Leveraging the Combined Power of Genetics and Imaging for Rare Diseases

Accurately diagnosing and identifying patients with rare diseases pose significant challenges in the development and commercialization of new treatments for this underserved patient population.

At Konica Minolta, we believe the best way to solve this problem is through an integrated approach that combines state-of-the-art imaging technologies with quality genetic testing.

Leveraging Konica Minolta's core technologies in advanced optics and machine-learning, our Precision Medicine Initiative brings together Invicro and Ambry Genetics, two leaders in imaging and genetic testing, respectively, to provide a comprehensive solution to de-risking and enhancing drug discovery, development, patient-identification, and commercialization for pharmaceutical and biotechnology companies.

To understand how these two technologies can be integrated into solutions in support of development of new therapies for rare diseases, we discuss with Matthew Silva, Ph.D., EVP at Invicro and Brigette Tippin Davis, Ph.D., FACMG, Sr. VP at Ambry Genetics, a case study involving a patient with amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease.

Specifically, we discuss the accuracy and time-saving of utilizing a combined approach to accurately diagnose this patient. Additionally, we highlight follow-up analysis that can be performed to inform clinical development.

Case study

A patient presented with muscle weakness in the neck and head region, respiratory weakness with ineffective cough and difficulty swallowing beginning in mid-adolescence. The patient was tentatively diagnosed with an unknown motor neuron disease (UMN). Standard tests examining muscle function revealed signs of neuromuscular dysfunction. However, additional testing with MRI and targeted genetic testing for a single early-onset neuromuscular disorder were inconclusive and did not identify the patient's disorder. Biochemical and genetic testing was normal. The family history was negative for similarly affected individuals.

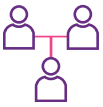
Why was this case a challenging case?

MATT: The patient had undergone conventional brain and cervical MRI without a clear indication for the underlying disease. While MRI enables non-invasive assessment of ALS-related pathology, the MRI findings correlate weakly with clinical score and must be interpreted with caution. Presentation of hyper intensities along the corticospinal tracts, which is indicative of ALS, can be variable and inconclusive. Additionally, mild decline in global brain volume and more significant regional frontotemporal atrophy may sometimes be observed; however, these volumetric changes may differ depending on the region of disease onset (i.e., spinal versus bulbar).

BRIGETTE: Although there were signs pointing to ALS, such as muscle weakness and respiratory issues, the age at which these symptoms started to present was inconsistent with the typical symptom onset age for ALS. The natural history of ALS indicates that most people who develop ALS are between the ages of 40 and 70, with the incidence in men occurring at a younger age than women. This patient was much younger than average. Additionally, this patient had a genetic test for spinal muscular atrophy (SMA) that was negative.

What was Ambry's solution to diagnose this patient?

BRIGETTE: Following previously negative genetic and metabolic testing, the patient's sample was sent to Ambry Genetics for trio exome sequencing along with their parents' samples. Whole-exome sequencing (WES) provides a one-step simultaneous interrogation of virtually all protein-coding sequences in the genome and has been remarkably successful both in a diagnostic setting (clinical exome sequencing) and as a discovery tool (research exome sequencing). In 2011, Ambry Genetics became the first commercial laboratory to offer clinical grade WES service (ExomeNext™) that leverages the power of trio data, a unique inheritance-based bioinformatics filtering pipeline, and robust data curation to bring an end to the diagnostic odyssey experienced by more than one-third of previously undiagnosed patients.[1] ExomeNext takes advantage of a database with a dynamic design for classifying genes as either characterized or uncharacterized for a genetic disorder using a standardized scoring method[2]. The Ambry scientific team evaluates newly-released peer-reviewed literature to incorporate the latest discoveries and the optimized scoring system.



Trio exome analysis in the patient and parents revealed a de novo pathogenic deletion (p.D502Tfs*27 c.1504delG), in the FUS gene in the patient which was absent in unaffected parents. Mutations in this gene have been associated with ALS (OMIM_608030) which is generally inherited in an autosomal dominant fashion. In an autosomal dominant disorder, the mutated gene is a dominant gene located on one of the non-sex chromosomes (autosomes). Only one mutated gene is required to be affected by this type of disorder. In this case, this deletion had been previously reported in a male patient who initially presented with spinal-onset of symptoms at 19 years of age and had rapid disease progression but was still alive at the time of report after a 15-month disease duration.[3] Functional analysis showed that a downstream alteration, c.G504fs*12, resulted in protein mislocalization.[4]

What would Invicro's solution be for this patient?

MATT: In patients with ALS, conventional MR imaging—including T2-weighted (T2W), proton-density-weighted (PDW), and FLAIR sequences—can reveal abnormalities along the corticospinal tracts; however, the presentation is variable among patients. To reduce variability, it has been shown that the merger of multi-spectral T2W, PDW, and FLAIR through image registration and combination methods may increase the sensitivity of detecting abnormalities in patients.[5] Beyond the MRI acquisition methods, advanced analytical tools developed at Invicro are assisting radiologists to identify and segment features that may be variable, uncommon, and subtle. Invicro deploys Machine Learning (ML) and Artificial Intelligence (AI) alongside rich domain knowledge in imaging physics and analysis to develop and deploy tools that enable quantification of global and regional disease markers that enhance the diagnostic value of medical imaging.

Having confirmation of the disease with imaging and genetics, what are some additional analyses that can help inform the drug development process?

