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Summary

FRAMESHIFT VARIANT IN FAM129C DRIVES ACHALASIA THROUGH B CELL ACTIVATION-MEDIATED SECRETION OF ANTI-GABAA RECEPTOR AUTOANTIBODIES

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Whole-genome sequencing in 22 achalasia trios identified FAM129C as a novel genetic susceptibility gene, with a CRISPR-engineered mouse model demonstrating that FAM129C mutation drives B cell expansion and anti-GABAA receptor autoantibody production, leading to selective inhibitory neuronal loss and achalasia features.

KEY POINTS

- A CRISPR/Cas9-engineered Fam129c-mutant mouse model recapitulated key achalasia features including growth retardation, elevated LES pressure, and selective loss of inhibitory neurons.
- Multi-omics analyses revealed substantial B cell expansion and activation within the LES, with time-course experiments showing B cell accumulation preceded neuronal loss.
- B cell depletion via anti-CD20 antibodies or IVIG treatment partially rescued the achalasia phenotype in mutant mice.
- Protein profiling and cell-based assays identified GABAA receptor as a potential neuronal antigen targeted by circulating autoantibodies.
- The findings redefine achalasia as a neuroimmune-mediated disorder and highlight the potential of early-stage immunomodulatory interventions such as anti-CD20 therapy and IVIG.

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