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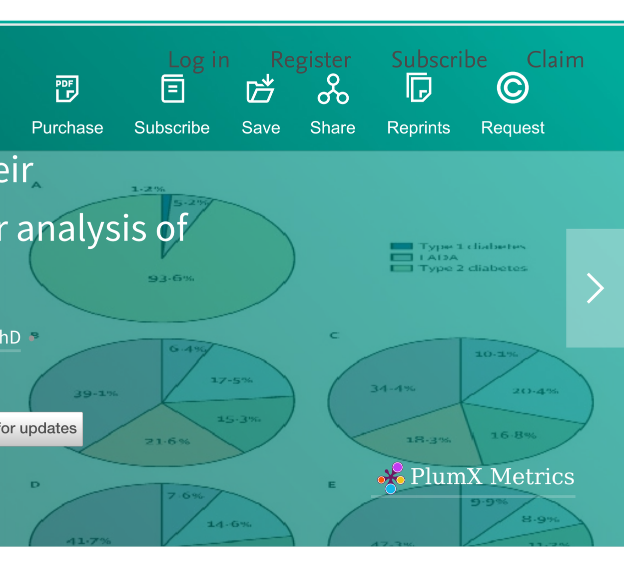
Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables



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Background

Diabetes is presently classified into two main forms, type 1 and type 2 diabetes, but type 2 diabetes in particular is highly heterogeneous. A refined classification could provide a powerful tool to individualise treatment regimens and identify individuals with increased risk of complications at diagnosis.

Methods

We did data-driven cluster analysis (k-means and hierarchical clustering) in patients with newly diagnosed diabetes (n=8980) from the Swedish All New Diabetics in Scania cohort. Clusters were based on six variables (glutamate decarboxylase antibodies, age at diagnosis, BMI, HbA_{1c}, and homoeostatic model assessment 2 estimates of β-cell function and insulin resistance), and were related to prospective data from patient records on development of complications and prescription of medication. Replication was done in three independent cohorts: the Scania Diabetes Registry (n=1466), All New Diabetics in Uppsala (n=844), and Diabetes Registry Vaasa (n=3485). Cox regression and logistic regression were used to compare time to medication, time to reaching the treatment goal, and risk of diabetic complications and genetic associations.

Findings

We identified five replicable clusters of patients with diabetes, which had significantly different patient characteristics and risk of diabetic complications. In particular, individuals in cluster 3 (most resistant to insulin) had significantly higher risk of diabetic kidney disease than individuals in clusters 4 and 5, but had been prescribed similar diabetes treatment. Cluster 2 (insulin deficient) had the highest risk of retinopathy. In support of the clustering, genetic associations in the clusters differed from those seen in traditional type 2 diabetes.

Interpretation

We stratified patients into five subgroups with differing disease progression and risk of diabetic complications. This new substratification might eventually help to tailor and target early treatment to patients who would benefit most, thereby representing a first step towards precision medicine in diabetes.

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References

1. NCD Risk Factor Collaboration (NCD-RisC)
Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4·4 million participants.
Lancet. 2016; 387: 1513-1530
View in Article
Scopus (273) • PubMed • Summary • Full Text • Full Text PDF • Google Scholar

2. Tuomi, T • Groop, LC • Zimmet, PZ • Rowley, MJ • Knowles, W • Mackay, IR
Antibodies to glutamic acid decarboxylase reveal latent autoimmune diabetes mellitus in adults with a non-insulin-dependent onset of disease.
Diabetes. 1993; 42: 359-362
View in Article
Scopus (475) • PubMed • Crossref • Google Scholar

3. Froguel, P • Zouali, H • Vionnet, N et al.
Familial hyperglycemia due to mutations in glucokinase. Definition of a subtype of diabetes mellitus.
N Engl J Med. 1993; 328: 697-702
View in Article
Scopus (646) • PubMed • Crossref • Google Scholar

4. Yamagata, K • Oda, N • Kaisaki, PJ et al.
Mutations in the hepatocyte nuclear factor-1alpha gene in maturity-onset diabetes of the young (MODY3).
Nature. 1996; 384: 455-458
View in Article
Scopus (911) • PubMed • Crossref • Google Scholar

5. Reddy, MA • Zhang, E • Natarajan, R
Epigenetic mechanisms in diabetic complications and metabolic memory.
Diabetologia. 2015; 58: 443-455
View in Article
Scopus (106) • PubMed • Crossref • Google Scholar

6. Brownlee, M
The pathobiology of diabetic complications: a unifying mechanism.
Diabetes. 2005; 54: 1615-1625
View in Article
Scopus (2649) • PubMed • Crossref • Google Scholar

7. Pearson, ER • Flechtner, I • Njolstad, PR et al.
Switching from insulin to oral sulfonylureas in patients with diabetes due to Kir6.2 mutations.
N Engl J Med. 2006; 355: 467-477
View in Article
Scopus (585) • PubMed • Crossref • Google Scholar

8. Lindholm, E • Agardh, E • Tuomi, T • Groop, L • Agardh, CD
Classifying diabetes according to the new WHO clinical stages.
Eur J Epidemiol. 2001; 17: 983-989
View in Article
Scopus (48) • PubMed • Crossref • Google Scholar

9. Manjer, J • Carlsson, S • Elmstahl, S et al.
The Malmo Diet and Cancer study: representativity, cancer incidence and mortality in participants and non-participants.
Eur J Cancer Prev. 2001; 10: 489-499
View in Article
Scopus (265) • PubMed • Crossref • Google Scholar