BRIGETTE: Ambry has a team of scientists that can go beyond the mutation to uncover the potential biological consequence of this mutation. For example, our structural biologists can identify the structural context of the deletion and frameshift to help elucidate the mechanism of pathogenicity. In the case of the FUS mutation, Ambry scientists were able to determine that the identified mutation altered the sequence of the protein towards the C-terminus which likely prevented binding of the mutant FUS protein to Transportin, a protein shown to be important for correct cellular localization of FUS (Fig. 1).[6] A clear understanding of how the mutation affects the 3-D protein interaction can guide rational drug design potentially informing druggability of the target.

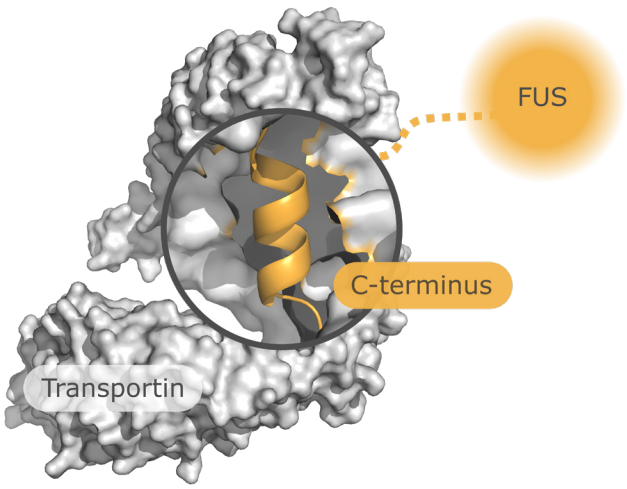


Figure 1. The interaction between the c-terminus of FUS (yellow) and Transportin (gray) is necessary for the healthy function of FUS. Structure generated using PDB ID: 4FQ3.[6]

MATT: At Invicro, we have a long history of developing and applying advanced imaging to neurodegenerative diseases. Through a combination of novel imaging methods and complex imaging analytics, we can improve diagnostic sensitivity and provide best-in-class monitoring of CNS-targeted molecules to improve drug development. In this case of ALS, in addition to convention MRI methods, monitoring patient progression and interventional drug response could benefit from brain metabolite assessment by magnetic resonance spectroscopy (MRS) or neuronal tractography by diffusion tensor imaging (DTI). Across several studies, MRS has demonstrated a marked reduction in N-acetyl-aspartate (NAA) in ALS that corresponds to neuronal dysfunction and integrity and may correlate with UMN clinical signs.[7,8,9] In ALS, declines in two critical DTI features—fractional anisotropy and mean diffusivity—are observed in corticospinal tracts and may improve diagnostic sensitivity when deployed alongside conventional MRI.[10]

Beyond MRI, there are also nuclear imaging methods, including positron emission tomography (PET) and single photon emission computed tomography (SPECT) that may enable two critical aspects of drug discovery and development: (1) Detection and monitoring of molecular signatures of the disease and (2) evaluation of the pharmacokinetics and pharmacodynamics (PK/PD) of novel investigational compounds. Emerging PET imaging methods may offer customized insight to the underlying impact of FUS mutations on ALS. FUS mutations have been associated with dysfunction in DNA damage response and inhibition of motor neurons to repair oxidative damage leading to neurodegeneration[11,12,13]. PET ligands that monitor both ROS[14] and HDAC[15] have been advanced to clinical studies and could be applied to evaluate drug efficacy in the FUS pathway for ALS.

Another emerging PET tool that may provide a powerful tool in the monitoring of neurodegenerative diseases is synaptic vesicle protein SV2A.[16] An example of an SV2A assessment by brain PET imaging with a selective tracer, [^{18}F]MNI-1126, is shown in Figure 2.[17]

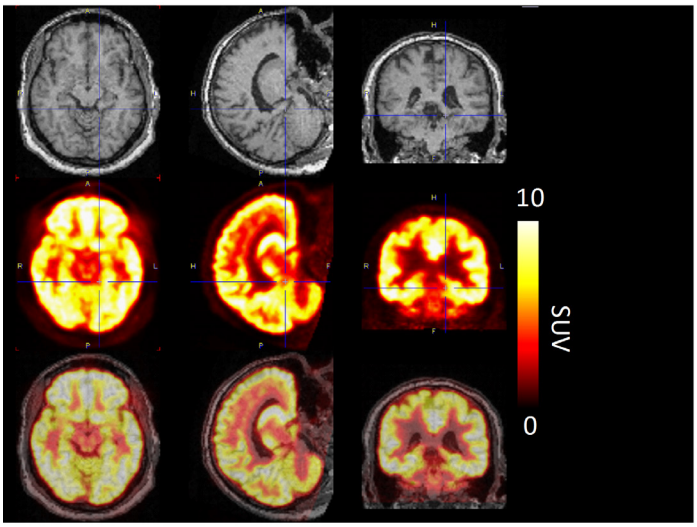


Figure 2. Example brain PET scan using the SV2A ligand [18F]MNI-1126 from a healthy volunteer. The PET image (averaged from 30 to 90 min following tracer injection) is shown in the pseudo-color SUV scale and overlaid on an MRI for anatomical reference. Regional brain kinetics obtain from dynamic PET may better describe disease signatures as compared to a whole brain composite metric. (Unpublished, Invicro data)

In summary, our case study highlights where standard imaging and routine genetic analysis may not be enough for patients with rare diseases. Ambry Genetics' advanced clinical genetic exome testing combined with Invicros' state-of-the art imaging analytics and customized PET ligand capabilities provide comprehensive profiling of rare disease patients to reduce time to accurate diagnosis and accelerate drug trials. Our successful partnerships with companies developing drugs for rare diseases have enabled access to therapies and improve outcomes for patients.

Learn more: PrecisionMedicine.KonicaMinolta.com

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