Shared Genetic Basis for Type 1 Diabetes, Islet Autoantibodies, and Autoantibodies Associated With Other Immune-Mediated Diseases in Families With Type 1 Diabetes

Type 1 diabetes (T1D) is a polygenic autoimmune disease that is often present with autoantibodies directed against pancreatic islet proteins. Many genetic susceptibility loci are shared with other autoimmune or immune-mediated diseases that also cosegregate in families with T1D. The aim of this study was to investigate whether susceptibility loci identified in genome-wide association studies (GWAS) of T1D were also associated with autoantibody positivity in individuals with diabetes. Fifty single nucleotide polymorphisms (SNPs) were genotyped in 6,556 multiethnic cases collected by the Type 1 Diabetes Genetics Consortium (T1DGC). These were tested for association with three islet autoantibodies—against autoantibodies to GAD (GADA), IA-2 (IA-2A), and zinc transporter 8 (ZnT8A)—and autoantibodies against thyroid peroxidase (TPOA) in autoimmune thyroid disease, gastric parietal cells (PCA) in autoimmune gastritis, transglutaminase (TGA) in celiac disease, and 21-hydroxylase (21-OHA) in autoimmune hypoadrenalism. In addition to the MHC region, we identify SNPs in five susceptibility loci (IFIH1, PTPN22, SH2B3, BACH2, and CTLA4) as significantly associated with more than one autoantibody at a false discovery rate less than 5%. IFIH1/2q24 demonstrated the most unrestricted association, as significant association was demonstrated for PCA, TPOA, GADA, 21-OHA, and IA-2A. In addition, 11 loci were significantly associated with a single autoantibody.

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General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Integrative Systems Biology, University Hospital Herlev
Contributors: Brorsson, C. A., Pociot, F.
Number of pages: 6
Pages: S8-S13
Publication date: 2015
Peer-reviewed: Yes

Publication information
Journal: Diabetes Care
Volume: 38
Issue number: Supplement 2
ISSN (Print): 0149-5992
Ratings:
BFI (2019): BFI-level 2
Web of Science (2019): Indexed yes
BFI (2018): BFI-level 2
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 2
Scopus rating (2017): CiteScore 7.81 SJR 6.693 SNIP 3.847
Web of Science (2017): Impact factor 13.397
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 7.48 SJR 5.548 SNIP 3.7
Web of Science (2016): Impact factor 11.857
BFI (2015): BFI-level 2
Scopus rating (2015): CiteScore 7.24 SJR 5.749 SNIP 3.642
Web of Science (2015): Impact factor 8.934
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): CiteScore 7.25 SJR 5.09 SNIP 3.49
Web of Science (2014): Impact factor 8.42
BFI (2013): BFI-level 2
Scopus rating (2013): CiteScore 8.03 SJR 4.67 SNIP 3.6
Web of Science (2013): Impact factor 8.57
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2