one female affected. In addition the diagnosis was further validated by finding 50DAG deficiency by immunofluorescence analysis of one muscle specimen^{5,7,8} (patient 8 of family 4, figure). The SCARMMD families were genotyped using the following microsatellite markers assigned to the proximal long arm of chromosome 13: D13S221 (AFM 248wcl)⁹ D13S175 (AFM2 49xbl),⁹ and D13S115,¹⁰ as described in Azibi *et al.*⁶

The cumulated two point lod scores¹¹ obtained with the three markers in the six families and a comparison with the data obtained in 13 families from Algeria⁶ are shown in the table. A search for genetic heterogeneity among the cumulated 19 SCARMMD families was carried out with the HOMOG program (version 3.31¹²) on the three sets of lod score values. No evidence for heterogeneity was found for informative families (data not shown).

The homogeneity of our linkage data in Morocco compared to those previously



Pedigrees of six families with SCARMMD. Arrow indicates patient in whom 50DAG was investigated.

Département de
Génétique et Biologie
Moléculaire, INH,
Rabat, Morocco
F El Kerch
A Sefiani

Service de Neurologie,
Hôpital des
Spécialités,
Rabat, Morocco
N Boutaleb
M Yahyaoui

Service de Pédiatrie,
Hôpital d'Enfants,
Rabat, Morocco
A Bentahila

Hôpital Bologhine,
CHU Alger-Ouset,
Algeria
K Azibi

CEPH, 27 rue Juliette
Dodu, 75010 Paris,
France
J Beckmann

Howard Hughes
Medical Institute,
University of Iowa
College of Medicine,
Iowa City, Iowa 52242,
USA
K P Campbell

INSERM 153 and
CNRS URA614, 17 rue
du Fer à Moulin,
Paris, France
M Fardeau
F M S Tomé

INSERM 129, Institut
Cochin de Génétique
Moléculaire, 75014
Paris, France
F Leturcq
L Bachner
M-C Vinet
J-C Kaplan

Correspondence to
Professor Kaplan.

Received 6 October 1993
Accepted for publication
10 November 1993

Cumulated lod scores in the six families with SCARMD

Marker	θ								
	0-000	0-001	0-01	0-05	0-1	0-15	0-20	0-30	0-40
D13S175									
Morocco*	−∞	−7.03	−3.03	−0.39	0.50	0.81	0.89	0.64	0.23
Algeria†	−∞	−9.87	−4.60	0.25	2.00	2.49	2.43	1.59	0.56
Cumulated	−∞	−16.90	−7.63	−0.14	2.50	3.30	3.32	2.23	0.79
D13S221									
Morocco*	−∞	−5.31	−1.35	1.15	1.85	1.96	1.82	1.15	0.37
Algeria†	−∞	−8.85	−2.98	1.43	2.64	2.78	2.51	1.56	0.61
Cumulated	−∞	−14.16	−4.33	2.58	4.49	4.74	4.33	2.71	0.98
D13S115									
Morocco*	−∞	−5.54	−0.63	2.36	3.08	3.10	2.83	1.79	0.60
Algeria†	−∞	−4.85	−1.34	1.60	2.45	2.49	2.21	1.37	0.58
Cumulated	−∞	−10.39	−1.97	3.96	5.53	5.59	5.04	3.16	1.18

* This study.

† 13 families of Azibi *et al.*⁶

obtained in Tunisia and Algeria suggests that SCARMD may be the result of the same defective gene and possibly the same mutation in all three Maghreb countries. This is not surprising because of the common origin of these populations. It would be interesting to determine whether the same locus is involved in SCARMD outside North Africa,¹³⁻¹⁵ and ultimately to define whether the 50DAG defect is primary or secondary to the gene defect.

This work was supported by the Association Française contre les Myopathies. We are grateful for the invaluable help of the Association Marocaine contre les Myopathies (Mr M I Alaoui), and the Cooperation Division of the French Embassy in Rabat. We thank Professor M Hassar for his support. KPC is an Investigator of the Howard Hughes Medical Institute.

- 1 Ben Hamida M, Fardeau M. Severe, autosomal recessive, limb-girdle muscular dystrophies frequent in Tunisia. *Exc Med Muscular Dystrophy Research* 1980;527:43-146.

- 2 Ben Hamida M, Fardeau M, Attia N. Severe childhood muscular dystrophy affecting both sexes and frequent in Tunisia. *Muscle Nerve* 1983;6:469-80.
- 3 Ben Othmane K, Ben Hamida M, Pericak-Vance M, *et al.* Linkage of Tunisian autosomal recessive Duchenne-like muscular dystrophy to the pericentromeric region of chromosome 13q. *Nature Genet* 1992;2:315-17.
- 4 Azibi K, Chaouch M, Reghis A, *et al.* Linkage analysis of 19 families with autosomal recessive (Duchenne-like) muscular dystrophy from Algeria. *Cytogenet Cell Genet* 1991;58:1907.
- 5 Matsumura K, Tomé FMS, Collin H, *et al.* Deficiency of the 50 K dystrophin-associated glycoprotein in severe childhood autosomal recessive muscular dystrophy. *Nature* 1992;359:320-2.
- 6 Azibi K, Bachner L, Beckmann JS, *et al.* Severe childhood autosomal recessive muscular dystrophy with the deficiency of the 50 kDa dystrophin-associated glycoprotein maps to chromosome 13q12. *Hum Mol Genet* 1993;2:1423-8.
- 7 Ohlendieck K, Campbell KP. Dystrophin-associated proteins are greatly reduced in skeletal muscle from *mdx* mice. *J Cell Biol* 1991;115:1685-94.
- 8 Ohlendieck K, Matsumura K, Ionasescu VV, *et al.* Duchenne muscular dystrophy: deficiency of dystrophin-associated proteins in the sarcolemma. *Neurology* 1993;43:795-800.
- 9 Weissenbach J, Gyapay G, Dib C, *et al.* A second-generation linkage map of the human genome. *Nature* 1992;359:794-801.
- 10 Hudson TJ, Engelstein M, Lee MK, *et al.* Isolation and chromosomal assignment of 100 highly informative human simple sequence repeat polymorphisms. *Genomics* 1992;13:622-9.
- 11 Lathrop M, Lalouel JM, Julier C, Ott J. Multilocus linkage analysis in humans: detection of linkage and estimation of recombination. *Am J Hum Genet* 1985;37:482-98.
- 12 Ott J. *Analysis of human genetic linkage*. Baltimore: The Johns Hopkins University Press, 1991.
- 13 Farag TI, Teebi AS. Duchenne-like muscular dystrophy in the Arabs. *Am J Med Genet* 1990;37:290.
- 14 Salih MAM, Omer MIA, Bayoumi RA, Karrar O, Johnson M. Severe autosomal recessive muscular dystrophy in an extended Sudanese kindred. *Dev Med Child Neurol* 1983;25:43-52.
- 15 Fardeau M, Matsumura K, Tomé FMS, *et al.* Deficiency of the 50 kDa dystrophin associated glycoprotein (adhalin) in severe autosomal recessive muscular dystrophies in children native from European countries. *C R Acad Sci [III]* 1993;316:799-804.