



Brain Center  
**Rudolf Magnus**

# Meta-analysis on GWAS in intracranial aneurysms

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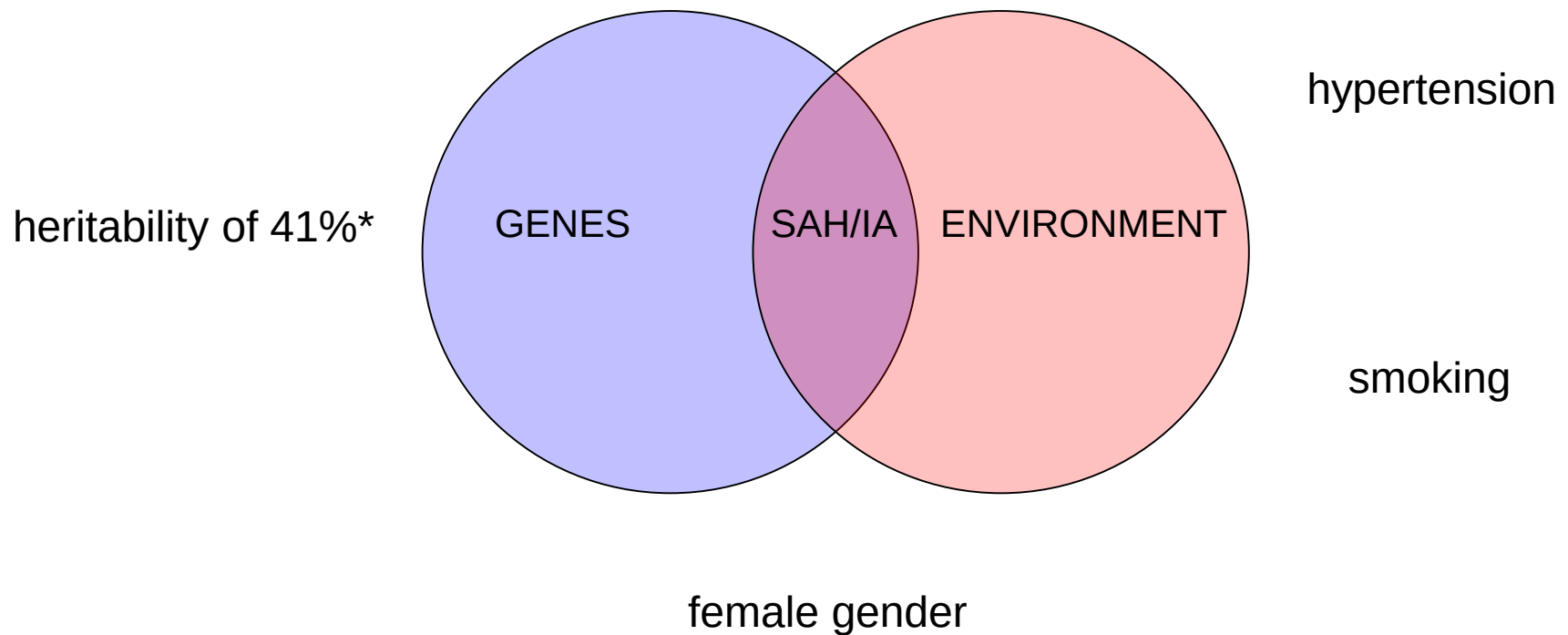
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# contents presentation

- current knowledge on risk loci identified by GWAS
- explanation on current meta-analysis of GWAS
- introduction ISGC working group on IA genetics

