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Implications of confirmed *de novo* pathogenic SOD1 mutations

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Leading sentence: The implications of confirmed de novo pathogenic mutations in SOD1 are far-reaching for current clinical practice and future genetic research.

Progress has been made in the study of ALS genetics in recent years but there remains debate regarding the role of mutations which develop *de novo* in a patient, rather than being inherited from one or both parents. Theoretically such mutations should occur but relatively few are reported. The mutation rate is estimated at 1.8×10^{-8} per nucleotide per generation [1], and therefore all individuals must carry *de novo* genetic changes. Moreover, ALS-associated mutations are not embryonically lethal and so there is no obvious reason why *de novo* forms of such mutations should not be present in ALS patients. Occurrence of *de novo* mutations could explain minimal or even absent family history for patients carrying mutations which otherwise behave in a monogenic fashion. Such observations are often attributed to 'variable penetrance' which has led to a search for therapeutic targets to reduce penetrance.

Conversely, if penetrance is actually 100%, but sporadic instances of monogenic disease are the result of *de novo* changes, then searching for therapeutic modifiers may prove futile. To differentiate between these two alternatives requires genetic profiling of patients and their biological parents to demonstrate that a candidate *de novo* mutation is not inherited. That is exactly what Müller and colleagues have achieved in their study published in this issue of the journal [2]. By sequencing 4,100 sporadic ALS patients and their parents, the authors discovered four instances of mutations within SOD1 which were absent from both parents. They took important steps to be sure that the correct biological parents had been sequenced. Moreover, in each case, the reported SOD1 mutations had been previously reported in familial SOD1-ALS and co-segregation with disease confirmed: this helps to overcome any doubts about the validity of the changes observed.

The authors extended their work with evidence for mutational hot-spots within the SOD1 gene associated with codons Ala5 and Asp102. This was based on observed clusters of mutations associated with limited or absent family history which had arisen in multiple population groups. This is contrasted with other mutations, such as p.Asp91Ala, where a common founder is postulated based on haplotype analysis. This important observation will help the search for further *de novo* mutations.

The study by Muller and colleagues addresses the issue of somatic mosaicism which is linked to *de novo* mutations. Presumably the patients described in this report were the product of germline mutations, although it remains plausible that similar *de novo* mutations could occur at any stage of nervous system development. ALS is a nervous system-specific disease and as a result, a mutation may cause disease and still be absent from peripheral blood, which is the usual source of DNA for routine diagnostic screening. To uncover the role of such somatic mutations will require substantial investment to sequence not only multiple individuals but also multiple tissues. This work lays the foundation for such a study. It is possible that somatic mutations play a role in the apparent disparity between broad-sense heritability for ALS which is measured at ~50%, and the much smaller (<10%) SNP-based heritability [3] measured from peripheral blood.

Finally, the authors point out the important clinical implications of their observations. If *de novo* mutations are a significant cause of apparently sporadic ALS, then clinicians will only detect these patients through routine genetic screening rather than confining screening to patients with a family history of disease [4]. In an age where gene therapy for SOD1-ALS is a reality, this is a pertinent truth [5].

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