This study[1] prompts a reappraisal of the Ashkenazi Jewish carrier screening panels currently in use in Israel and an analysis of the factors that determine what is a 'Jewish disease' to justify its inclusion in a carrier-testing panel. Carrier screening for GD in Ashkenazi Jews was included because it is one of the most prevalent recessive disorders in this community, for which testing is simple, and the test sensitivity is high. This may have occurred without a careful consideration of the benefits and/or harms of this choice; it may have been assumed that screening for more disorders is always desirable—a variation on the theme of 'bigger is better' or 'can do, will do'. As Zuckerman *et al* suggest, 'availability, rather than utility, of a test could be a major determinant of its introduction'.

In addition to this 'technological imperative', could it be that an 'ethnic identity imperative' has also operated as an important factor? Perhaps Jewish health services were reluctant to omit from their genetic screening programme a disease that is so strongly associated with this population—despite the lack of a solid rationale for its inclusion.

Despite formal opposition,[7–9] carrier screening for GD continues to be offered■

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ALS predisposition modifiers

Knock NOX, who's there? SOD1 mice still are

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The discovery that Zn/Cu superoxide dismutase (SOD1) gene mutations are responsible for 15–20% of familial forms of amyotrophic lateral sclerosis (ALS)[1] led to extensive studies of the susceptibility of the motor neuron to oxidative stress. The role of the normal SOD1 function—the conversion of toxic superoxide into less damaging hydrogen peroxide—in ALS pathogenesis remains unclear. It is, however, known that the restricted expression of mutant SOD1 in either motor neurons, microglia or astrocytes has repeatedly been demonstrated to be insufficient for an effective triggering of ALS symptoms.[2] Microglia, in particular, have the capacity to recognize a stressed neuron and either attempt to restore the function (immune response) or release toxic factors to prune the compromised neurons. In the case of ALS, this is particularly damaging because the neurons already have difficulty coping with superoxide radicals, which wildtype SOD1 would typically reduce and remove. It was observed that one of the redox-related genes, which is specifically upregulated in activated microglia in spinal cords responding in ALS, is *NOX2*.[3] The NADPH oxidase (NOX) enzymes operate by generating reactive oxygen species in a coordinated manner, often in response to inflammatory signals or microorganisms (Figure 1). Thus, by knocking out *NOX2* or other redox-related genes, it could be predicted that motor neurons would have less damaging and fewer insults from activated microglia. In an article by Marden *et al*[4], a hemizygous mouse that harbors a G93A SOD1 mutation was crossed with a mouse null for the *NOX1* or the *NOX2* genes. This result had a dramatic effect on the lifespan, in particular of *NOX2*-null mutant SOD1 mice, which survived on average 229 days compared with 132 days for the mice only with a G93A point mutation. This increase of almost 100 days is one of the largest effects observed for SOD1 mutant mice; most manipulations influence lifespan by at most 10–20 days. The exact nature of this benefit is not fully understood and should be the source of compelling future research.