# Subarachnoid hemorrhage (SAH) intracranial aneurysms (IA)



\*Korja et al. Stroke 2010;41:2458-62

# Genome wide association studies on IA

| study                       | year | discovery                          | replication                      | loci     | candidate genes   | OR (95% CI)      | p-value               |
|-----------------------------|------|------------------------------------|----------------------------------|----------|-------------------|------------------|-----------------------|
| Bilguvar et al<br>Nat Genet | 2008 | 1580 ca<br>6276 co<br>(Caucasian)  | 494 ca<br>676 co<br>(Japanese)   | 2q33.1   | BOLL<br>PLCL1     | 1.24 (1.15-1.34) | 4.4x10 <sup>-8</sup>  |
|                             |      |                                    |                                  | 8q11.23  | SOX17             | 1.36 (1.24-1.49) | 1.4x10 <sup>-10</sup> |
|                             |      |                                    |                                  | 9p21.3   | CDKN2A-<br>CDKN2B | 1.29 (1.19-1.40) | 1.4x10 <sup>-10</sup> |
| Yasuno et al<br>Nat Genet   | 2010 | 2780 ca<br>12515 co<br>(Caucasian) | 3111 ca<br>1666 co<br>(Japanese) | 8q11.23  | SOX17             | 1.36 (1.24-1.49) | 1.4x10 <sup>-10</sup> |
|                             |      |                                    |                                  | 9p21.3   | CDKN2A-<br>CDKN2B | 1.29 (1.19-1.40) | 1.4x10 <sup>-10</sup> |
|                             |      |                                    |                                  | 10q24.32 | CNNM2             | 1.29 (1.19-1.40) | 1.2x10 <sup>-9</sup>  |
|                             |      |                                    |                                  | 13q13.1  | STARD13           | 1.20 (1.13-1.28) | 2.5x10 <sup>-9</sup>  |
|                             |      |                                    |                                  | 18q11.2  | RBBP8             | 1.22 (1.15-1.28) | 1.1x10 <sup>-12</sup> |
| Yasuno et al<br>PNAS        | 2011 |                                    |                                  | 4q31.23* | EDNRA             | 1.22 (1.14-1.31) | 2.2x10 <sup>-8</sup>  |

\* Based on analysis of SNPs with posterior probability of association 0,1-0,5

# Genome wide association studies on IA

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\* Based on analysis of SNPs with posterior probability of association 0,1-0,5

# Genome wide association studies on IA

| study                        | year | discovery                      | replication*                   | loci | candidate genes | OR (95% CI) | p-value                     |
|------------------------------|------|--------------------------------|--------------------------------|------|-----------------|-------------|-----------------------------|
| Akiyama et al<br>J Hum Genet | 2010 | 288 ca<br>194 co<br>(Japanese) | 739 ca<br>659 co<br>(Japanese) |      |                 |             | no genome wide significance |

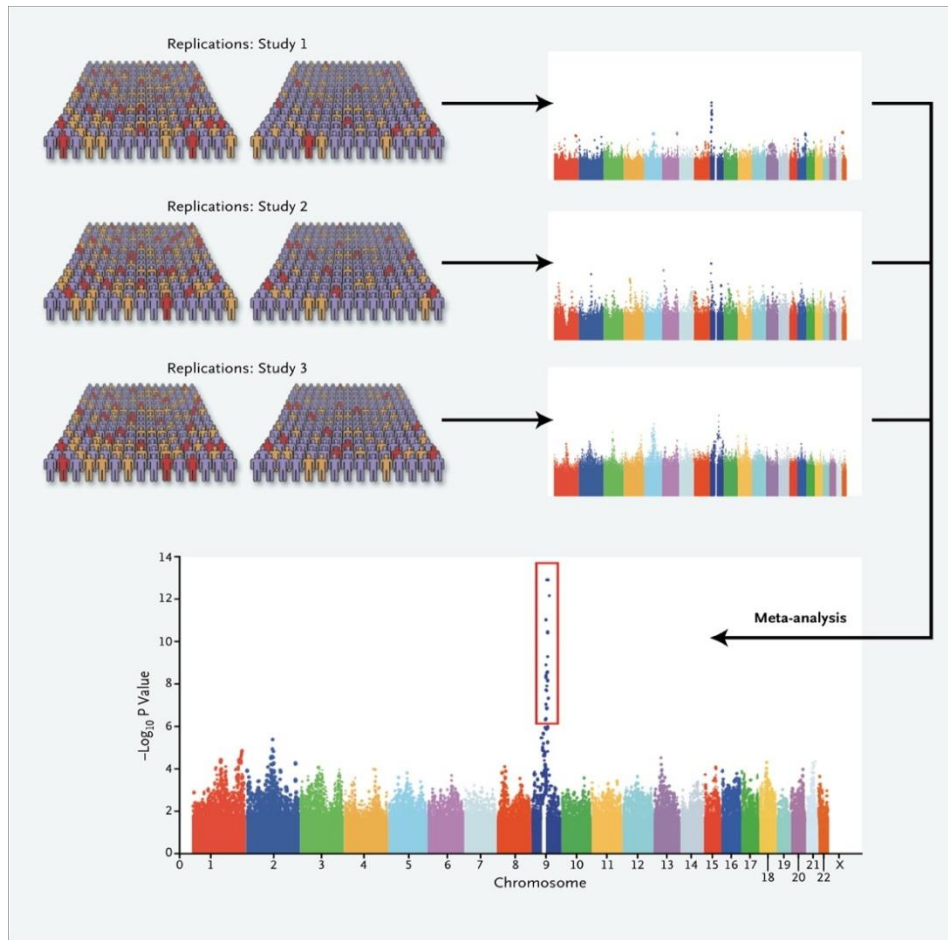
\*the top-ranked 1% of the genotyped SNPs were replicated

