



**LOW-DENSITY LIPOPROTEIN-RELATED  
RECEPTOR 5 (*LRP5*) GENE  
POLYMORPHISMS  
AND AAA GENETIC SUSCEPTIBILITY**

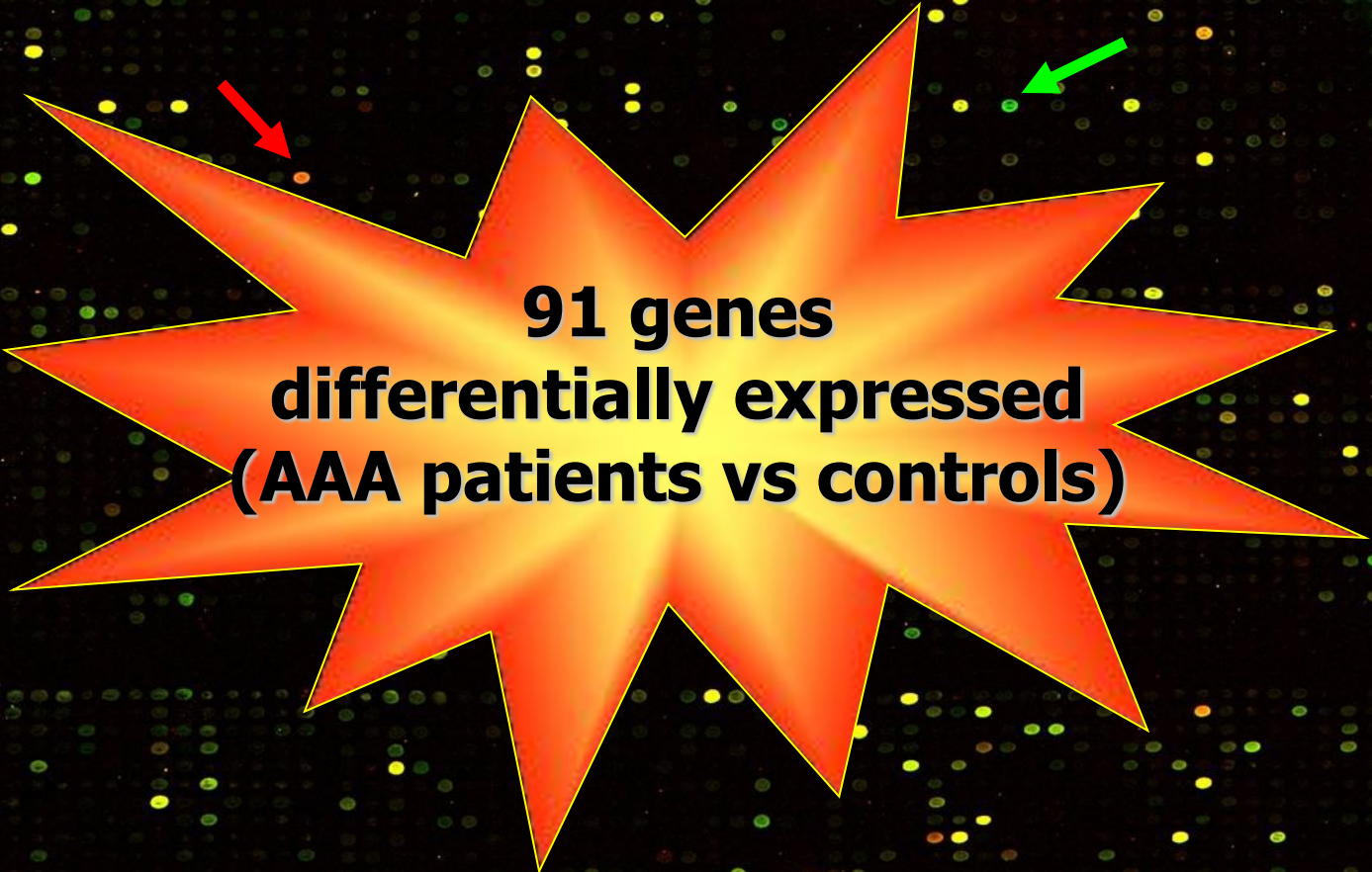
**Betti Giusti**

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Florence

3<sup>rd</sup> International Meeting on Aortic Diseases - IMAD  
Liege, Belgium October 4-6 2012

