RHAPSODY
for precision therapy and prevention of diabetes

A new diabetes patient sub-classification: What's next?

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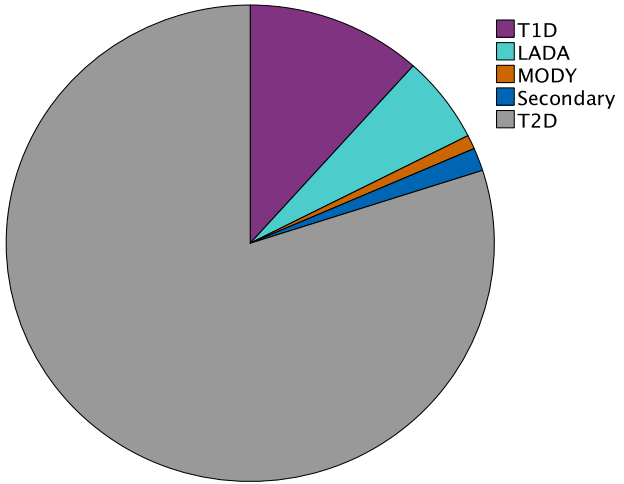
Current diabetes classification

- **Type 1 diabetes** – autoimmune diabetes in the young (<35 years)
- **LADA** – latent autoimmune diabetes of the adult (>35 years)
- **Monogenic diabetes** – rare mutations (MODY, neonatal)
- **Secondary**
- **Type 2 diabetes** – everyone else



Is this not enough?

- Individuals with diabetes, especially type 2 diabetes, are **very different**
  - Risk of complications
  - Need for treatment
  - Response to diabetes medication

- Can we divide diabetes patients into **smaller more homogeneous groups** that are clinically useful for **predicting progression** and **need for medication**?

A new diabetes sub-classification

March 2018, Lancet Diabetes and Endocrinology

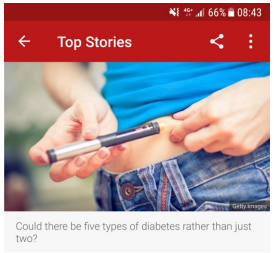
Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables

Emma Ahlqvist, Petter Storm, Annemari Käräjämäki, Mats Martinell*, Mozhgan Dorkhan, Annelie Carlsson, Petter Vikman, Rashmi B Prasad, Dina Mansour Aly, Peter Almgren, Ylva Wessman, Nael Shaat, Peter Spégel, Hindrik Mulder, Eero Lindholm, Olle Melander, Ola Hansson, Ulf Malmqvist, Åke Lernmark, Kaj Lahti, Tom Forsén, Tiinamaija Tuomi, Anders H Rosengren, Leif Groop*

Summary

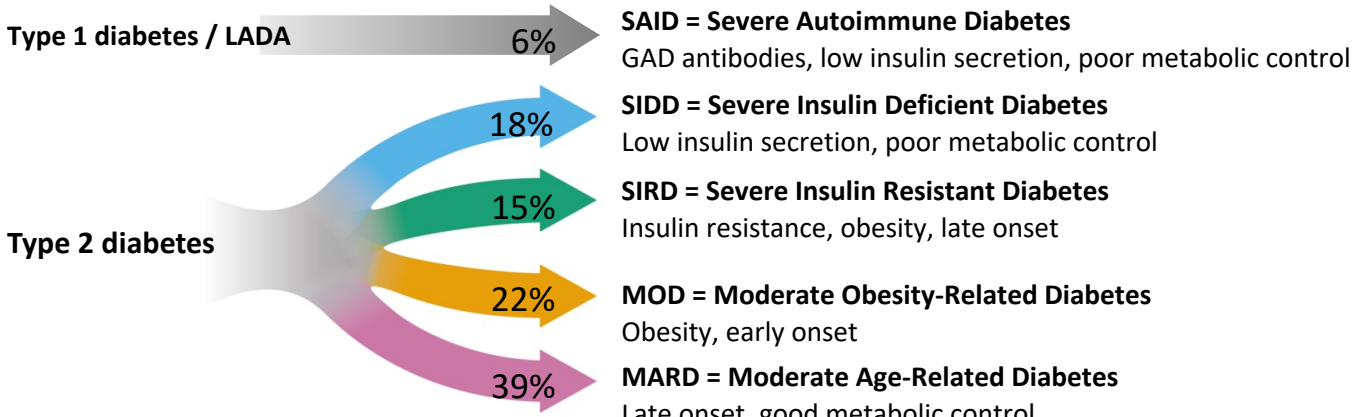
Background Diabetes is presently classified into two main forms, type 1 and type 2 diabetes, but type 2 diabetes in particular is highly heterogeneous. A refined classification could provide a powerful tool to individualise treatment regimens and identify individuals with increased risk of complications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

Lancet Diabetes Endocrinol 2018
Published Online
March 1, 2018
http://dx.doi.org/10.1016/

