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Common variants in the HLA-DQ region confer susceptibility to idiopathic achalasia.

Gockel I[1], Becker J[2], Wouters MM[3], Niebisch S[4], Gockel HR[4], Hess T[5], Ramonet D[6], Zimmermann J[6], Vigo AG[7], Trynka G[8], de León AR[9], de la Serna JP[9], Urcelay E[7], Kumar V[8], Franke L[8], Westra HJ[8], Drescher D[4], Kneist W[4], Marquardt JU[10], Galle PR[10], Mattheisen M[11], Annese V[12], Latiano A[13], Fumagalli U[14], Laghi L[15], Cuomo R[16], Sarnelli G[16], Müller M[17], Eckardt AJ[17], Tack J[3], Hoffmann P[18], Herms S[18], Mangold E[5], Heilmann S[5], Kiesslich R[19], von Rahden BH[20], Allescher HD[21], Schulz HG[22], Wijmenga C[8], Heneka MT[8], Lang H[4], Hopfner KP[23], Nöthen MM[5], Boeckxstaens GE[3], de Bakker PI[24], Knapp M[25], Schumacher J[2].

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Abstract

Idiopathic achalasia is characterized by a failure of the lower esophageal sphincter to relax due to a loss of neurons in the myenteric plexus. This ultimately leads to massive dilatation and an irreversibly impaired megaesophagus. We performed a genetic association study in 1,068 achalasia cases and 4,242 controls and fine-mapped a strong MHC association signal by imputing classical HLA haplotypes and amino acid polymorphisms. An eight-residue insertion at position 227-234 in the cytoplasmic tail of HLA-DQβ1 (encoded by HLA-DQB1*05:03 and HLA-DQB1*06:01) confers the strongest risk for achalasia ($P = 1.73 \times 10(-19)$). In addition, two amino acid substitutions in the extracellular domain of HLA-DQα1 at position 41 (lysine encoded by HLA-DQA1*01:03; $P = 5.60 \times 10(-10)$) and of HLA-DQβ1 at position 45 (glutamic acid encoded by HLA-DQB1*03:01 and HLA-DQB1*03:04; $P = 1.20 \times 10(-9)$) independently confer achalasia risk. Our study implies that immune-mediated processes are involved in the pathophysiology of achalasia.