# COMMUNICATION AGENDA

-  **presentation of new data on the role of polymorphisms in the low density lipoprotein receptor-related protein 5 gene (*LRP5*) as genetic markers of abdominal aortic aneurysm (AAA)**
-  **brief summary of ongoing and published data obtained by our group in the same cohort of AAA patients and controls on the identification of other AAA genetic susceptibility factors, in order to point out a future challenge**



**91 genes  
differentially expressed  
(AAA patients vs controls)**

**76 genes with increased expression**

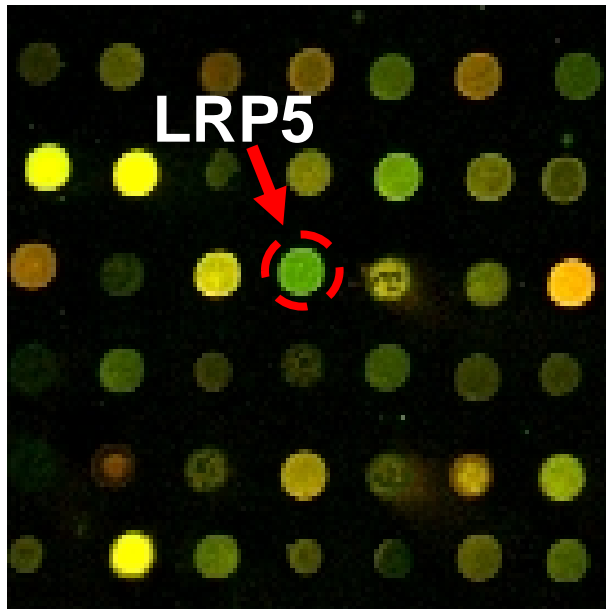
**15 genes with decreased expression**

**Gene expression profiling in whole peripheral blood**

# Gene Ontology in AAA patients

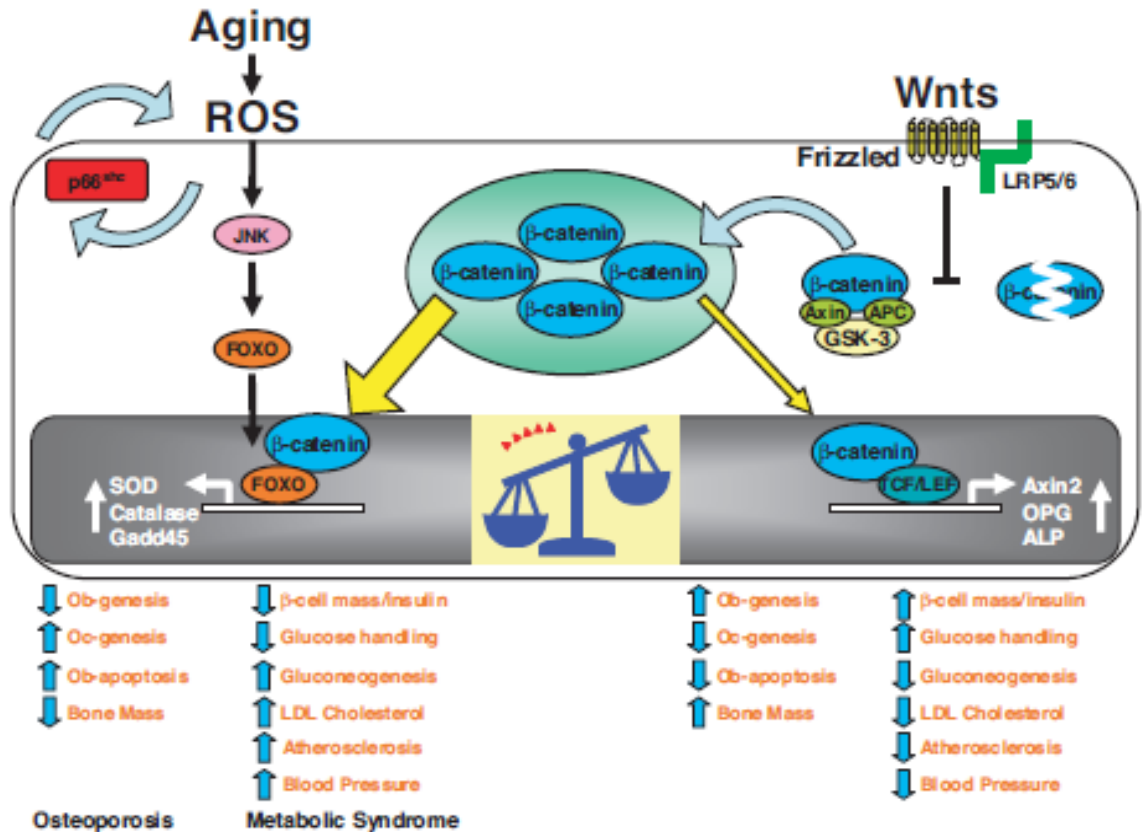
| GO Term  | N   | n | Geni  | P       |