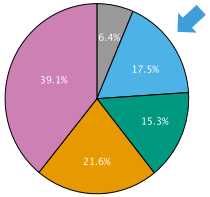


Novel subtypes

- We can reproducibly divide patients into **five subgroups** with **different characteristics and progression**



- This clustering approach has been **replicated in numerous cohorts**



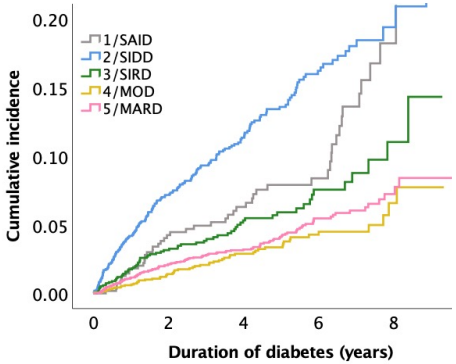
SIDD - Severe insulin-deficient diabetes

- 17.5% of patients
- Low insulin secretion
- High HbA1c at diagnosis
- Relatively early onset (mean 57 years)

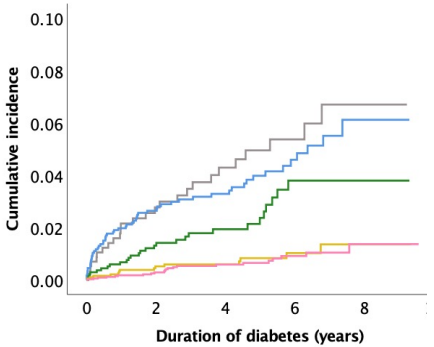
- Receive the most treatment but still the last to reach treatment goals

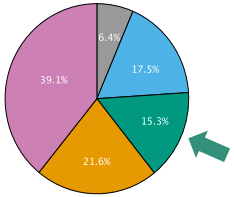
- Increased risk of retinopathy and neuropathy

Retinopathy



Neuropathy

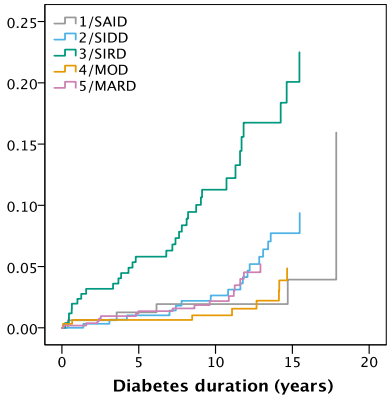




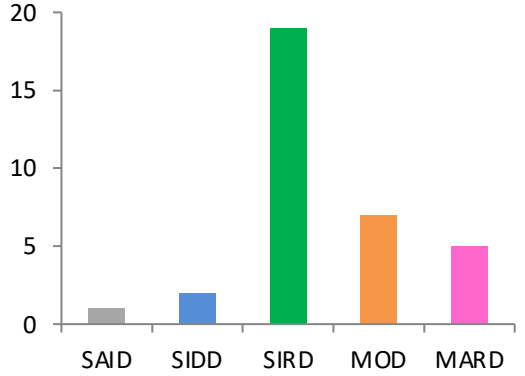
SIRD - Severe insulin-resistant diabetes

- 15.3% of patients
- Very insulin resistant
- Obese (mean BMI 34)
- Late onset (mean 65 years)
- Low HbA1c
- Higher risk of kidney complications
- Higher prevalence of non-alcoholic fatty liver disease

End-stage renal disease



Hepatocellular lipid content



What is next?

Are the subtypes different diseases?
When can they be implemented in the clinic?

- Clinical characterisation
- Replication in other ethnicities
- Genetics
- Epigenetics
- Response to medication
- Biomarkers

