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Title: Real-Time Clinical Pathogenicity Assessment of HSP Variants in a Commercial U.S. Laboratory

Abstract:

Athena Diagnostics is a molecular genetics diagnostics company specializing in the diagnosis of rare neurological, renal and endocrine disorders including Hereditary Spastic Paraplegia. For up to 25% of Athena's patients, the most significant result is a DNA sequence variant of unknown clinical significance (VUS). Overall, up to 50% of our DNA sequence variants do not have a reference in literature, common databases or control/normal populations. Our clients are most often physicians and geneticists for whom a clear and complete clinical report is very important. Enhanced interpretation of VUS is critical for achieving a clear and complete clinical report. To address this issue, we have developed Athena Insight™ to translate the latest research and powerful databases to the clinic by significantly enhancing VUS result reports. A Virtual Grand Rounds presentation with audio-supported slideshow describing the Athena Insight™ service and reporting can be found at: www.athenadiagnostics.com/athenainsight

AI is a validated structure comprised of wide but finite scope, robust databasing of information and rules-based report text generation for enhanced clinical reporting. Central to AI is a newly developed database akin to an "Athena Variome Project" which allows for archival of data from as many sources as we can routinely and efficiently obtain for which we can assign a high degree of reliability. Quality is a central tenant and data of questionable origin or value, even if published in a peer-reviewed journal is not considered in our dataset. Alamut is an important software tool which allows for an easy interface with much of this data, particularly alignment of multiple gene splice activity algorithms. The BioBase database of published literature is also an important source of information. Other critical sources of information include high quality locus-specific databases, SIFT, PolyPhen, normal population study data (internal and published), co-occurrence and family segregation data (internal and published), and functional domain information (UniProt and others). Strong collaborations have been important, as evidenced by our work with several HSP researchers as well as the new HSP databasing project (part of the Human Variome Project). A key ingredient to AI's power is Athena's internal database of clinical results that can be mined as part of our variant investigation. In the past 18 months, over 15,000 unique variants have been identified at Athena as result of our full-gene resequencing tests; including 427 AI scored HSP variants amongst the 8 HSP genes we sequence. Of these 427 unique HSP variants, about 59% are classified as Pathogenic (the majority causing premature truncations of the protein product), about 11% are classified as Benign (a little more than half of those are silent variants) and the remainder are VUS (60/40 are missense/silent variants). Athena Insight™ is being rolled out to an increasing number of product lines each month and will be completely rolled out by mid-2011.