10. Rahmati, K • Lernmark, A • Becker, C et al.
A comparison of serum and EDTA plasma in the measurement of glutamic acid decarboxylase autoantibodies (GADA) and autoantibodies to islet antigen-2 (IA-2A) using the RSR radioimmunoassay (RIA) and enzyme linked immunosorbent assay (ELISA) kits.
Clin Lab. 2008; 54: 227-235
View in Article
PubMed • Google Scholar

11. Tuomi, T • Carlsson, A • Li, H et al.
Clinical and genetic characteristics of type 2 diabetes with and without GAD antibodies.
Diabetes. 1999; 48: 150-157
View in Article
Scopus (350) • PubMed • Crossref • Google Scholar

12. Vaziri-Sani, F • Delli, AJ • Elding-Larsson, H et al.
A novel triple mix radiobinding assay for the three ZnT8 (ZnT8-RWQ) autoantibody variants in children with newly diagnosed diabetes.
J Immunol Methods. 2011; 371: 25-37
View in Article
Scopus (40) • PubMed • Crossref • Google Scholar

13. Almgren, P • Lindqvist, A • Krus, U et al.
Genetic determinants of circulating GIP and GLP-1 concentrations.
JCI insight. 2017; 2: 93306
View in Article
PubMed • Crossref • Google Scholar

14. Levey, AS • Stevens, LA • Schmid, CH et al.
A new equation to estimate glomerular filtration rate.
Ann Intern Med. 2009; 150: 604-612
View in Article
Scopus (7140) • PubMed • Crossref • Google Scholar

15. Martinell, M • Dorkhan, M • Stalhammar, J • Storm, P • Groop, L • Gustavsson, C
Prevalence and risk factors for diabetic retinopathy at diagnosis (DRAD) in patients recently diagnosed with type 2 diabetes (T2D) or latent autoimmune diabetes in the adult (LADA).
J Diabetes Complications. 2016; 30: 1456-1461
View in Article
Scopus (5) • PubMed • Summary • Full Text • Full Text PDF • Google Scholar

16. Levy, JC • Matthews, DR • Hermans, MP
Correct homeostasis model assessment (HOMA) evaluation uses the computer program.
Diabetes Care. 1998; 21: 2191-2192
View in Article
Scopus (1074) • PubMed • Crossref • Google Scholar

17. Hennig, C
Cluster-wise assessment of cluster stability.
Comput Stat Data An. 2007; 52: 258-271
View in Article
Scopus (147) • Crossref • Google Scholar

18. Marchini, J • Howie, B • Myers, S • McVean, G • Donnelly, P
A new multipoint method for genome-wide association studies by imputation of genotypes.
Nat Genet. 2007; 39: 906-913
View in Article
Scopus (1482) • PubMed • Crossref • Google Scholar

19. Prasad, RB • Groop, L
Genetics of type 2 diabetes—pitfalls and possibilities.
Genes. 2015; 6: 87-123
View in Article
Scopus (91) • PubMed • Crossref • Google Scholar

20. Lyssenko, V • Lupi, R • Marchetti, P et al.
Mechanisms by which common variants in the TCF7L2 gene increase risk of type 2 diabetes.
J Clin Invest. 2007; 117: 2155-2163
View in Article
Scopus (479) • PubMed • Crossref • Google Scholar

21. Liu, YL • Reeves, HL • Burt, AD et al.
TM6SF2 rs58542926 influences hepatic fibrosis progression in patients with non-alcoholic fatty liver disease.
Nat Commun. 2014; 5: 4309
View in Article
Scopus (163) • PubMed • Crossref • Google Scholar

22. Nguyen, C • Varney, MD • Harrison, LC • Morahan, G
Definition of high-risk type 1 diabetes HLA-DR and HLA-DQ types using only three single nucleotide polymorphisms.
Diabetes. 2013; 62: 2135-2140
View in Article
Scopus (31) • PubMed • Crossref • Google Scholar

23. Li, L • Cheng, WY • Glicksberg, BS et al.
Identification of type 2 diabetes subgroups through topological analysis of patient similarity.
Sci Transl Med. 2015; 7: 311ra174
View in Article
Scopus (85) • PubMed • Crossref • Google Scholar

24. Groop, L • Ekstrand, A • Forsblom, C et al.
Insulin resistance, hypertension and microalbuminuria in patients with type 2 (non-insulin-dependent) diabetes mellitus.
Diabetologia. 1993; 36: 642-647
View in Article
Scopus (233) • PubMed • Crossref • Google Scholar

25. Gnudi, L • Coward, RJ • Long, DA
Diabetic nephropathy: perspective on novel molecular mechanisms.
Trends Endocrinol Metab. 2016; 27: 820-830
View in Article
Scopus (35) • PubMed • Summary • Full Text • Full Text PDF • Google Scholar

26. Welsh, GI • Hale, LJ • Eremina, V et al.
Insulin signaling to the glomerular podocyte is critical for normal kidney function.
Cell Metab. 2010; 12: 329-340
View in Article
Scopus (219) • PubMed • Summary • Full Text • Full Text PDF • Google Scholar

27. Lee, SH • Wray, NR • Goddard, ME • Visscher, PM
Estimating missing heritability for disease from genome-wide association studies.
Am J Hum Genet. 2011; 88: 294-305
View in Article
Scopus (433) • PubMed • Summary • Full Text • Full Text PDF • Google Scholar

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