The ALS Association has supported the creation of multiple efforts to harness the power of “big data” to understand the causes of ALS and to discover new approaches to treatment. Among the most innovative is GTAC, or Genomic Translation for ALS Care, led by Matthew Harms, M.D., Associate Professor of Neurology at Columbia University Medical Center in New York. In a recent webinar, Dr. Harms spoke about the search for understanding of ALS in the genomic era, and how GTAC is helping to lay the foundation for “precision medicine” in ALS.

Among the most striking facts about ALS is that there appear to be multiple forms of the disease, characterized by different ages of onset, rates of progression, pattern of spread among the muscle groups and other aspects of the disease. This heterogeneity likely points to different underlying causes, Dr. Harms said, “and if we could figure them out, we could develop different treatments based on them for each group.”

That is the promise of precision medicine, which, Dr. Harms explained, is an emerging approach for disease prevention or treatment that considers the uniqueness of an individual’s genetics, environment and lifestyle to determine the best forms of treatment. Precision medicine, which is a goal for medicine as a whole, is only beginning to take shape as more is learned about the complex factors that lead to disease in each individual.

Exploring genes has been extremely fruitful for understanding the different types of ALS, he said. “We are now discovering a new ALS gene every four months, on average. So we can now start to look for patterns among these genes, and find the cellular pathways they disrupt, to understand the biology of the disease.”

The almost three dozen known genes for ALS appear to be grouped into fewer than half a dozen pathways, including regulation of protein folding, recycling of damaged cellular material, transport of materials along neurons and metabolism of the cellular messenger RNA.

For people with ALS, sequencing of either the entire genome (all a person’s DNA) or just their exome (the 2% of their DNA that encodes proteins) has revealed that even those without a family history may harbor gene variants that increase risk of disease. As whole genome sequencing becomes more common, and scientists learn more about interpreting the sequences they find, it is likely that yet more ALS risk genes will be discovered.

While several individual genes, such as C9orf72 and SOD1, account for the lion’s share of known inherited causes of ALS, there is much more to be found. The combination of several genes, each of which increases ALS risk only slightly, can lead to a person developing ALS who has no family history of the disease, Dr. Harms pointed out. Multiple studies, including those from Dr. Harms’s group, have found that multiple genes are involved in up to 14% of familial ALS, and up to 3% of sporadic ALS. It is likely that many more such low-risk genes will turn up as more whole genomes are sequenced.
Bringing together multiple research groups, each with large data sets of people with ALS, has led to new discoveries, including the recently announced genes TBK1 and NEK1. “TBK1 works in the recycling pathway, and so designing drugs to accelerate that pathway may be helpful,” Dr. Harms said.

“Largely because of the support of patient advocacy groups such as The ALS Association, multiple research teams are continuing to work together,” he added, noting the recent effort to pool existing whole exome data to search for more risk genes.

Newer studies are focused on prospectively collecting samples and detailed clinical data and performing whole genome sequencing. That is the focus of GTAC, which is funded through a partnership of The ALS Association national organization, The Greater New York Chapter of The ALS Association and the biotech firm Biogen.

The GTAC consortium includes 9 sites across the US and 1 in Scotland. The study, which is now enrolling people with ALS, will collect biosamples and clinical information over a three-year period to serve as a rich source of data for precision-medicine-focused gene discovery and treatment development. In addition, participants enrolling in the study will be asked to complete questionnaires on environmental exposures, modules similar to those that have been developed for the CDC National ALS Registry. “We expect to find that ALS is a combination of genetic problems and environmental exposures,” Dr. Harms said.

Anyone over 18 with a motor neuron disease may be eligible. “We want all comers, even if you already have a genetic diagnosis,” he said. PALS can be enrolled in other studies, with few exceptions. A unique aspect of GTAC is that those enrolled can learn about their individual genomes, with genetic counseling, if they so choose.
The efforts of GTAC will synergize with those of several other studies currently in progress, including the CReATE consortium, Project MinE and Answer ALS. “The ALS Association has been instrumental in helping all these projects and in promoting collaboration among them,” Dr. Harms said.

You can learn more about GTAC, including your eligibility [here](#) using the clinicaltrials.gov trial number NCT02795897.

Visit the GTAC strategic initiative page [here](#) for more information.