|--|-----|---|---|---------|
| Oxygen Transport                                     | 9   | 4 | HBA2(↑), HBD(↑),<br>HBE1(↑), HBQ1(↑)                              | <0.0001 |
| Positive regulation<br>of protein kinase<br>activity | 3   | 2 | MAP2K3(↑),PTPRC(↓)  | 0.029   |
| lipid metabolic<br>process                           | 190 | 6 | ACADS(↑), CIDEA(↑),<br>LRP5(↓),MGLL(↑),<br>ADIPOR1(↑),HSD17B14(↑) | 0.049   |

# Lipid metabolic process



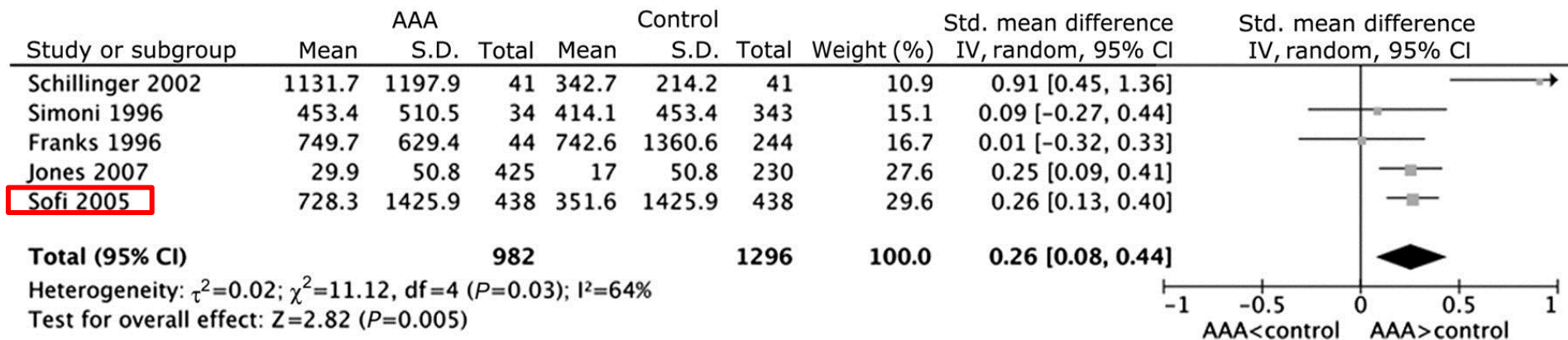
**LRP5 = low density lipoprotein receptor-related protein 5**

*Giusti B et al.,  
Eur J Vasc Endovasc Surg 2009*



**Bone, lipid and glucose metabolism**

# Forest plot of standardized mean difference of circulating lipoprotein(a) concentrations between cases with abdominal aortic aneurysm (AAA) and controls without AAA.



