Clustering on baseline clinical variables identifies subgroups of type 2 diabetes patients with different rate of progression over 18 months: a DIRECT study

Brorsson, Caroline Anna; Pedersen, H. Krogh; Gudmundsdottir, Valborg; Mari, A.; Kurbasic, A.; Vinuela, A.; Fernandez, J.; Mahajan, A.; Gupta, R.; Dermitzakis, E.; MacCarthy, M.; Franks, P.; Pearson, E.; Brunak, Søren

Published in:
Diabetologia

Publication date:
2017

Document Version
Publisher's PDF, also known as Version of record

Link back to DTU Orbit

Citation (APA):

General rights
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain.
- You may freely distribute the URL identifying the publication in the public portal.

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.
Classifying diabetes

Clustering of diabetes into novel subgroups provides improved prediction of outcome

E. Ahlvist1, A. Kärjäjärvi2, M. Martinelli3, P. Storm1, M. Dorkhan1, P. Vikman1, R.B. Prasad1, D. Mansour Aly1, N. Shaat1, E. Lindholm1, T. Tuomi4,5, A.H. Rosencreng1, L. Groom1,6
1Lund University Diabetes Centre, Lund University, Malmö, Sweden, 2Primary Health Care, Vaasa Central Hospital, Vaasa, Finland, 3Public Health and Caring Sciences, Uppsala University, Uppsala, Sweden, 4Finnish Institute for Molecular Medicine, Helsinki University, 5Folkhälso Research Center, Helsinki, Finland.

Background and aims: The current classification of diabetes into two main forms (T1D and T2D) has been useful in delineating T1D as an insulin-deficient form requiring insulin therapy but less useful for dissecting the heterogeneity of T2D. A refined classification could provide a powerful tool to identify those at greatest risk of complications already at diagnosis and tailor individualized treatment.

Materials and methods: We performed unsupervised clustering (k-means) on 836 newly diagnosed individuals enrolled in the DIRECT study. The clustering was based on 20 clinical variables from the baseline visit consisting of anthropometric, biochemical and glycaemic modeling variables. We clustered the individuals using an unsupervised, agglomerative clustering method. Diabetes progression was assessed using individual HbA1c slopes obtained from a conditional linear mixed-model using data at 0, 9 and 18 month adjusted for weight, diabetes medication and baseline HbA1c. An extra time-varying covariate defined to be 1 at baseline and zero for all other visits was introduced to account for presence of effect from baseline to subsequent visits. Linear regression models with cluster membership as predictor was used to calculate effect, 95% CI and p-values for differences between subgroups. A genetic risk score (GRS) was calculated from the cumulative number of risk alleles of other GWAS SNPs for type 2 diabetes.

Results: Full clinical data was available for 790 individuals. We identified three major diabetes subgroups that differed significantly in regards to their baseline characteristics. The three groups could broadly be described as insulin resistant (IR), β-cell deficient (βD), and mixed. The most significant difference was seen in insulin sensitivity (lnMatsuda), beta (95% CI): Mixed= -0.61 (-0.68- -0.55), p=9.9*10^-4; IR= -1.3 (-1.3- -1.2), p=4.9*10^-205) compared to the βD group, but also insulin secretion, C-peptide, BMI, basal glucose, triglycerides and ALT (p=10^-14). The IR group was treated with significantly more metformin compared to the βD group (% maximum dose: IR= 5.13 (1.79-8.47), p=0.003). Investigating the rate of progression in HbA1c between baseline and 18 months showed that the IR group had the fastest progression compared to the βD group, which had the slowest progression (change in HbA1c mmol/mo/year: IR=0.77 (0.32-1.22), p=0.0008). There was no difference for the GRS constructed of 65 GWAS SNPs.

Conclusion: We have demonstrated that the newly diagnosed type 2 diabetes cohort from DIRECT has a heterogeneous presentation of their diabetic phenotype at baseline. Clustering identified three major subgroups, driven by their level of insulin resistance-related traits. The subgroups showed differences in their rate of progression over 18 months with the insulin resistant group showing the fastest progression.

