Distribution of Mutations Associated With Congenital Myasthenic Syndromes (CMS): Results From the First 54 Specimens Tested at a Clinical Reference Laboratory

Background
- Congenital myasthenic syndromes (CMS) refer to a group of rare inherited disorders that cause muscle weakness. They can present at different ages with varying symptoms and severity.
- Each CMS type is associated with variants in specific genes, and treatment depends on the CMS type. Genetic diagnoses can help in the management of CMS, but genetic testing is not widely available.
- The investigators of this study previously developed an assay to test 13 genes associated with CMS.
- Objective: In this study, they examined the frequency of CMS-associated variants determined with this test in patient specimens submitted to a clinical reference laboratory.

Methods
- This study included the first 54 patient specimens (deidentified) submitted to Athena Diagnostics to be tested using the panel described below.
- A next-generation sequencing (hybrid capture) assay targeted the coding regions and at least 10 adjacent noncoding nucleotides for the following genes: AGRN, CHAT, CHRNA1, CHRN1, CHRD, CHRNE, COLQ, DOK7, DPAGT1, GFPT1, MUSK, RAPSN, and SCN4A.
  - In prior validation testing, DNA sequence variations were detected with 99% sensitivity and specificity.

Results
- Of the specimens submitted for testing, 12 (22%) were positive for deleterious variant(s), 16 (30%) had variants of uncertain significance (VUS), and 26 (48%) were negative for CMS-associated variants.
- Among the specimens with deleterious variants, patient age ranged from 3 to 53 years.
- Deleterious mutations were most commonly detected in CHRNA6 (n=6), followed by DOK7 (n=2); COLQ, MUSK, and RAPSN (n=1 each); and GFPT1 (n=1 carrier).

Conclusions
- The targeted gene-sequencing panel detected deleterious variants associated with CMS in 22% of tested specimens.
- Many VUS were also identified, which may provide insight into CMS in the future.