SPECIAL COMMENTARY

The importance of offering early genetic testing in everyone with amyotrophic lateral sclerosis

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Several genetically-targeted therapies are being developed for ALS. Research is increasingly supportive of a greater incidence of clinically actionable variants in sporadic ALS than previously reported. Salmon et al. outline the need to improve access, and offer genetic testing to all people diagnosed with ALS.

Amyotrophic lateral sclerosis (ALS) is a fatal and heterogeneous neurodegenerative disease, with only modestly effective therapies currently approved. While the underlying cause of the majority of ALS cases remains unknown, genetic variations linked to ALS have provided a tangible target for therapeutic development. As such, development of therapies aimed specifically at ALS-causing genes has been rapidly evolving in recent years. With clear evidence demonstrating incidence of ALS-associated pathological variants in isolated cases of ALS, it is becoming increasingly untenable to reserve testing for those with a family history alone. To ensure that all ALS patients with clinically actionable variants are...
identified, and can access treatments, there needs to be both broader access to and earlier offering of
genetic testing for people newly diagnosed with ALS.

Genetic research has revealed genetic variations in more than 40 genes to be associated with
causing ALS.\textsuperscript{7, 8} Expansions of chromosome 9 open reading frame 72 (C9orf72), and variants in
superoxide dismutase 1 (SOD1), TANK-binding kinase 1 (TBK1), fused in sarcoma (FUS), and
TAR DNA-binding protein 43 (TARDBP) are the most prevalent globally.\textsuperscript{9} Regionally,
prevalence varies, with C9orf72 predominantly affecting European and North American
populations, and SOD1 being the most prevalent genetic variation in many parts of continental
Asia.\textsuperscript{10, 11} Mendelian dominant inheritance with high penetrance accounts for approximately 5-
10\% of ALS, often as familial cases; however, reduced disease penetrance, recessive inheritance,
and pleiotropism (particularly for frontotemporal dementia; FTD) appear to be frequent, with
pathological variants found in many cases diagnosed with apparently isolated disease (Table 1).
In addition, it is expected than even variants with high penetrance will be found in people with
no family history of disease\textsuperscript{12} and the distinction between familial and apparently sporadic
disease is outdated.\textsuperscript{13} \textit{De novo} mutations and risk genes have also been associated with causing
isolated ALS.\textsuperscript{14}

There are currently different definitions of familial ALS (fALS) versus sporadic ALS (sALS) in the
literature, without consensus within the scientific and clinical communities. From a clinical perspective,
these entities are indistinguishable.\textsuperscript{7, 15} While causative ALS genetic variants are largely associated with
having a family history of the disease, incidence of known variants in the sporadic ALS population is well
reported in the literature (Table 1).\textsuperscript{7, 8, 16, 17} Therefore, with underlying genetic causes being present in both
fALS and sALS, as can be seen in Table 1, there is often no clinically useful difference between the two
terms.

An underlying genetic cause of disease provides a more tangible target for drug development,\textsuperscript{18} and
antisense oligonucleotide (ASO) and siRNA therapies have taken centre stage as being first out of the
gate. Data from the clinical trial of tofersen, an ASO targeting SOD1 – causing reduced expression of
both the mutant and wild-type protein – were recently released.\textsuperscript{19} While the trial failed to meet the
primary endpoint as was anticipated, neurofilament, a marker of neurodegeneration, was reduced, as were
SOD1 protein levels. Encouraging trends in the data indicate a need to treat early, and a clinical trial using
tofersen in presymptomatic carriers, ATLAS (NCT04856982), is already underway. This emphasizes an
urgent need to proactively address predictive testing in at-risk family members, while recognizing the
added considerations regarding benefits and risks, as well as the psychosocial implications. While it took
more than 20 years from the discovery of SOD1 for this novel ASO to reach large scale human trials, the
knowledge gained has laid the foundation for significantly decreasing drug development timelines in this
area. For example, launch of a first-in-human trial of an ASO targeting the C9orf72 repeat expansion
(NCT03626012) was achieved in less than seven years from its discovery in 2011. There are now
active clinical trials targeting SOD1 (NCT02623699), FUS (NCT04768972), C9orf72 (NCT03626012,
NCT04931862) and ATXN2 (NCT04768972). While presence of the underlying genetic alteration is a
requirement for participation in these clinical trials, presence of a family history is not. Genetically-
targeted therapies are likely to soon become mainstream in ALS, and confining testing to individuals with
a family history is no longer tenable. There are numerous reasons why a family history of the disease
could be missed. In particular, smaller family sizes and reduced or age-dependent gene penetrance
results in an increased probability of ALS appearing sporadic, furthering the concept that distinguishing
fALS and sALS is purely artificial. As such, restricting clinical genetic testing to individuals reporting a
family history will inevitably lead to patients with a genetic aetiology being unable to access emerging
therapies, and it is imperative that all people living with ALS are offered genetic testing.

