

PRELIMINARY RESULTS FROM EUROCLOT: HERITABILITY ESTIMATES AND LINKAGE ANALYSIS FOR COAGULATION AND FIBRINOLYTIC PARAMETERS



EuroClot – genetic regulation of the end-stage clotting process that leads to thrombotic stroke

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INTRODUCTION

- Thrombotic stroke is a disabling condition affecting an estimated 650,000 Europeans annually, with considerable mortality, and costing over 30 billion euros a year.
- Family and twin studies have established that genetic factors account for a substantial component of the incidence and mortality of stroke.
- EuroClot will research the genetic regulation of end-stage coagulation leading to thrombotic stroke by identifying and validating loci and genes that determine the speed and magnitude of thrombus formation and lysis.

METHODS

- Citrated plasma and serum, DNA isolated by standard technique, as well as detailed demographic data, have been obtained for the whole study from over 4600 dizygotic (DZ) and monozygotic (MZ) twins in UK, Sweden, Finland, Italy; the Danish samples are supplied by the Danish Twin Registry, University of Southern Denmark.
- Coagulation turnover was assessed using D-dimer and fibrin assessed for turbidity and speed of lysis. (*D-dimer is a degradation product of cross-linked fibrin*).
- Multipoint genome-wide linkage analysis was conducted through variance components maximum likelihood in the UK sample using 2231 genetic markers.

HERITABILITY OF COAGULATION AND FIBRINOLOYTIC PARAMETERS (BASED ON UK TWINS)

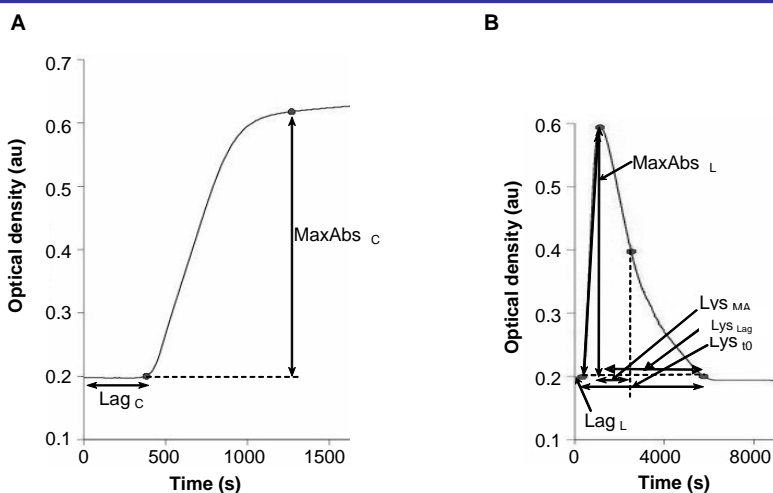
Estimates / 95% confidence intervals for A (heritability), C (familial common environment) and E (specific individual effects and measurement error)

Phenotype	A		C		E	
Lag _C	17%	(8%-25%)	62%	(55%-69%)	21%	(18%-25%)
Lys50 _{Lag}	17%	(6%-29%)	51%	(41%-60%)	32%	(28%-36%)
Lag _L	21%	(7%-33%)	45%	(34%-54%)	34%	(30%-40%)
Lys50 _{MA}	22%	(11%-32%)	52%	(43%-61%)	26%	(23%-30%)
Lys50 ₁₀	23%	(11%-35%)	47%	(37%-55%)	30%	(27%-35%)
D-dimer	25%	(6%-44%)	18%	(3%-33%)	57%	(50%-64%)
AUC	28%	(15%-40%)	41%	(30%-51%)	31%	(28%-37%)
MaxAbs _C	46%	(30%-62%)	15%	(2%-28%)	39%	(34%-45%)
MaxAbs _L	65%	(60%-69%)	-		35%	(31%-48%)

CONCLUSIONS

These results show that end-stage coagulation is under genetic influence. We have uncovered at least three significant linkages with LOD scores between 3 and 5 suggesting QTLs for further study.

Illustration of the turbidimetric clotting and lysis variables analysed



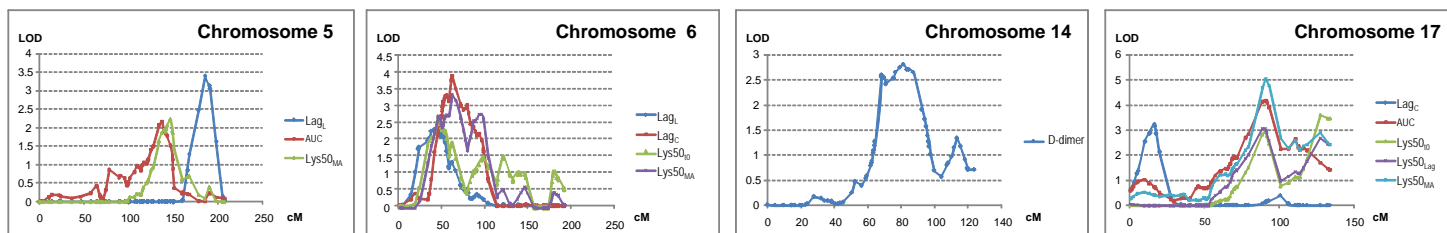
Panel A Turbidimetric clotting assay variables:

lag time (Lag_C) taken as time to exponential increase in absorbance; maximum absorbance (MaxAbs_C) taken as absorbance where 3 consecutive readings were identical corrected for the Lag_C.

Panel B Turbidimetric lysis assay variables:

lag time (Lag_L); maximum absorbance (MaxAbs_L) taken as highest absorbance value adjusted for Lag_L; Lys50₁₀, taken as time at which a 50% fall in absorbance from MaxAbs_L occurred; Lys50_{Lag}, taken as time from Lag_L to the time at which a 50% reduction in absorbance occurred; Lys50_{MA}, taken as the time from MaxAbs_L to the time at which a 50% reduction in absorbance occurred; area under the curve (AUC).

LINKAGE RESULTS (BASED ON UK TWINS)



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