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OP 45 Classifying diabetes

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Clustering of diabetes into novel subgroups provides improved prediction of outcome

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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 and hierarchical) based on six variables (age, BMI, HbA1c, HOMA2-B, HOMA2-IR and GAD auto-antibodies) in ANDIS, a Swedish cohort of 15,000 newly diagnosed diabetes patients. Disease progression, treatment and development of complications were followed using medical records and national registries. Risk of complications was analyzed using cox regression with the largest cluster as reference. Genetic loci known to be associated with T2D and related traits were analysed using MLE comparing each cluster to a non-diabetic cohort from the same geographical region.

Results: ANDIS patients clustered into one GADA-positive cluster (referred to as SAID, Severe Autoimmune Diabetes) and four GADA-negative clusters. This was replicated in three independent cohorts from Sweden and Finland. Cluster 2 (SIDD, Severe Insulin Deficient Diabetes; 17.5% of patients) was characterized by early onset, insulin deficiency and high HbA1c. During a mean follow-up of 4 years SIDD had higher HbA1c, was more likely to be prescribed insulin and develop diabetic retinopathy compared to other GADA-negative clusters. Cluster 3 (SIRD, Severe Insulin Resistant Diabetes; 15.3%) had the highest risk of kidney disease including CKD stage 3B (HR 3.30[2.67-4.08], $p=3.6 \times 10^{-28}$) and macroalbuminuria/end-stage renal disease (ESRD; HR 2.40[1.69-3.42], $p=9.8 \times 10^{-7}$). This was replicated in a cohort with longer follow-up (SDR, mean 11 years), where SIRD had five-fold increased risk of ESRD (HR 5.04[2.76-9.23], $p=1.5 \times 10^{-7}$). Cluster 4 (MOD, Mild Obese Diabetes; 21.6%) and cluster 5 (MARD, Mild Age-Related Diabetes; 39.1%) showed only modest metabolic derangements. Using $p<0.01$ as cut-off, no genetic variant was associated with all clusters. Strikingly, the T2D-associated variant, rs7903146, in the *TCF7L2* gene was associated with SIDD (OR 1.51[1.33-1.71], $p=2.8 \times 10^{-10}$), MOD (OR 1.38[1.21-1.56], $p=25.7 \times 10^{-7}$) and MARD (OR 1.41 [1.28-1.55], $p=1.1 \times 10^{-12}$), but not with SIRD (OR 1.00[0.87-1.15], $p=0.86$). A variant in *IGF2BP2* (rs4402960) was associated with SIDD (OR 1.23[1.08-1.40], $p=2.0 \times 10^{-4}$) and MARD (OR 1.22[1.11-1.33], $p=2.1 \times 10^{-6}$), but not with SIRD (OR 1.01[0.88-1.16], $p=0.53$) or MOD (OR 1.04[0.92-1.18], $p=0.31$).

Conclusion: This study provides a first step towards a more precise, clinically useful, classification of diabetes representing an important step towards precision medicine in diabetes.

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

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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 65 published GWAS SNPs for type 2 diabetes.

Results: Full clinical data was available for 790 individuals. We identified three major patient subgroups that differed significantly in regards to their baseline characteristics. The three groups could broadly be described as insulin resistant (IR), β -cell deficient (β D), and mixed. The most significant difference was seen in insulin sensitivity (ln(Matsuda), beta (95% CI): Mixed= -0.61 (-0.68- -0.55), $p=9.9 \times 10^{-68}$; IR=-1.3 (-1.3- -1.2), $p=4.9 \times 10^{-203}$) compared to the β D group, but also insulin secretion, C-peptide, BMI, basal glucose, triglycerides and ALT ($p<10^{-16}$). The IR group was treated with significantly more metformin compared to the β D 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 β D group, which had the slowest progression (change in HbA1c (mmol/mol)/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.

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Single antibody positivity associates with two distinct phenotypes in people with young-onset diabetes: insights from the MY DIABETES study

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Background and aims: Pancreatic autoantibody status may be used as a biomarker to differentiate diabetes subtype. Single antibody positivity in individuals presenting at older age has uncertain significance, but has not been