|                            |      |                                   |                                  |                |                           |                         |                            |
|----------------------------|------|-----------------------------------|----------------------------------|----------------|---------------------------|-------------------------|----------------------------|
| Low et al<br>Hum Mol Genet | 2012 | 1383 ca<br>5484 co<br>(Japanese)  | 1048 ca<br>7212 co<br>(Japanese) | <b>4q31.23</b> | <b>EDNRA</b>              | <b>1.22 (1.14-1.31)</b> | <b>2,2x10<sup>-8</sup></b> |
|                            |      |                                   |                                  | 9p21.3         | CDKN2A-<br>CDKN2B         | 1.21 (1.13-1.30)        | 1,6x10 <sup>-7</sup>       |
| Foroud et al<br>Stroke     | 2012 | 1480 ca<br>1683 co<br>(Caucasian) |                                  | <b>9p21.3</b>  | <b>CDKN2A-<br/>CDKN2B</b> | <b>1.35 (NR)</b>        | <b>3.6x10<sup>-8</sup></b> |
|                            |      |                                   |                                  | 8q11.23        | SOX17                     | 1.25 (NR)               | 8.7x10 <sup>-5</sup>       |

# Genome wide association studies on IA

| study               | 4q31.23 | 8q12.1 | 9p21.3 | 10q24.32 | 13q13.1 | 18q11.2 |
|---------------------|---------|--------|--------|----------|---------|---------|
| Bilguvar/<br>Yasuno | +       | +      | +      | +        | +       | +       |
| Low                 | +       |        | +/-    |          |         |         |
| Foroud              |         | +/-    | +      |          |         |         |

# Combine different cohorts aimed at detecting more genetic risk loci



Currently being performed for IA/SAH

# meta-analysis of GWAS

Yasuno et al

2780 cases  
12515 controls (Caucasian)

|                                 |                                                |
|---------------------------------|------------------------------------------------|
| + additional cases and controls | +/- 1000 cases (Caucasian and Japanese)        |
| Low et al                       | 1383 cases<br>5484 controls (Japanese)         |
| FIA study group, Foroud et al   | 1480 cases<br>1683 controls (Caucasian)        |
| + additional cases and controls | 1164 cases<br>865 controls (Caucasian)         |
| <b>TOTAL</b>                    | <b>7807 cases</b><br><b>&gt; 20547controls</b> |

for replication: 1700 cases and 3000 controls (Caucasian) available

# ISGC working group on IA genetics

Helsinki University Hospital: Emilia Gaal-Paavola

Hopitaux Universitaire de Geneve: Philippe Bijlenga

Indiana University: Tatiana Foroud

Kuopio University hospital: Juha Jaaskelainen, Mikael von und zu Fraunberg, Mitja Kurki

Jagiellonian University: Joanna Pera, Agnieszka Slowik

UCL London: David Werring, Varinder Singh Alg

UMC Utrecht: Paul de Bakker, Femke vt Hof, Gabriel Rinkel and Ynte Ruigrok

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# Future plans: e.g. phenotype-genotype correlations

- ruptured vs unruptured
- familial vs non-familial
- aneurysm size
- aneurysm location
- interaction with environmental risk factors
- outcome after SAH



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