While genetic testing does not contribute to confirming or excluding a diagnosis of ALS, which is
highlighted in the recent Gold Coast diagnostic criteria, many current guidelines for clinical
management of ALS are outdated or do not address genetic testing at all. The 2009 American Academy of
Neurology ALS Practice Parameters, the 2020 Canadian Best Practice Recommendations for the
Management of ALS, and the 2015 UK National Institute for Health and Care Excellence ALS
Guideline do not discuss genetic testing. The 2007 Clinical Guidelines from the European ALS
Consortium Working Group, and the 2011 European Federation of Neurological Societies Guidelines on
Clinical Management of ALS indicate that clinical genetic testing should be reserved for those patients
with a family history of the disease or the D90A-SOD1 phenotype. In addition, all of these were
published prior to the discovery of the C9orf72 repeat expansion, which confirmed the previously
reported notion of phenotypic variance in ALS, furthering that practice of including frontotemporal
dementia, and related disorders, in family history enquiries. The lack of guidelines for genetic testing in
ALS has led to divergent testing practices globally. Guidelines on genetic testing for ALS are
necessary given the scientific complexities, such as variant interpretation, and knowledge translation
requirements, regardless of the specialist providing counselling, to ensure an informed decision is being
made.

Recent studies have demonstrated that the previously conceived idea that ordering genetic testing on the
basis of family history alone results in patients with a monogenetic etiology to their disease not being
identified. A study of apparently sporadic ALS showed that there was an increased risk to relatives
because a proportion of people subsequently had a second relative affected. A UK study performed clinical genetic testing, using a 44-gene panel, in 100 new ALS diagnoses. Pathogenic variants were identified in 21 patients, with 15 cases meeting inclusion criteria for genetically-targeted therapy trials, despite only 7 patients reporting a family history of ALS. An Italian study using whole genome sequencing in a population-based cohort identified clinically significant pathogenic variants in almost 30% of their ALS cases. Additionally, 13% of their ALS cases were found to have clinically actionable variants. Furthermore, genome-wide association studies of people with apparently sporadic ALS consistently find Mendelian disease gene variants. Finally, studies have concluded that the number of SOD1 and C9orf72 ALS cases should be greater in the sALS population than in the fALS population.

Early identification of patients is also crucial. In fALS, it is unclear how much of the observed pathology seen in post-mortem studies is directly due to the gene defect, and how much damage may be attributed to secondary effects, collateral damage and compensatory mechanisms, particularly since the remaining cells are the ones that have survived the disease process so far. Studies using transgenic rodent models indicate that the disease process begins a considerable amount of time prior to any physical symptoms. Therefore, targeting the initial upstream pathological mechanism is likely critical in arresting disease progression and limiting widespread pathology.

Advances in genetic technologies have undoubtedly contributed to identifying new variants. Increased testing will contribute valuable data to resources, such as the ClinGen Variant Curation (CGVC), and guidelines, such as the American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG/AMP), which can aid in variant interpretation and guide development of therapeutic strategies and precision medicine.

The offer of genetic testing to all people newly diagnosed with ALS does not come without the need for reflection. Appropriate genetic counselling, ensuring an informed decision based on an evaluation of both risks and benefits, and consideration for challenging psychosocial scenarios, such as a variant identified in an individual with no previous family history, need to be addressed. Much like our understanding of genetics in ALS and the advent of genetic therapies, this discussion is an evolution that anticipates a, hopefully, not so distant future when a therapy is approved.

In conclusion, drug development for genetically targeted therapies in ALS is rapidly advancing, and all people with ALS who could potentially benefit from these emerging therapies need to be identified. There is an increasing body of evidence for a genetic component to all ALS. Given that fALS and sALS are clinically indistinguishable, and the lack of relevance for therapeutic access, there is a need to retire this distinction with regards to access to genetic testing, and treat all new ALS diagnoses equal. ALS-
associated genetic variations in seemingly isolated ALS are expected, well reported in the literature, and not infrequent, and recent studies have demonstrated that widespread genetic testing identifies patients living with ALS who have clinically actionable variants. All patients diagnosed with ALS, regardless of clinical presentation or family history, need to be offered appropriate genetic counselling, and clinical genetic testing for ALS-associated genetic variations. Genetic testing needs to be offered early to ensure timely access to therapeutic intervention.

Current clinical management guidelines are lacking when it comes to genetic testing in ALS. Recognizing the need to change practices, and introduce widespread genetic counselling and testing in ALS, needs to start occurring now, and cannot wait for these publications to be updated.

Finally, there are numerous regions, globally, that do not have access to genetic testing for ALS. There is a need for further engagement with ALS clinicians practicing in under-represented geographies to better understand how these practices would fit into diverse cultural and socioeconomic populations. It is of the utmost importance that this disparity be addressed, as it is clear from the literature that our current understanding of genetic ALS is predominantly biased towards populations and countries that have had the privilege of conducting such research. Broader access to genetic testing will not only provide access to novel therapies but increase our overall understanding of ALS.

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Table 1 Reported incidence of some ALS-causing genetic variants in familial and sporadic ALS populations

| Gene   | fALS | sALS |
|--------|-----|-----|
| C9orf72 | 40% | 7–10% |
| SOD1   | 20% | 2–4% |
| TDP-43 | 5%  | 1%  |
| FUS    | 4%  | <1% |
| ATXN2  | 1%  | 1%  |
| Total  | 70% | 11–16% |

Although numerous genes have been associated with ALS, this table includes those for which therapeutics are currently being developed. It should be noted that frequency of these variants vary greatly from region to region, with some countries having no significant incidence. Our knowledge is biased towards countries where epidemiology and population studies have been conducted, and this information remains unknown for numerous regions globally.
Several genetically-targeted therapies are being developed for amyotrophic lateral sclerosis (ALS). Research is increasingly supportive of a greater incidence of clinically actionable variants in sporadic ALS than previously reported. Salmon et al. outline the need to improve access, and offer genetic testing to all people diagnosed with ALS.