

A possible heterozygous advantage in muscular dystrophy

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In certain autosomal recessive disorders there is suggestive evidence that heterozygous carriers may have some selective advantage over normal homozygotes. These include, for example, cystic fibrosis, Tay-Sachs disease and phenylketonuria. The best example so far, however, is that of significant heterozygous advantage in sickle-cell anaemia with increased resistance to falciparum malaria.

S Afr Med J 2016;106(6 Suppl 1):S65-S66. DOI.10.7196/SAMJ.2016.v106i6.10998

I have known Peter since our early post-military days in the 1960s, and we have remained very close friends ever since. When he applied for the post of Professor in South Africa, I was very pleased indeed to support him. Later, in 1988, he would successfully propose me for Honorary Fellowship of the Royal Society of South Africa.

However, very few people know of a certain incident from our distant past, one which has cemented our ties. Peter once saved my life, and in a most incredible way. I had been lecturing in Pondicherry in India and had been housed in a local 'hotel'. But what a hotel! I was the only resident, there was no food and the manager, I discovered, dressed each evening as a woman and cycled into the village, leaving me the sole, unfed occupant of the lonely hotel. I developed a severe intestinal infection, the worst I had ever had. After 3 days I could no longer get out of bed; I was so weak and ill that I began to write my will. And on the fourth or fifth day I was awoken suddenly by banging on the bedroom door. It was Peter, who said he had heard of 'a foreigner in the village'. He more-or-less carried me to a taxi he had ordered, but when the young taxi driver learned that we wanted to travel to the British Consulate in Madras, he refused to take us. So Peter, and this is typical, said, 'If I buy your taxi, will you take us?' The young lad was astonished, and then delighted, to accept Peter's offer, and so for about £50 Peter was the proud owner of the taxi, with chauffeur. After the journey, which must have been about 3 hours (I wasn't aware of my surroundings at this point), we reached the British Consulate in Madras, whereupon Peter told the incredulous driver that he could keep his taxi. The young man no doubt left promptly, before these mad Englishmen changed their minds. The consulate immediately arranged for me to be flown home, and in Edinburgh I was treated with intravenous fluids and appropriate

therapy. It turned out to be giardiasis (a protozoan infection), and within a week or so I fully recovered – but had lost two stone in weight. I never forgot Peter's miraculous intervention, but never found out what on earth Peter was doing in Pondicherry! So Peter and I do have a bond for life.

In certain autosomal recessive disorders, there is suggestive evidence that heterozygous carriers may have some selective advantage over normal homozygotes. These include, for example, cystic fibrosis, Tay-Sachs disease and phenylketonuria. The best example so far, however, is that of significant heterozygous advantage in sickle-cell anaemia with increased resistance to falciparum malaria.^[1]

How a possible heterozygous advantage can be calculated has been detailed.^[2]

More recently, the possibility of heterozygous advantage has been suggested in the case of a rare autosomal recessive form of congenital muscular dystrophy (MDC1D).^[3] This disorder is caused by the mutation LARGE, in the gene locus at 22q12, which results in reduced glycosylation of α -dystroglycan, a protein located outside the muscle basement membrane (basal lamina) (Fig. 1).^[4]

The extracellular protein α -dystroglycan is known to bind to various extracellular proteins (perlecan, agrin and laminins).^[5] But most importantly, from the present point of view, α -dystroglycan provides a receptor for various pathogenic viruses, and this depends on effective glycosylation. There have been several recent reports detailing this molecular mechanism.^[6-9] The defective and reduced glycosylation in MDC1D might therefore be expected to affect its function as a receptor for several viruses including Lassa fever and other arenaviruses.^[10] In fact, glycosylation defects in fibroblasts are associated with resistance to murine leukaemia virus.^[11]

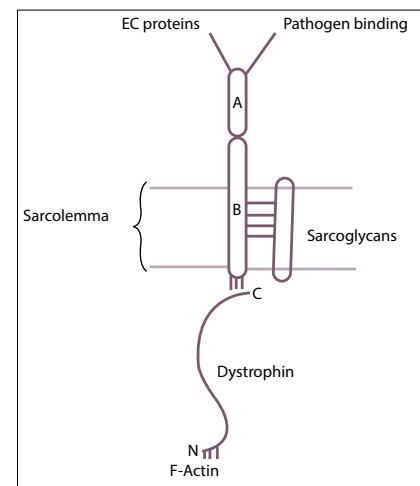


Fig. 1. Simplified diagrammatic representation of the relationship of α - and β -dystroglycans in the skeletal muscle membrane.

Those disorders that could be relevant in the present context include many haemorrhagic viral diseases in Central Africa, South America and India, which have been described in detail by Garrett^[12] and Karlen.^[13]

These haemorrhagic diseases all present with internal bleeding, shock and the majority of patients succumb, though a few do survive. These diseases include Ebola fever, of which there has recently been an outbreak in West Africa. The question therefore is: could heterozygotes for α -dystroglycan LARGE mutations be in any way resistant to these diseases? Could this be tested for by determining heterozygosity in those who succumb to the disease and those who survive?

Such studies would not have to be confined to one disorder but to any of the haemorrhagic disorders. Furthermore, screening for any other defects in α -dystroglycan could be revealing even if unrelated to congenital muscular dystrophy, which is presumably rare in such populations anyway.

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