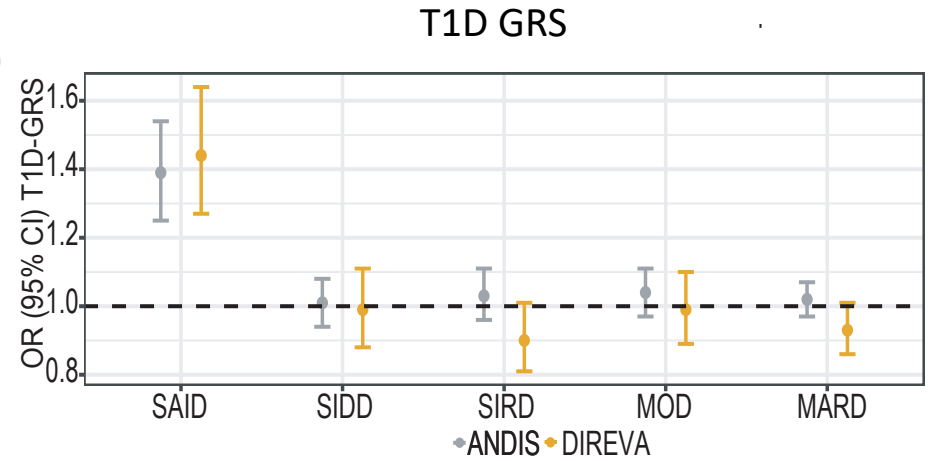
Replication in other ethnicities

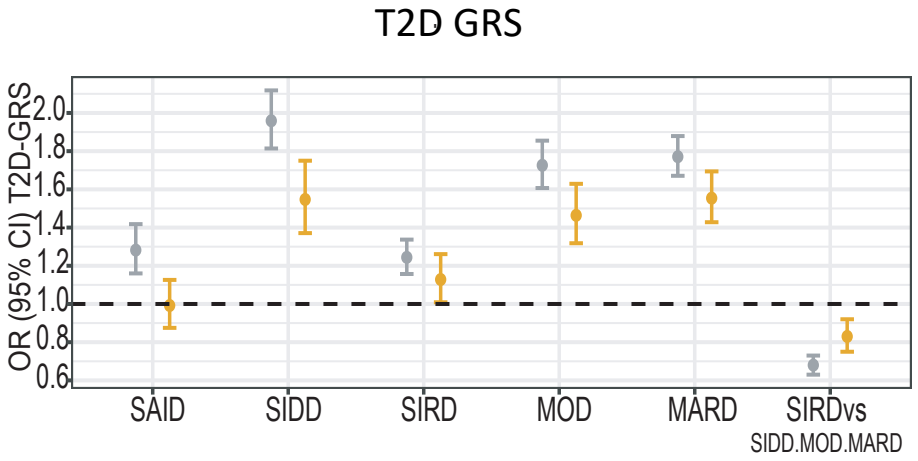
- The same subtypes have been identified in cohorts from all over the world
- Most find the same five subtypes
- Some have identified additional subtypes e.g. in India
- Comparisons are complicated by use of slightly different methods and cluster variables

Genetic risk score (GRS) analysis

Dina Mansour Aly

Om Prakash Dwivedi

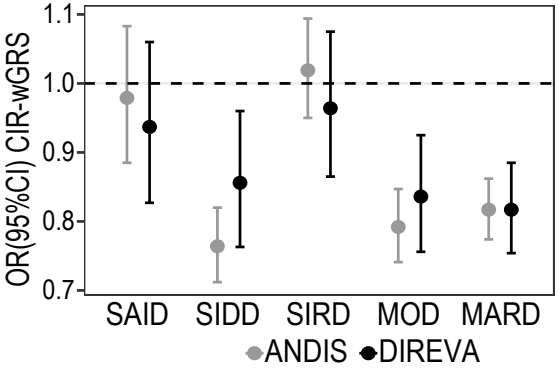




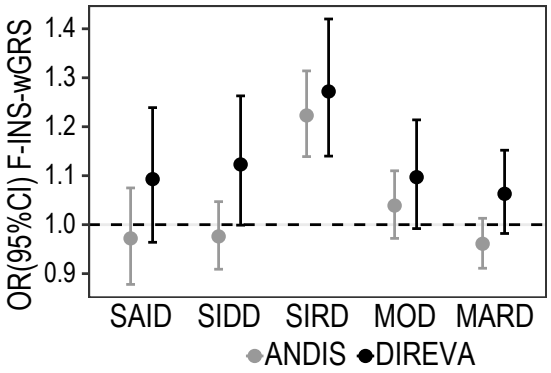
Mansour Aly et al, MedRxiv, 2020

GRS for insulin secretion and fasting insulin

Corrected insulin response



Fasting insulin



- SIRD is associated with fasting insulin but not insulin secretion

Mansour Aly et al, MedRxiv, 2020

Subtype specific genetic risk variants

	ANDIS		DIREVA		META-ANALYSIS	
	OR	p	OR	P	OR	P
SAID	1.03	0.65	0.94	0.45	0.99	0.85
SIDD	1.08	0.18	1.10	0.95	1.05	0.28
SIRD	1.13	0.01	1.06	0.47	1.11	0.02
MOD	**1.35**	**$1.3x10^{-9}$**	**1.14**	**0.04**	**1.27**	**$4.3x10^{-9}$**
MARD	1.10	0.01	1.03	0.55	1.07	0.03

- Genetic variants in the LRMDA gene increase the risk of developing MOD but not other subtypes

Mansour Aly et al, MedRxiv, 2020

Response to treatment

- SIDD would likely benefit from early treatment with insulin or insulin secretagogues
- SIRD would likely benefit from insulin sensitizers
- Needs to be proven before clinical implementation
- **Randomized trial** – SIDD and SIRD ongoing in ANDIS
- **Analysis of existing trials** in collaboration with AstraZeneca and Sanofi

Clinical implementation

- Information about subtype will soon be returned to the treating doctor for newly registered ANDIS participants
- Treatment cannot be recommended yet but SIDD and SIRD could benefit from screening for complications

Conclusions

- Diabetes patients can be reproducibly subdivided into **five subtypes**
- The insulin deficient and insulin resistant subtypes have the **highest risk of complications**
- Better science today – better treatment in the near future!
- Learn more on the **RHAPSODY outcomes webpages**:

https://imi-rhapsody.eu/outcomes/

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Thank you for your attention!

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