Progress has been made in the study of amyotrophic lateral sclerosis (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 $1.8 \times 10^{-8}$ per nucleotide per generation, 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 patients with ALS. 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. By sequencing 4100 patients with sporadic ALS 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 changes should occur but relatively few are reported. The mutation rate is estimated at $1.8 \times 10^{-8}$ per nucleotide per generation, 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 patients with ALS. 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.

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Correspondence to Dr Johnathan Cooper-Knock, Sheffield Institute for Translational Neuroscience (SITraN), University of Sheffield, Sheffield, UK; j.cooper-knock@sheffield.ac.uk

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. In an age where gene therapy for SOD1-ALS is a reality, this is a pertinent truth.

Contributors J-C-K conceived and drafted the manuscript.

Funding This work was supported by Wellcome Trust (216596/Z/19/Z).

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Commissioned; internally peer reviewed.

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To cite Cooper-Knock J. J Neurol Neurosurg Psychiatry 2022;93:118.

Received 19 September 2021
Accepted 22 September 2021
Published Online First 1 October 2021

http://dx.doi.org/10.1136/jnnp-2021-327520

J Neurol Neurosurg Psychiatry 2022;93:118.

doi:10.1136/jnnp-2021-327935

ORCID ID

Johnathan Cooper-Knock http://orcid.org/0000-0002-0873-9689

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