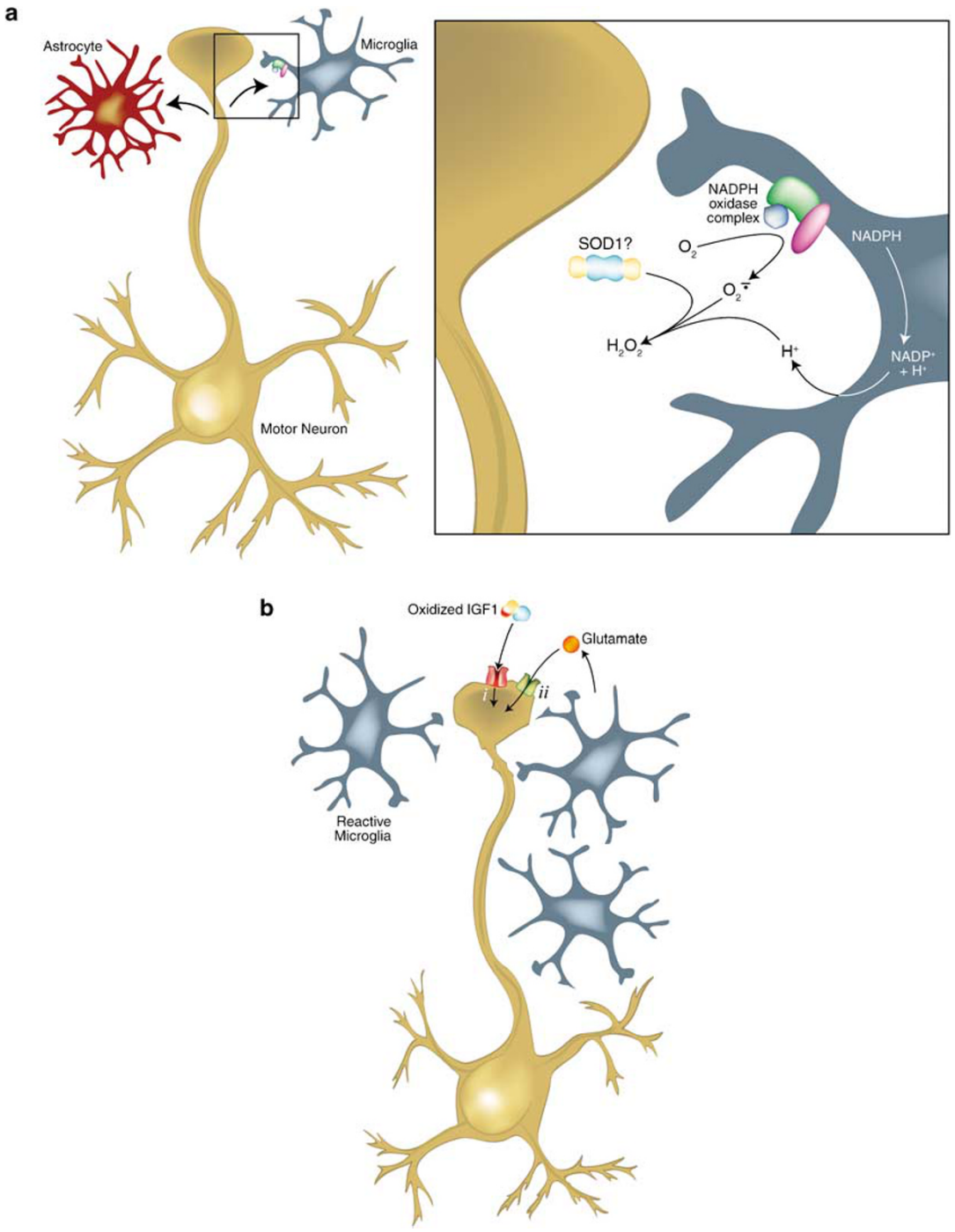

Figure 1 Effect of *NOX* genes on motor neuron physiology and motor neuron disease. (**a**) Prior to the onset of the disease, the motor neuron in mutant (G93A) SOD1 transgenic mice becomes stressed over time and sends signals to astrocytes and microglia. Microglia, in response to this stress (similar to their response to foreign attack by microorganisms), increase levels of NOX2, part of the NADPH oxidase complex. This complex generates toxic superoxide radicals that are converted to hydrogen peroxide by SOD1. (**b**) Increased superoxide and hydrogen peroxide concentration signals the recruitment and activation of additional microglia. Microglia activation and infiltration are often hallmarks of some of the detrimental effects of disease progression in the mouse. These reactive microglia can release toxic factors, including glutamate, a range of cytokines leading to high oxidative stress and excitotoxicity. This could lead to activation of receptors (GluR2, AMPA or IGF1 receptors) in the surface of motor neurons resulting in activation of signaling pathways (such as IGF1/Akt pathway) that target motor neurons for destruction. Knocking down *NOX2* may prevent the generation of superoxide anions, further activation of microglia and inhibition of some of these signaling cascades, thus preventing death of motor neurons. (*i*) IGF1/Akt pathway, (*ii*) GluR2 AMPA receptors.

