GENETIC RISK FACTORS FOR TYPE 2 DIABETES MELLITUS AND RESPONSE TO SULFONYLUREA TREATMENT (PHC007)

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Introduction

- Sulfonylureas (SUs) are part of the mainstay of treatment with oral antidiabetic drugs.
- There is significant interpatient variability in response to SUs.
- SUs are initiated at a low dose and escalated to the optimal dose with intervals of 2-4 weeks.
- Following the identification of Type 2 Diabetes Mellitus (T2DM) risk alleles, models have been developed to identify subjects at high risk to develop T2DM.
- We hypothesize that these risk alleles influence treatment response to SUs.

Objective

To investigate if genetic risk factors for T2DM are associated with response to sulfonylurea treatment.

Conclusion

Patients with an increased genetic risk for T2DM are less responsive to sulfonylureas.

Methods

- Incident SU users with T2DM were recruited from 4 primary care centers.
- Retrospective clinical and prescription data were retrieved from the electronic patient record.
- 20 SNPS consistently associated with T2DM in 19 genes were selected: *TCF7L2, KCNJ11, HHEX/IDE, SLC30A8, CDKAL1, CDKN2A/CDKN2B, IGF2BP2, KCNQ1, PPARG, FTO, NOTCH2, WFS1, JAZF1, THADA, CDC123/CAMK1D, TSPAN8/LGR5, ADAMTS9, HNF-1β, MTNR1B.*
- For each patient a cumulative genetic risk score (0-40) was calculated based on the number of present risk-alleles.
- Patients were categorized in 3 genetic risk groups. Low-risk group; quintile with the lowest number of T2DM risk alleles. High-risk group; quintile with the highest number of T2DM risk alleles. Remaining patients were categorized in the intermediate-risk group.
- Primary endpoint was achieving stable SU dose defined as the 1st period of ≥270 consecutive days without dose adjustment, initiation of other SUs, insulin or metformin.
- Secondary endpoints were stable SU dose and time to stable SU dose.

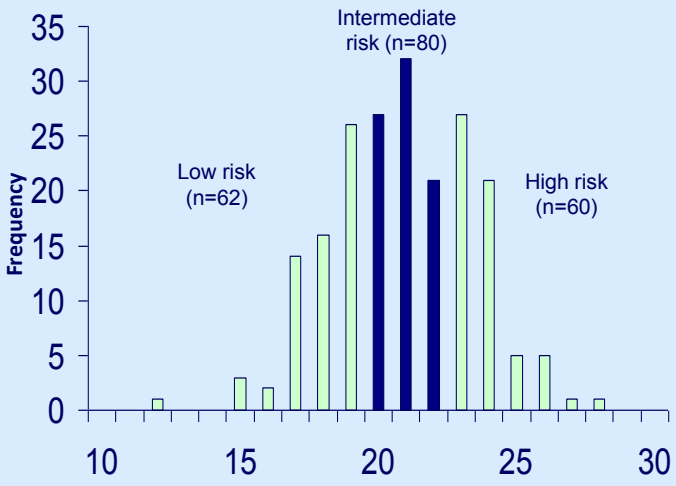

Figure 1: Distribution of Type 2 Diabetes Mellitus risk alleles and subsequent classification in risk groups. Low-risk group; patients with ≤19 risk alleles. Intermediate-risk group; patients with 20-22 risk alleles. High-risk group; patients with ≥23 risk alleles.

References

[1] Swen JJ. et al. Effect of CYP2C9 polymorphisms on prescribed dose and time-to-stable dose of sulfonylureas in primary care patients with Type 2 diabetes mellitus. *Pharmacogenomics*. 2010 Nov;11(11):1517-23.

Results

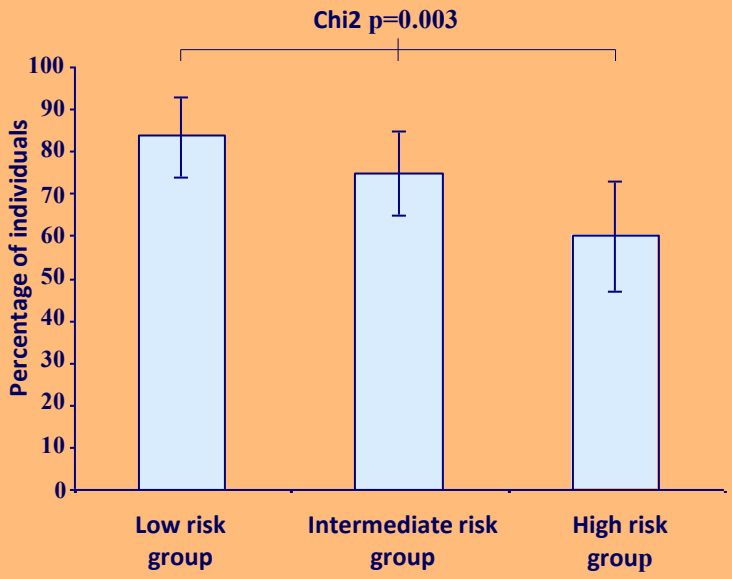

Figure 2: Percentage of Type 2 Diabetes Mellitus patients that reached stable SU dose. Low-risk group; patients with ≤19 risk alleles. Intermediate-risk group; patients with 20-22 risk alleles. High-risk group; patients with ≥23 risk alleles.

