



Uppsala University SciLifeLab

WP 2 update


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Agenda

- Angioedema recruitment
 - Uppsala *Mia Wadelius*
 - Utrecht *Ekaterina Baranova*
 - Dundee *Myra White*
 - Liverpool *Ana Alfirevic*
- PRE-PREDICTION GWAS
 - Danish cohort *Eva Rye Rasmussen*
- WP2 discussion



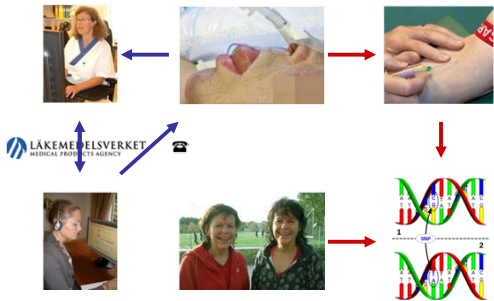
Why?

72 year old man got acute breathing difficulties. Difficult to ventilate due to swelling in the tongue and throat. Died due to anoxic brain damage.

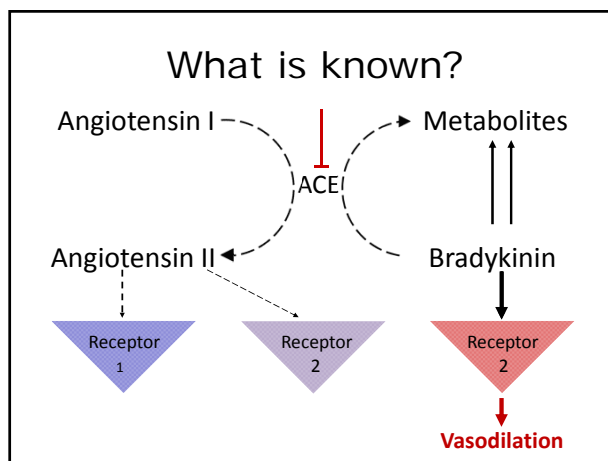
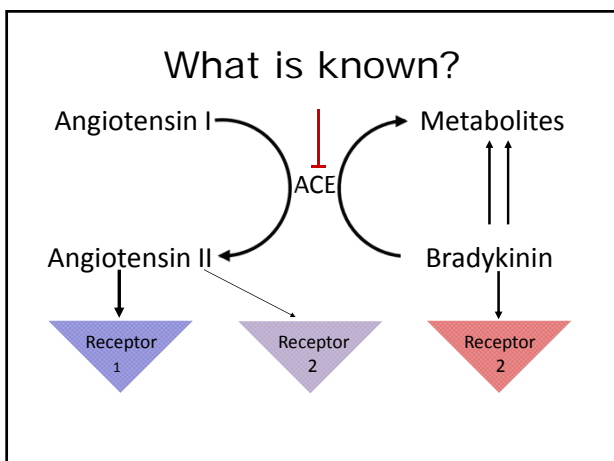


Medicines: aspirin, digoxin, metoprolol (beta-blocker), enalapril (ACE inhibitor)

How?

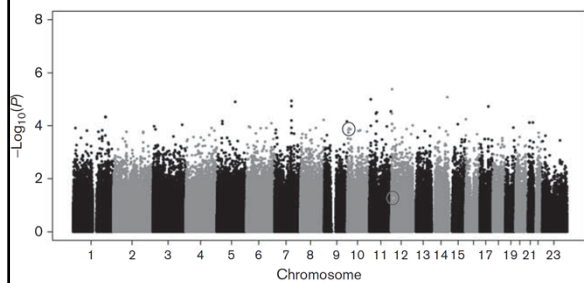


LÄKEMEDELSVERKET
 MEDICAL PRODUCT REGULATORY



Published GWAS

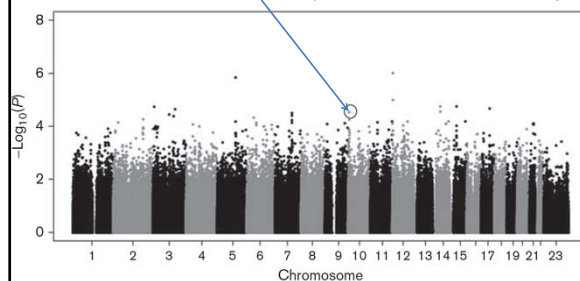
- 175 cases, 489 treated controls, all



Paré G, ..., Brown NJ. Pharmacogenet Genomics 2013;23:470-478.

Published GWAS

- 109 cases, 330 treated controls, Caucasians only
Reduced risk SNP in PRKCCQ, replication in 16 cases, 48 controls, $p=0.03$



Paré G, ..., Brown NJ. Pharmacogenet Genomics 2013;23:470-478.

Tasks

- ✓ Standardised phenotype criteria
- ✓ Recruit 250 cases for sequencing
- ✓ Recruit 250 controls for sequencing
- Recruit 250 cases for replication
- Recruit 250 controls for replication
- Set up a common phenotype database



Recruitment

Discovery cohort	Sweden	Holland	Scotland	England	Total
Adjudicated cases to seq	173	63	14	2	249
Treated controls to seq	175	175?	175?	175	?

