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Odds and SODs

The recent report in *Nature* that the gene for amyotrophic lateral sclerosis (ALS), often referred to as Lou Gehrig's disease, is none other than Cu, Zn-superoxide dismutase (*SOD1*)[1], has prompted a considerable amount of media coverage on both sides of the Atlantic, and for good reason. After all, the baseball legend Lou Gehrig played a staggering 2,130 consecutive games for the New York Yankees, from 1925 until 1939, before becoming too ill to continue. He retired one month after he was diagnosed with ALS, and died in 1941. (The fact that Gehrig's playing streak may finally be surpassed by one Cal Ripken, Jnr in about 1995 makes it no less remarkable.) And in Britain, the achievements of the renowned theoretical physicist Stephen Hawking are all the more astounding because he has survived ALS for some 25 years[2]. The *Nature* paper was dedicated to Oscar Horvitz, a victim of ALS whose son, Robert Horvitz, a distinguished geneticist, was a co-author. The vast majority of ALS cases (about 1–2 per 100,000 people) are sporadic with no clear epidemiological cause. The hope now, of course, is that the discovery of the familial ALS gene (which accounts for about 5% of ALS) may give epidemiologists the lead that they have been searching for[3,4].

The search for the ALS gene intensified in 1991 when it was mapped (after a seven year effort) by an international consortium headed by Teepu Siddique and Robert Brown to chromosome 21 (in some families)[5]. Interestingly, *SOD1* has been one of the mainstays of the chromosome 21 genetic map since it was localized 20 years ago. And so, after the discovery of linkage, the possible connection between ALS and *SOD1* was entertained, at least for a while. The apparent genetic heterogeneity the consortium encountered prevented a precise localization for the ALS gene. But according to Siddique, SOD1 had been mentioned as a possible candidate in the first draft of the linkage manuscript, but was subsequently removed. Unfortunately, in a scene reminiscent of the search for the Alzheimer's gene — examination of the gene for the amyloid precursor protein, also on chromosome 21, was delayed in the face of conflicting linkage data — it was another two years before this possibility was pursued in earnest for ALS.

The original linkage report[5] presented an analysis of 23 ALS families that resulted in a significant logarithm-of-odds (lod) score (>5) 10 centimorgans away from the marker *D21S58*. This placed the ALS gene at chromosome 21q22.1-22.2; however, almost half of these families did not show linkage, thereby deflating the overall score and casting a shadow over the results. Moreover, *SOD1* was only rarely polymorphic, and so could not usefully be examined in the linkage investigations. The next 18 months saw considerable effort in isolating new informative markers to refine the localization of the ALS gene. But when, just a few months ago, the glutamate receptor subunit GluR5 was mapped in the vicinity of the ALS gene[6], many gladly speculated that the glutaminergic hypothesis (which proposes that neurons may be destroyed through exposure to excessive levels of glutamate), and specifically a defect in the GluR5 gene, were the cause of familial

ALS. Meanwhile, members of the ALS consortium had defined a dozen or so microsatellite markers to compile a haplotype of the *ALS* region. One such marker, *D21S223*, was amplified from a cosmid in this region and showed tight linkage to *ALS*. Initially, it was reported that the peak lod score occurred with *SOD1* at 2 cM (suggesting at that time a significant physical separation between the two). But, says Brown, the idea of *SOD1* as a candidate gene resurfaced at a muscular dystrophy meeting late last year. This notion was sealed when first, *D21S223* did not recombine with *ALS* in six families known to map to chromosome 21, and second, a portion of *SOD1* was found in the same cosmid as *D21S223*, placing them just kilobases apart.

From that moment, the pieces fell into place in short order. Mutations in *SOD1* were found in exons 2 and 4 in affected members of 18 ALS families, leaving no doubt as to the genetic defect and provoking interesting speculation as to the biochemical basis of the disease[7]. Siddique told *Newsweek*: "We haven't slain Goliath, but we certainly feel like a David who's been introduced to the slingshot." Quite.

SOD is an extraordinarily well studied (if not yet fully understood) enzyme about which volumes of research papers have been published during the past two decades. In simple terms, its role is to remove damaging oxygen free radicals from the cell by reducing them to hydrogen peroxide, which in turn is removed by other enzymes. SOD1 is not only found in virtually all organisms, but it is also expressed in the majority of mammalian tissues. How, then, could a putative defect in *SOD1* manifest itself only in motor neurons? Could it simply be a consequence of the lack of turnover of motor neurons, or is there a more specific target of free radical damage? And how do a cluster of missense mutations in an enzyme give rise to a dominantly inherited disease, unless they somehow result in a gain of function? The fact that SOD1 exists as a homodimer provides an adequate, if unspectacular, explanation[1].

In the wake of the ALS finding, interest has turned towards the two other known SODs: the mitochondrial form (Mn,SOD) which maps to chromosome 6q25, and an extracellular form that has been localized to chromosome 4 (ref. 8). Neither location corresponds to the only other known form of ALS that has been mapped — a recessive trait on chromosome 2 (ref. 9) — but they are enticing candidate genes for other disorders. Some 25% of dominantly inherited cases of ALS have still to be accounted for.

Meanwhile, work continues on unravelling another great mystery associated with ALS — the bizarre explosion of cases on the Pacific island of Guam after the Second World War[3,4]. The incidence of Guamanian ALS as well as outbreaks in areas of Japan and New Guinea, has been linked to the ingestion of the highly toxic cycad seeds, popular among the native population. (The disease is now on the decline, presumably due to the improved education of the general public.) Two constituents of these seeds, the amino acid β-*N*-methylamino-L-alanine (BMAA) and the cytotoxin cycasin, are the chief suspects. Although BMAA can produce ALS-like symptoms when injected into monkeys[10], it is unlikely to be the sole explanation of Guamanian ALS. Recent work has shown that cycasin is taken up by cortical explants of neurons (possibly through the glucose transporter), leading to neurodegeneration in a matter of days[11]. One interesting hypothesis is that cycasin is hydrolysed in neurons to an aglycone known as methylazoxymethanol (MAM). MAM is capable of alkylating DNA, and as DNA repair is notoriously poor in nerve cells, a cumulative effect on protein synthesis might result in neurodegeneration. Perhaps free radicals affect a similar pathway. □

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Lorenzo Odone

In *Nature Genetics* **3**, 95–96; February 1993, Lorenzo Odone (the boy suffering from adrenoleukodystrophy who is featured in the film *Lorenzo's oil*) was wrongly said to be in a "vegetative state". On the contrary, his parents quote a teacher as saying that Lorenzo can see, hear and communicate by gesture and Dr Donald Fishman, the neurologist who originally diagnosed Lorenzo's condition, as saying that "the child's survival to date ... must be considered marvellous". □