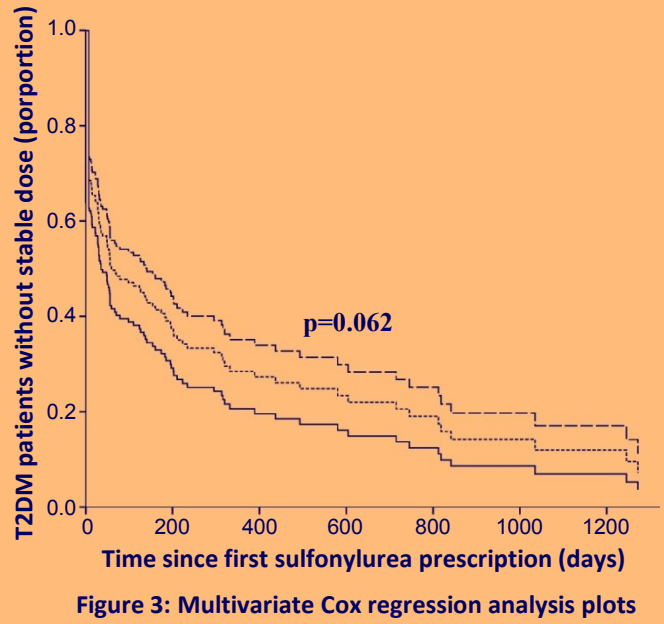

Figure 3: Multivariate Cox regression analysis plots of time to the first stable dose of SUs in Type 2 Diabetes Mellitus patients in primary care
Low-risk group (——); patients with ≤19 risk alleles. Intermediate-risk group (---); patients with 20-22 risk alleles. High-risk group (— —); patients with ≥23 risk alleles.

Table 1:Characteristics of the population of Type 2 Diabetes Mellitus patients in primary care.

		Risk group			
Variable No (%)	All patients	Low	Intermediate	High	P-value
Subjects	202	62 (30.7)	80 (39.6)	60 (29.7)	NA
Men	106 (52.2)	31 (50.0)	44 (55.0)	31 (51.7)	0.83
Women	96 (47.5)	31 (50.0)	36 (45.0)	29 (48.3)	
Age in years, mean (SD)	61.4 (10.7)	64.0 (9.4)	62.5 (10.6)	57.2 (11.0)	0.001
Follow-up in years, mean (SD)	5.9 (3.0)	6.1 (3.0)	5.7 (3.1)	6.1 (3.0)	0.62
Visits in year one (SD)	9.6 (4.7)	8.7 (3.7)	9.9 (5.3)	10.1 (4.6)	0.35
Metformin use	62 (30.7)	19 (30.6)	27 (33.8)	16 (26.7)	0.67
Primary sulfonylurea					
Glibenclamide	12 (5.9)	7 (11.3)	1 (1.3)	4 (6.7)	0.11
Tolbutamide	85 (42.1)	19 (30.6)	41 (51.3)	25 (41.7)	
Gliclazide	24 (11.9)	8 (12.9)	9 (11.3)	7 (11.7)	
Glimepiride	81 (40.1)	28 (45.2)	29 (36.3)	24 (40.0)	

Discussion

- This is the first study exploring the relationship between SU response and T2DM risk alleles.
- Patients with >19 risk alleles have a reduced likelihood to achieve stable dose and show a trend towards an increased time to achieve stable SU dose.
- Patients with a higher number of risk alleles were younger at the date of their first SU prescription.
- None of the individual risk alleles were significantly associated with the achievement of stable dose.
- In a recent study we found no statistically significant effect of the CYP2C9*2 or CYP2C9*3 allele on the prescribed stable dose in this cohort.[1]
- Although many of the genes are associated with β-cell function, the exact mechanism behind our finding remains to be elucidated.
- For complex diseases such as T2DM, there may be multiple genetic backgrounds resulting in similar phenotypic disease, each requiring a different drug treatment.
- Our results support this concept, and support the use of disease related genes in pharmacogenetic studies.
- Individualization of T2DM treatment according to genetic profile may be an opportunity to improve clinical outcome.

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