An online ALS database that has been ten years in the making is offering researchers a comprehensive look at the genetics of ALS. Researchers using the database—and there are a lot of them—can not only find information quickly and efficiently, they can use it to ask new questions and develop new hypotheses about the disease, speeding the search for a cure. The database, called ALSoD (ALS online genetics database) is freely available at http://alsod.iop.kcl.ac.uk.

ALSoD was the topic of a recent webinar featuring Ammar Al-Chalabi, M.D., Ph.D., Professor of Neurology and Complex Disease Genetics at King’s College, London. The webinar was hosted by ALS Association Chief Scientist Lucie Bruijn, Ph.D., who began by noting that she is often asked whether ALS scientists share data, given the reputation for competition among researchers. “ALS researchers really do share a lot of data. This database is a major testament to that.”

The understanding of the genetics of ALS has progressed exponentially over the past decade. Three genes are widely accepted as causing ALS: SOD1, TDP43, and FUS. But many others have been implicated, Dr. Al-Chalabi said, a total of 96 so far. The evidence for some is stronger than for others.

“Keeping up with this ever-changing genetic field is challenging, and reviewing the credibility of new genes is also challenging,” he said. The traditional way of evaluating that credibility, and of seeing new patterns emerge in a changing field, was in a review paper, written by an expert in the field. But the ALSoD database offers a new way.

“The aim of the database is to summarize everything that is known about ALS genetics in one place,” allowing researchers to evaluate new genes and look for new patterns themselves.

The value of this open approach is due to the complexity of the genetics of ALS, Dr. Al-Chalabi said. “In five percent of families, there is a positive family history,” meaning more than one member is affected. “But that is likely to be an underestimation.” Many gene mutations are “incompletely penetrant,” meaning not everyone carrying the mutation will be affected. In addition, environment, lifestyle, and other factors probably play a role. “Only if your risk burden passes a certain level will you develop the disease,” he continued.

Despite this complexity, a stark fact emerges. “By age 85, every person has a 1 in 300 chance of developing ALS,” an incidence similar to that of multiple sclerosis.

In the database, each of the 96 genes is listed and linked to a wide variety of information about it in the context of ALS. The data about genes can be organized and viewed in terms of mutation, protein function, associated symptoms, geographical distribution of patients, or other parameters.

For instance, it is possible to view the rough location of each mutation across a country or a continent, revealing “founder effects” (the inheritance of a rare mutation by a group of descendants). Other data, such as climate and industry, can be overlaid on a map of ALS cases, allowing epidemiologists to ask questions about environmental influences.
The proteins made by each gene take part in biological “pathways,” a series of reactions and signal exchanges that contribute to cell function. Just by clicking a few buttons, a researcher can see how different genes might interact in such pathways, allowing them to form hypotheses about cause and effect in the development of disease. Both TDP43 and FUS, for instance, affect the processing of RNA. Might other genes in this pathway also cause ALS?

The different symptomatic effects of each gene can also be compared side by side. Patients with SOD1 mutations are more likely to have onset in the limbs, while symptoms in those with TDP43 mutations are more likely to begin in the swallowing muscles. By looking at these and other differences, researchers may be able to uncover new leads to explore in animal models. While such information has been available outside the database, the ability to immediately make many such comparisons suggests new questions and speeds research.

The database is currently accessed 18,000 times per month, and its content grows with each new publication in ALS, requiring the efforts of several volunteers and full-time staff. They have plans to expand it, both in terms of its function and accessibility. An iPhone app is on the way, for instance, allowing a scientist to explore an idea while sitting in a meeting or riding on a train. Dr. Al-Chalabi would also like to expand the database to include information on frontotemporal dementia, a disease that occurs in some people with ALS.

“This is an incredible resource,” Dr. Bruijn said, “and it is highly appreciated by researchers. Its value only increases as it grows, and as more of the ALS research community takes advantage of it.”

No one database, device, or technique can solve the challenges of finding new treatments for ALS, she added. “But this database is an important tool in kit for speeding the discovery of those treatments.”

To view Dr. Al-Chalabi’s presentation in its entirety, you may do so by following this link: https://alsa.webex.com/alsa/ldr.php?AT=pb&SP=MC&riID=63243002&rKey=28e9859addf9e092