**S.D., standard deviation; CI, confidence interval.**

**Takagi H et al. Interact CardioVasc Thorac Surg 2009;9:467-470**

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INTERACTIVE CARDIOVASCULAR  
AND THORACIC SURGERY

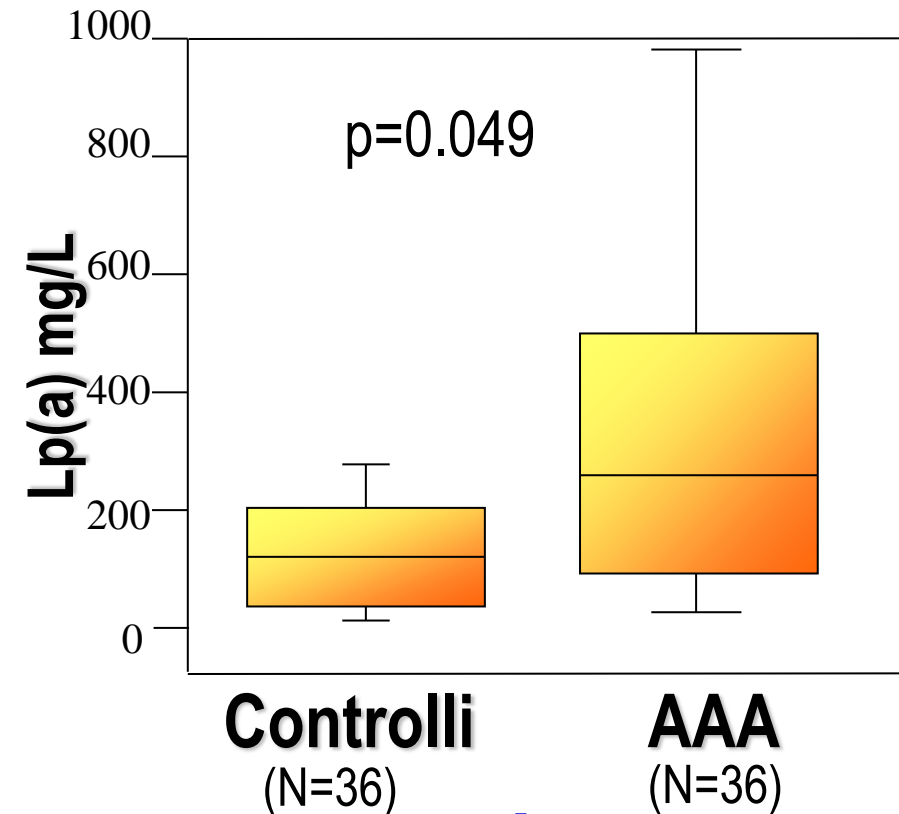


# Relationship between LRP5 expression levels and Lp(a) levels in AAA patients

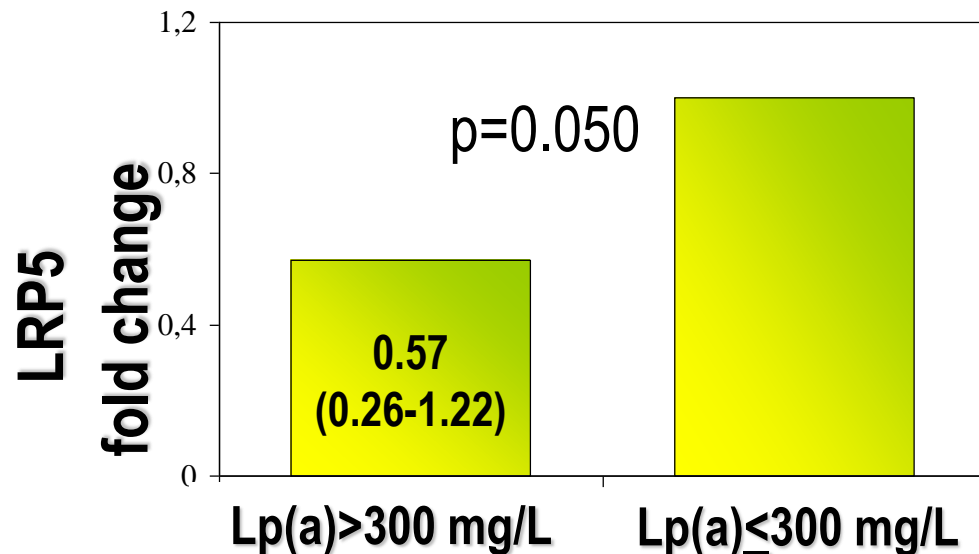
Giusti et al, Eur J Vasc Endovasc Surg 2009

A: Lp(a) levels in AAA patients and control subjects

B: LRP5 expression levels according to Lp(a) levels in AAA patients (n=36).



