Key Summary of Published Letter

Detection of IGF-1 Variants by Mass Spectrometry: Results from a Clinical Reference Laboratory

Background

- Insulin-like growth factor-1 (IGF-1) is an anabolic hormone and a biomarker for some growth disorders.
- A high-resolution, top-down liquid chromatography-mass spectrometry (LC-HRMS) assay that is highly specific for IGF-1 was previously developed at Quest Diagnostics.[1] The assay has been routinely used for clinical testing of IGF-1 since 2012.
- In a study that used a similar LC-HRMS assay, a polymorphic variant of IGF-1 was identified (A70T).[2] Other IGF-1 pathogenic variants have been identified in case studies of patients with growth disorders and include V44M, R36Q, and R50W.[3-5]
- **Objective:** For this study, the investigators examined whether the LC-HRMS assay, guided by a single-nucleotide polymorphism (SNP) database, can detect IGF-1 variants during routine analysis of clinical specimens.

Methods

- Clinical specimens were submitted for IGF-1 testing, presumably for a growth disorder. They were analyzed by the LC-HRMS assay for detection of wild type (WT) IGF-1 and polymorphic variants.
- IGF-1 variants were identified from the general population ExAC database and monitored according to their predicted mass. WT IGF-1 was detected at mass-to-charge ratio (*m/z)* 1093.5215; variants were screened for at *m/z* 1089.0850, 1097.8087, and 1098.0889.
- To confirm the variants, DNA sequencing was conducted on specimens that had IGF-1 variants detected by LC-HRMS and enough residual volume.

Results

- Heterozygous IGF-1 variants were detected from 79 unique patients.
- DNA sequencing was conducted on 41 specimens. The single amino-acid change variants were:
  - A70T: 30 specimens
  - A67T: 8 specimens
  - A38V: 3 specimens
- The A70T variant was >3 times more prevalent than the A67T variant in our clinical population; in contrast, A67T was the >2 times more prevalent than A70T in the ExAC database.

Conclusions

- The LC-HRMS assay for IGF-1 can be used to identify IGF-1 variants during routine analysis of clinical specimens.
- The relative prevalences of the IGF-1 variants identified in this study (from specimens likely evaluated for growth disorder) differed from those predicted by the SNP database (general population). This suggests that individual variants may be associated with pathogenicity, though further study is warranted.

Letter published in the journal *Clinical Chemistry*

Authors

Zengru Wu, Heather Sanders, Ievgen Motorykin, Michael P Caulfield, Michael J McPhaul

Affiliation

Quest Diagnostics, San Juan Capistrano, CA

Citation

Wu Z, Sanders H, Motorykin I, et al. *Clin Chem*. 2019;65:8.

References

1. Bystrom CE, Sheng S, Clarke NJ. *Anal Chem*. 2011;83:9005-9010.
2. Hines J, Milosevic D, Ketha H, et al. *Clin Chem*. 2015;61:990-991.
3. Walenkamp MJE, Karperien M, Pereira AM, et al. *J Clin Endocrinol Metab*. 2005;90:2855-2864.
4. Netchine I, Azzi S, Houang M, et al. *J Clin Endocrinol Metab*. 2009;94:3913-3921.
5. Shaheen R, Faqeih E, Ansari S, et al. *Genome Res*. 2014;24:291-299.