FUNCTIONAL VERIFICATION AND MECHANISM OF FAM129C GENE MUTATION IN ACHALASIA

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Researchers identified FAM129C as a new genetic mutation in esophageal achalasia and demonstrated that Fam129c mutant mice develop achalasia through a B-cell-dependent autoimmune pathway involving GABA-AR autoantibodies.

KEY POINTS

- FAM129C was identified as a new genetic mutation locus through whole-exome sequencing of 22 Trios core families with achalasia in the Han population
- Fam129c mutant mice constructed by CRISPR/Cas9 technology exhibited EA phenotype with anatomical features, pathological changes in the esophageal intermuscular plexus, and diastolic dysfunction consistent with EA patients
- FAM129C was localized in B cells, and abnormal activation of plasma cells with increased immunoglobulin secretion was observed in mutant mice
- Anti-inhibitory neuron autoantibody GABA-AR was elevated in serum and tissue of mutant mice, and specific deletion of B cells or IvIgG treatment partially alleviated the achalasia phenotype
- The pathogenic mechanism involves a B-cell-dependent pathway where increased autoantibody secretion causes specific injury to esophageal inhibitory intermuscular neurons leading to neuromuscular dysfunction

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