European Journal of Human Genetics (2008) 16, 139–144

www.nature.com/ejhg

NEWS AND COMMENTARY

Carrier screening: look before you leap

Carrier screening for type 1 Gaucher disease: difficult questions

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European Journal of Human Genetics (2008) **16,** 139–140;
doi:10.1038/sj.ejhg.5201960; published online 28 November 2007

Since the introduction and success of the Tay–Sachs carrier screening programme in the 1970s, carrier screening for diseases common in the Ashkenazi Jewish community has expanded. The carrier screening panel now commonly offered includes up to 14 autosomal recessive diseases. A recent article[1] examined the scope and outcomes of carrier screening for type 1 Gaucher disease (GD) in Israel.

Zuckerman *et al*[1] reported that 10 Israeli genetic centres screened an estimated 28 893 individuals for GD between 1995 and 2003, identifying 82 carrier couples at risk for offspring affected by GD type 1. In subsequent pregnancies of these couples, there was a 76% uptake of prenatal diagnosis, leading to a termination of pregnancy for 15% (2 of 13) of the fetuses predicted to be no more than mildly affected and 67% (two of three) of the fetuses with predicted moderate disease.

This study[1] raises questions regarding the appropriateness of a carrier screening programme for GD. Although GD is one of the most prevalent Ashkenazi Jewish genetic diseases, with a carrier frequency in the population studied of almost 6%, there are strong arguments against providing carrier screening for this disorder. Firstly, the most common GD mutation in Ashkenazi Jews leads to a highly variable but usually mild or symptomless phenotype. In addition, those who are affected can be successfully treated with enzyme replacement therapy. Therefore, it is ethically questionable to set out systematically to identify carrier couples and offer them prenatal diagnosis and the termination of pregnancy for a condition that will usually not be severe and is treatable. Is GD type I simply too 'mild' to be included in a carrier screening programme?

A closely related topic for discussion is the goal of this screening programme. In the article of Zuckerman *et al*, they define the main goals as the 'reduction in birth prevalence of newborns affected with the disease through termination of pregnancies'. Taking this as a goal for genetic carrier screening implies that the success of that screening programme depends on the extent to which it influences the reproductive behaviour of (pregnant) participants. To the extent that genetic screening programmes are evaluated in terms of their success in reducing the incidence of particular genotypes, genetic services will inevitably have a stake in seeing that their clients make the 'right' reproductive options.[2,3] Therefore, several authoritative bodies have stated that 'the goal of reducing the incidence of genetic conditions is not acceptable; professionals should not present any reproductive decision as 'correct' or advantageous for a person or a society'.[4] These bodies state that the goal of a carrier screening programme 'consists in giving the participants the opportunity to make informed choices'.[5] Paradoxically, Zuckerman *et al*[1] state in their conclusion that the main possible benefit of their screening was 'allowing couples at risk to be identified and make an informed choice'. Are we to take any informed reproductive decision as good in itself, to be maximised, whatever the human cost of imposing the decision?

Although Zuckerman *et al*[1] reported that 'participation is voluntary', it seems that individuals participating in the carrier screening programme undergo testing for all disorders in the panel. While it may be unrealistic to expect individuals to select which genetic tests they want to undergo, offering the tests as an all-or-nothing battery is scarcely compatible with the rhetoric of informed reproductive decision making. Furthermore, when couples were provided with additional information and a discussion about GD type I with a clinical expert in the disease, there was a very substantial reduction in the proportion of 'affected' pregnancies that were terminated; this greatly weakens any rationale for offering this screening.

In the carrier screening programme for GD, the effect of testing has been to generate predictive genetic test results for a (mostly) adult-onset disorder both (a) directly, as asymptomatic homozygotes were identified through carrier screening, and (b) indirectly, through prenatal diagnosis performed on the pregnancies of some carrier couples. The use of genetic testing in this way is highly contentious. Predictive genetic testing promoted in the guise of carrier testing could mislead participants. Furthermore, predictive testing of minors is only recommended when established and effective therapeutic or preventive measures exist, which can be initiated before adulthood, so that prenatal predictive testing of the fetus most certainly contravenes many carefully considered recommendations.[6] In all other cases, it is stated that testing should be postponed until the person is old and/or competent enough to make an informed choice. This is based on the rationale that predictive testing in childhood or adolescence could create serious social, emotional, psychosocial, and educational consequences in minors and downplays ethical concerns regarding the autonomy of decision making and the privacy of genetic information. Furthermore, the clinical utility of the test is debatable as many homozygotes may never develop overt disease, and in those who do, disease severity is usually mild.

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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European Journal of Human Genetics (2008) **16**, 140–142;
doi:10.1038/sj.ejhg.5201961; published online 28 November 2007

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.