Replication cohort	Sweden	Holland	Scotland	England	Denmark
Cases with DNA	11				14
Additional cases identified	47	4	3	20	21
Treated controls with DNA	75				25
Treated controls identified	500				

Replication cohort with GWAS data	USA	USA
Caucasian cases	160	70
Caucasian treated controls	330	109



PRE-PREDICTION

Comparison of clinical factors between ACEI angioedema (AE) cases (n=161) and ACEI coughers (n=128)

Smoking

AE 31% vs coughers 8%, OR 4.9 [95% CI 2.4-10.2], $p=4.51 \times 10^{-6}$

Selective calcium channel blockers

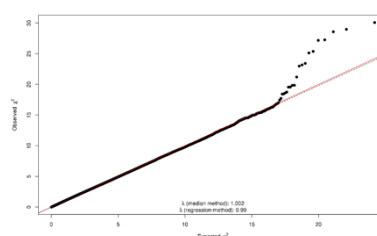
AE 34% vs coughers 12%, OR 3.6 [95% CI 1.9-6.8], $p=3.57 \times 10^{-5}$

Act on calcium channels in arterial vascular smooth muscle and lower blood pressure by causing vasodilation. Examples: amlodipine, clevidipine, diltiazem, felodipine, isradipine, lercanidipine, nifedipine, nimodipine, verapamil.

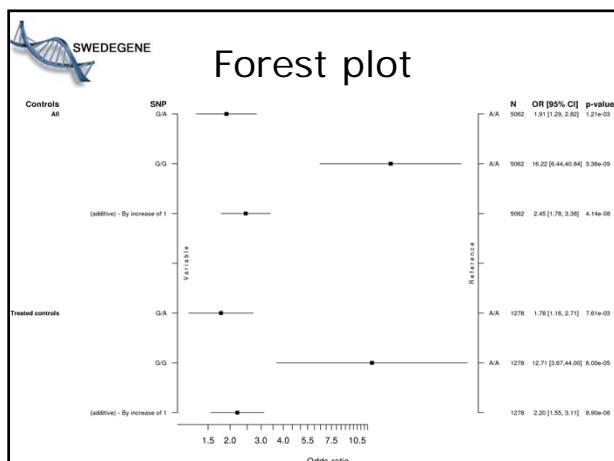
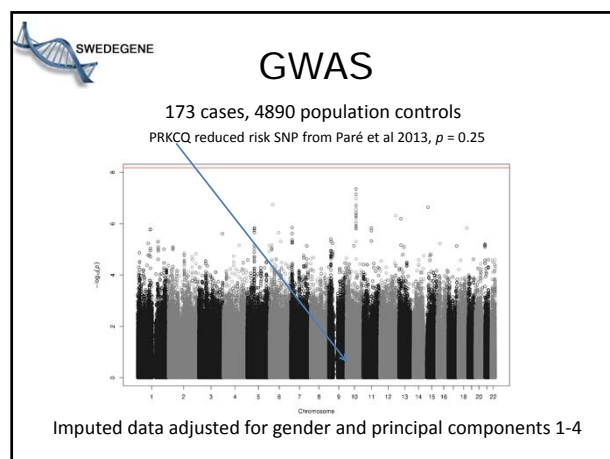
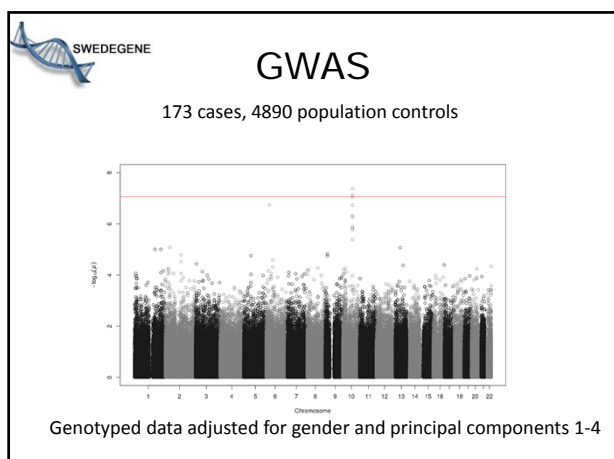


Q-Q plot

173 cases, 4890 population controls



Genotyped data adjusted for gender and principal components 1-4



Next steps

The PRE-PREDICTION top hits are intronic
- Will not be found by exome seq?

2 alternatives for PRE-PREDICTION

- Publish without replication
- Replicate top hits in PREDICTION

SWEDEGENE

Clinical Pharmacology, Uppsala University

- Pär Hallberg, MD ass prof
- Ulrica Ramqvist, research nurse
- Elisabet Stjernberg, research nurse
- Sofie Colin, research assistant
- Eva Prado, research assistant
- Hugo Kohnke, biomedical analyst
- Julia Nagy, clinical pharmacist
- Caroline Johansson, molecular biotechnology engineering student

Uppsala Clinical Research centre

- Niclas Eriksson, statistician PhD

Collaborating physicians

- Malgorzata Karawajczyk, Leif Nordang, Eva Rye Rasmussen.....