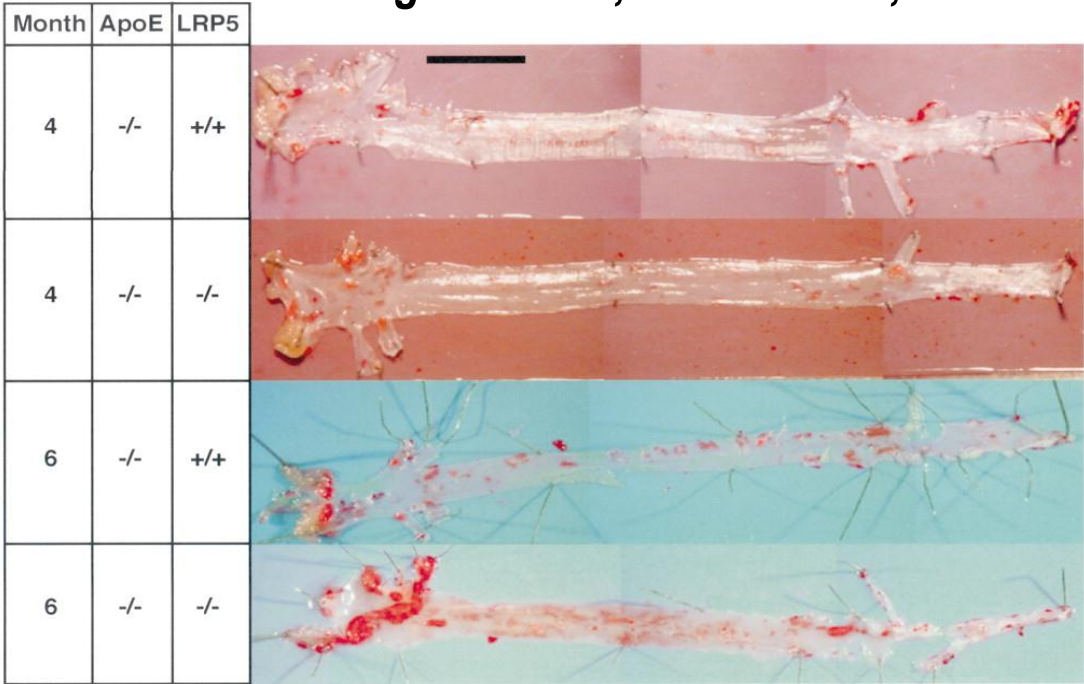
**A**



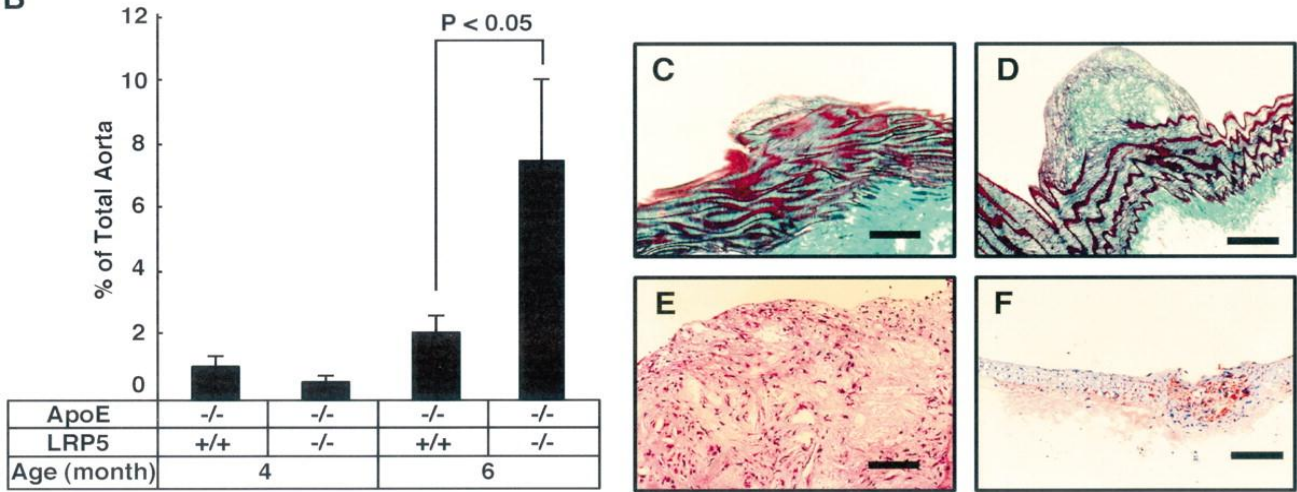
**B**

# Atherosclerotic lesions in apoE and apoE;LRP5 double knockout mice

**A** *Magoori et al., J Biol Chem, 2003*



**B**





***To evaluate the role of single nucleotide polymorphisms (SNPs) in LRP5 gene in determining the genetic susceptibility to abdominal aortic aneurysm (AAA)***

# Demographic and clinical characteristics of AAA patients and controls

|                      | Controls<br>(N=423) | AAA<br>(N=423) | p       |
|----------------------|---------------------|----------------|---------|
| Age                  | 72.0 (41-94)        | 73.5 (40-94)   | ns      |
| Sex (male) N (%)     | 366 (86.5)          | 376 (88.9)     | ns      |
| Smoking N (%)        | 267 (63.1)          | 366 (86.5)     | <0.0001 |
| Diabetes N (%)       | 49 (11.6)           | 41 (9.7)       | ns      |
| Hypertension N (%)   | 179 (42.3)          | 302 (71.4)     | <0.0001 |
| Dyslipidemia N (%)   | 50 (11.8)           | 195 (46.1)     | <0.0001 |
| COPD N (%)           | 66 (15.6)           | 311 (73.5)     | <0.0001 |
| CAD N (%)            | 107 (25.3)          | 163 (38.5)     | <0.0001 |
| CVD N (%)            | 38 (9.0)            | 111 (26.2)     | <0.0001 |
| POAD N (%)           | 67 (15.8)           | 118 (27.9)     | <0.0001 |
| Aortic diameter (mm) | 19 (12-47)          | 50 (31-98)     | <0.0001 |