To examine the role that redox genes have in prolonging the lifespan of G93A SOD1 mice, these animals were compared with animals that are heterozygous or homozygous for mutant *NOX1* or *NOX2* genes on the mutant G93A SOD1 mouse background. Median lifespan was extended by 11 days in heterozygous *NOX1* mice and by 33 days in *NOX1*-null homozygous mice. These levels were significantly different but much less than the levels observed for *NOX2*-deficient mice (54 days for heterozygous mice and 97 days for homozygous *NOX2*-null mice). Given the pronounced effects for *NOX2*-null mice, the morphological and behavioral effects on these mice were then carefully scrutinized. Superoxide production increases at the end-stage of disease for G93A SOD1 mice, but interestingly the levels were diminished to non-disease state following *NOX2* deletion. In addition, motor neuron counts, coordination and stride length were all increased in these mice. Muscle weight and size was also restored to near levels observed for wildtype mice with no SOD1 mutation.

These results are particularly encouraging in light of recent experiments that were quite similar but less spectacular. Wu *et al*[3] also crossed *NOX2* null mice with G93A mice, but they observed a more modest increase in lifespan of 14 days. Why do the mice bred by Marden *et al*[4] live dramatically longer? One key difference is the background strains used by the two groups (B6SJL[4] *versus* congenic C57BL/6J[3] strains). Modifier genes and other protective elements have been suggested to be present on the B6SJL background,[5] which could act additively or synergistically with the *NOX2* gene deletion for a more severe effect. This would correlate with human sporadic ALS cases where multiple genetic factors almost certainly exist and which interact to cause disease. Another explanation for the disparity in the results may have something to do with another unexpected feature of the mice studied by Marden *et al*[4]: 12.5% (1/8) of heterozygous mice and over 75% (19/25) of G93A mice homozygous for the *NOX2* deletion were affected with a severe eye infection positive for *Staphylococcus aureus* that leads to rapid death if left untreated. Eye abnormalities are not something present in ALS (in humans or in mice). In mice with a noticeable eye infection, an antibiotic treatment using gentamicin and ceftazidime was administered, followed by 14 enrofloxacin subcutaneous injections if the symptoms were not alleviated. Some of the mice without eye infections also had an increased lifespan. However, the antibiotic treatment could certainly have influenced the progression of the disease in the treated mice, particularly in combination with *NOX2* gene loss. This is something worth examining further.

Given the remarkable benefits observed from an absence of the *NOX2* gene in the SOD1 G93A mice, the potential effects in humans must be considered. The presence of both *NOX1* and *NOX2* on the X chromosomes has important implications if considering how modifier genes may act. Male ALS patients have an increased predisposition to ALS (1.3–1.6:1 ratio) in sporadic forms of the disease.[6] Thus, if the *NOX* genes are *bona fide* modifier genes, regulatory changes in these genes, which increase *NOX* gene production, would have a greater effect in males and help explain this gender bias. In addition, ALS patients who have SOD1 mutations (~2% of all ALS cases) could have their age of onset of disease or absolute susceptibility influenced by different *NOX* genotypes.

Another critical question is: How can these results translate to therapeutics? As is often the case with mice models, a fair deal of caution must be exercised when correlating mouse effects to human, especially when considering the unexpected discoveries (eye disease) and variable effects (based on mouse strain differences) described above. Nonetheless, these findings provide exciting potential for experiments that decrease *NOX* genes in ALS patients to prevent activation of microglia and build-up of superoxide, particularly in patients positive for SOD1 mutations. The theme of oxidative stress as an influential aspect in ALS has received a great deal of attention. The interplay between toxic SOD1 and NADPH oxidases releasing superoxide in surrounding microglia suggests that even more consideration for oxidative stress in ALS is warranted■

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