Supported by: IMJ Joint Undertaking n° 113517, FP7/2007-2013 and EFPFA companies in kind

Disclosure: C.A. Brorsson: None.

Clustering on baseline clinical variables identifies subgroups of type 2 diabetes patients with different rate of progression over 18 months: a DIRECT study

C.A. Brorsson1, H. Krogh Pedersen1, V. Gudmundsdottir1, A. Mari2, A. Kurbasic1, A. Viňuela3, J. Fernandez3, A. Mahajan4, R. Gupta1, E. Demitrakis4, M. MacCarthy5, P. Franks3, E. Pearson6, S. Brunak1,7, for the DIRECT Consortium;
1Department of Bioinformatics, Technical University of Denmark, Lyngby, Denmark, 2Institute of Neuroscience - National Research Council, Padova, Italy, 3Lund University, Malmö, Sweden, 4University of Geneva, Geneva, Switzerland, 5University of Oxford, Oxford, 6University of Dundee, Dundee, UK, 7University of Copenhagen, Copenhagen, Denmark.

Background and aims: Type 2 diabetes is characterized by a heterogeneous presentation with varying degrees of insulin resistance and β-cell failure. Taking advantage of the detailed clinical information collected for type 2 diabetes patients included in the DIRECT study, our aim was to characterize inter-individual heterogeneity and identify subgroups with different presentations of diabetic phenotypes at baseline, and investigate the effect on the rate of progression during follow-up. Genotyping data was used to evaluate genetic differences between subgroups.

Materials and methods: 836 newly diagnosed individuals were enrolled in the DIRECT study. The clustering was based on 20 clinical variables from the baseline visit consisting of anthropometric, biochemical and glycaemic modeling variables. We clustered the individuals using an unsupervised, agglomerative clustering method. Diabetes progression was assessed using individual HbA1c slopes obtained from a conditional linear mixed-model using data at 0, 9 and 18 month adjusted for weight, diabetes medication and baseline HbA1c. An extra time-varying covariate defined to be 1 at baseline and zero for all other visits was introduced to account for presence of effect from baseline to subsequent visits. Linear regression models with cluster membership as predictor was used to calculate effect, 95% CI and p-values for differences between subgroups. A genetic risk score (GRS) was calculated from the cumulative number of risk alleles of other GWAS SNPs for type 2 diabetes.

Results: Full clinical data was available for 790 individuals. We identified three major diabetes subgroups that differed significantly in regards to their baseline characteristics. The three groups could broadly be described as insulin resistant (IR), β-cell deficient (βD), and mixed. The most significant difference was seen in insulin sensitivity (lnMatsuda), beta (95% CI): Mixed= -0.61 (-0.68- -0.55), p=9.9*10^-4; IR= -1.3 (-1.3- -1.2), p=4.9*10^-205) compared to the βD group, but also insulin secretion, C-peptide, BMI, basal glucose, triglycerides and ALT (p=10^-14). The IR group was treated with significantly more metformin compared to the βD group (% maximum dose: IR= 5.13 (1.79-8.47), p=0.003). Investigating the rate of progression in HbA1c between baseline and 18 months showed that the IR group had the fastest progression compared to the βD group, which had the slowest progression (change in HbA1c mmol/mo/year: IR=0.77 (0.32-1.22), p=0.0008). There was no difference for the GRS constructed of 65 GWAS SNPs.

Conclusion: We have demonstrated that the newly diagnosed type 2 diabetes cohort from DIRECT has a heterogeneous presentation of their diabetic phenotype at baseline. Clustering identified three major subgroups, driven by their level of insulin resistance-related traits. The subgroups showed differences in their rate of progression over 18 months with the insulin resistant group showing the fastest progression.

Supported by: IMJ Joint Undertaking n° 113517, FP7/2007-2013 and EFPFA companies in kind

Disclosure: C.A. Brorsson: None.