Gene-Hunting in ALS and Related Disorders: Why It Matters to Every Family

In the search for new treatments for amyotrophic lateral sclerosis (ALS) and related disorders, nothing is more important than understanding the causes of the disease. Finding the cause is like finding the first domino in a chain—it explains how the whole disease cascade is set in motion. And researchers believe that attacking the disease at the beginning of the cascade—stopping that first domino from falling—is the best hope for effective treatments that can alter the course of the disease process.

While some proportion of cases are likely to be due to environmental factors, such as toxins, scientists increasingly believe that genes play a role in most cases of ALS. Some important genes have already been discovered (see Table), but the search to find new genes is urgent in order to better understand what causes ALS and related disorders. And a better understanding of the disease process will help development of treatments for all forms of these diseases, whatever their cause.

Weak Effects in Multiple Rare Mutations Can Add Up to ALS

In some cases, the presence of a single mutated gene is enough to cause the disease. That's the case with the SOD1 and C9orf72 genes, the most common genetic causes of ALS, as well as a growing number of rarer genes. C9orf72 is also a major cause of frontotemporal dementia (FTD). But researchers think there are likely to be many other genes, that, when mutated, each increase the risk of ALS by a small amount. In this scenario, ALS occurs when a person has not just one, but several of these mutations.

These weak, rare genes are much harder to discover than the strong, common ones like SOD1 and C9orf72. But finding them is likely to be the best way to really understand the large majority of ALS that is not caused by those common mutations.

The realization that ALS can develop from multiple weak genes also means that genes likely underlie many cases of "sporadic" ALS, or ALS that doesn't appear to be inherited, which makes up about 90% of all ALS cases.

While the genetics of primary lateral sclerosis (PLS), and progressive muscular atrophy (PMA) are not as well understood, it is likely that similar principles hold in these disorders. As its name implies, hereditary spastic paraplegia (HSP) is thought to be an inherited disorder, but here too, there are more genes to be found.

Finding New ALS Genes by Pooling Data

The search for genetic causes of neurodegenerative diseases has undergone a revolution in the past decade. Early studies were only able to find a gene mutation with a strong effect, such as SOD1, which was inherited within families. Later, "genome-wide association studies" of hundreds of people with ALS began to identify individual genes with weaker effects, such as TDP-43.

But such studies are unable to detect genes with the weakest, but still significant, effects. Nor can they detect the combined effect of multiple weak genes. For that, researchers need to pool data from many thousands of people with ALS, to amplify the weakest genetic "signals" so they rise above the background "noise."

Pooling data to promote population-wide genetic studies is beginning to provide researchers with an unprecedented look at the genes that cause ALS and related disorders. Already, such studies have identified several new genes. As the function of these new genes is explored, they are likely to lead to better understanding of the neurodegenerative disease process, the critical first step in developing treatments.

Just as pooling genetic data can provide new insights into ALS and related disorders, so can pooling clinical data. And combining the two can give researchers a far deeper understanding of how genes influence the onset, manifestation, and progression of the disease.

Accelerating Research with a GUID

People with ALS and related disorders stand out for their willingness to contribute to the research effort, volunteering for clinical trials, donating tissue samples, and encouraging others to get involved. For many, that means becoming involved in more than one clinical trial, or donating tissue to more than one study.

When data sets are pooled, it is important that scientists be able to know when the same individual is represented in each set. Removing such redundant entries is critical for accurate analysis. Currently, this is a laborious process. A new system, called the Global Unique Identifier (GUID), is increasingly being used to make the process as simple as pressing a button.

With the help of their clinician, a person with ALS can receive an encrypted, anonymous GUID, a combination of letters and numbers that is unique to them. The GUID is attached to the patient record, DNA sample, or other data source for that person. The GUID travels with the data wherever it goes, allowing easy identification of redundant samples, while maintaining patient anonymity.

To learn more about the GUID, and how you can receive your own unique identifier, click here. LINK

The Role of CReATe in the Search for New Treatments

The **Clinical Research in ALS and related disorders for Therapeutic Development** (CReATe) consortium is part of the collaborative effort to find new treatments for ALS, FTD, PLS, PMA, and HSP. The goals of the CREATE consortium are to advance therapeutic development for this group of neurodegenerative disorders through study of the relationship between clinical phenotype (the visible manifestations of disease) and underlying genotype (the gene or genes involved), and also through the discovery and development of biomarkers.

CReATe will promote the integration of collaborative, large-scale genetic sequencing analysis with clinical data, merged using the GUID, in order to accelerate the search for new treatments for ALS. Keep checking back at the CReATe website for updates, new information, and ways to be involved.

Table

Genes that Cause ALS
Genes in bold account for the largest proportion of cases

Gene	Protein
SOD1	**Cu/Zn superoxide dismutase**
ALS2	Alsin
ALS3	Unknown
SETX	Senataxin
SPG11	spastic paraplegia 11 (autosomal recessive)
FUS	Fused in sarcoma
ALS7	Unknown
VAPB	Vesicle-associated membrane protein-associated protein B
ANG	Angiogenin
TARDBP	TAR DNA binding protein 43
FIG4	FIG4 homolog, SAC1 lipid phosphatase domain containing (S. cerevisiae)
OPTN	Optineurin
ATXN2	ataxin 2
VCP	valosin-containing protein
UBQLN2	ubiquilin 2
SIGMAR1	sigma non-opioid intracellular receptor 1
CHMP2B	chromatin modifying protein 2B
PFN1	profilin 1
ERBB4	v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 4

HNRNPA1	heterogeneous nuclear ribonucleoprotein A1
MATR3	matrin 3
CHCHD10	coiled-coil-helix-coiled-coil-helix domain containing 10
C9orf72	**chromosome 9 open reading frame 72**
UNC13A	unc-13 homolog A (C. elegans)
DAO	D-amino-acid oxidase
DCTN1	Dynactin
NEFH	neurofilament, heavy polypeptide 200kDa, heavy chain
PRPH	Peripherin
SQSTM1	sequestosome 1
TAF15	TAF15 RNA polymerase II, TATA box binding protein (TBP)-associated factor, 68kDa
SPAST	Spastin
ELP3	elongation protein 3 homolog (S. cerevisiae)
LMNB1	lamin B1

Adapted from the ALS Online Database http://alsod.iop.kcl.ac.uk/Als/index.aspx