The heritability of HbA1c and fasting glucose is caused by different genetic factors

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Background and Aims

Although HbA1c is used worldwide to monitor long-term glycaemia in diabetes mellitus, the genetic contribution to variation in HbA1c has not been examined in detail. It is unclear whether the genetic factors that influence the variability of HbA1c are the same as those that influence fasting blood glucose.

Methods

We included 77 families with healthy same-sex twins and siblings, aged 20-45 years. Fasting blood glucose was measured during three different settings: at home before an OGTT and during two visits to the clinic. HbA1c was measured during the first clinic visit. A 4-variate structural equation model in the Mx software package was used, that incorporated sex and age as covariates and estimated heritability of each trait as well as genetic correlations among traits (fig 1).

Results

FBG and HbA1c results on the OGTT and meal test were obtained for 180 subjects (76 male), from which 51 MZ pairs and 60 DZ/sibling pairs could be formed. FBG results on the clamp test were obtained for 123 subjects (57) male from 54 twin families, from which 33 MZ pairs and 40 DZ / sibling pairs could be formed (table1). There was a significant sex effect on FBG in the hospital settings while age had a significant influence on HbA1c and FBG-C.

Table 1.The mean age and mean glycaemic parameters separately for men and women

	male	female
Age in years	30.32	30.84
HbA1c%	5.29	5.20
FBG-O in mmol/l	4.71	4.56
FBG-M in mmol/l	4.53	4.27
FBG-C in mmol/l	4.61	4.29

FBG-O: fasting blood glucose at home .FBG-M: fasting blood glucose before meal. FBG-C: fasting blood glucose before clamp.

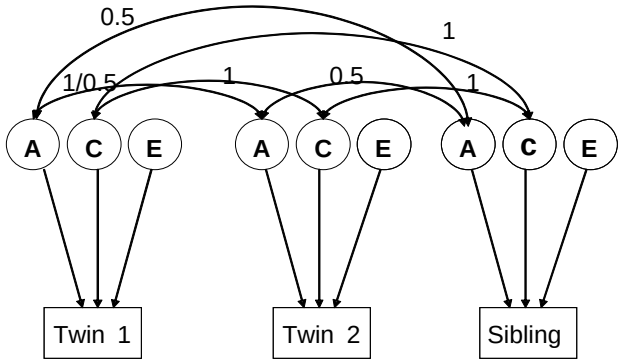

Figure 1. Univariate path diagram; A= additive genetic, C= shared environmental, E=non shared environmental influences. In MZ twins the correlation of the additive genetic factors is1.0, and 0.5 in DZ twins and between twins and siblings. The correlation of the shared environmental effects is 1.0 between twins and between twins and siblings.

Results continued

- There were significant correlations among fasting blood glucose levels (r= 0.34-0.54).
- The correlation among HbA1c and fasting blood glucose was low (r=0.11-0.23).
- Twin and sibling correlations were significant for all traits (tabl2); for HbA1c heritability explained 75% of the variance in HbA1c.
- The heritability of fasting blood glucose was prominent in all settings: at home 0.66 and at the clinic 0.57 (before meal) and 0.38 (before clamp)..
- Cross-twin cross-trait correlations (tabl2) were generally low. Genetic factors influencing HbA1c and fasting blood glucose were non-overlapping.
- The correlation among the fasting blood glucose levels was mostly due to common genetic factors influencing glucose levels in all three settings.

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Table 2. Correlations among traits (upper part), among twins and traits for MZ twins (middle part), for DZ twins- siblings (lower part).

		HbA1c	FBG-O	FBG-M	FBG-C
phenotypic	HbA1c	1			
	FBG-O	0.11ns	1		
	FBG-M	0.15ns	0.49	1	
	FBG-C	0.23	0.34	0.54	1
MZ corr	HbA1c	**0.75**			
	FBG-O	0.14ns	**0.63**		
	FBG-M	0.12ns	0.36	**0.56**	
	FBG-C	0.16ns	0.27	0.24	**0.35**
DZ and twin-sib	HbA1c	**0.47**			
	FBG-O	0.08ns	**0.53**		
	FBG-M	0.07ns	0.31	**0.37**	
	FBG-C	0.18ns	0.26	0.32	**0.39**

ns: non significant

Discussion and Conclusion

These results suggest that the heritability of HbA1c might reflect metabolic processes independent of fasting glycaemia.

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