## SNP selection



We studied 7 SNPs in *LRP5* gene ( chromosome 11q13.4) according to **literature data**

obesity

obesity, BMI,  
bone mass and  
geometry

bone density

osteoarthritis

bone density,  
hypercholester  
olemia

bone density

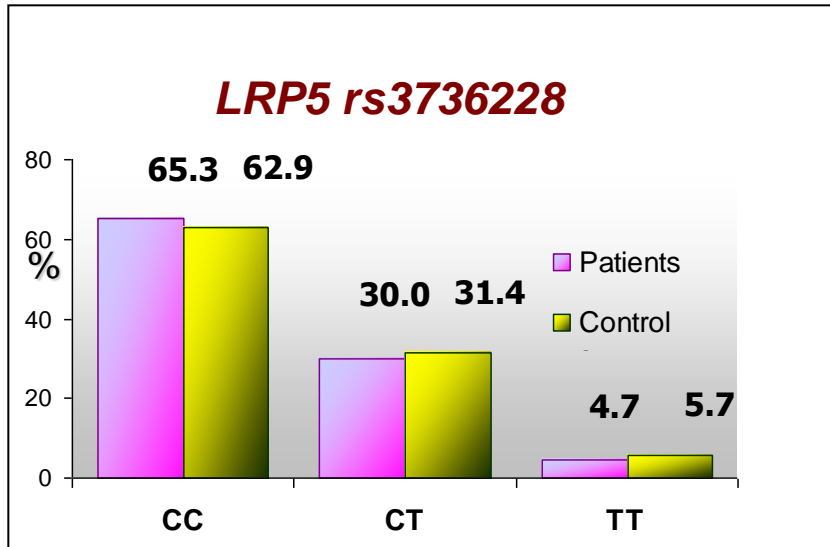
bone density

| SNP ID           | Nucleotide substitution | MAF*     | Characterization        |
|------------------|-------------------------|----------|-------------------------|
| <i>rs312016</i>  | <i>T/C</i>              | T= 0.325 | intron                  |
| <i>rs4988300</i> | <i>T/G</i>              | T= 0.442 | intron                  |
| <i>rs3781590</i> | <i>C/T</i>              | T= 0.258 | intron                  |
| <i>rs667126</i>  | <i>C/T</i>              | C= 0.239 | intron                  |
| <i>rs3736228</i> | <i>C/T</i>              | T= 0.138 | Non syn<br>(Ala1330Val) |
| <i>rs627174</i>  | <i>C/T</i>              | C= 0.177 | intron                  |
| <i>rs556442</i>  | <i>A/G</i>              | G= 0.279 | Syn°<br>(Val1119Val)    |

**Taqman®  
technology**

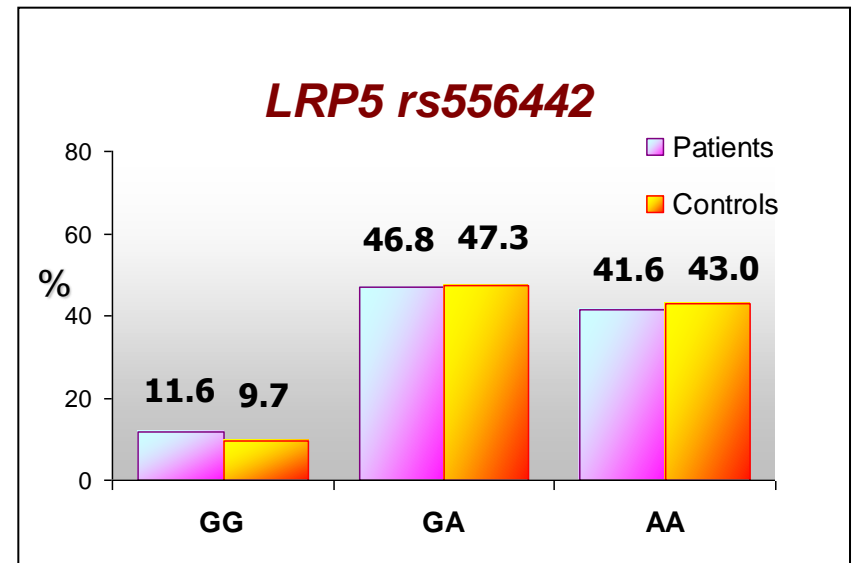
\*minor allele frequency;  
° synonymous

# Genotype distribution of polymorphisms of *LRP5* gene in AAA patients (n=423) and control subjects (n=423)

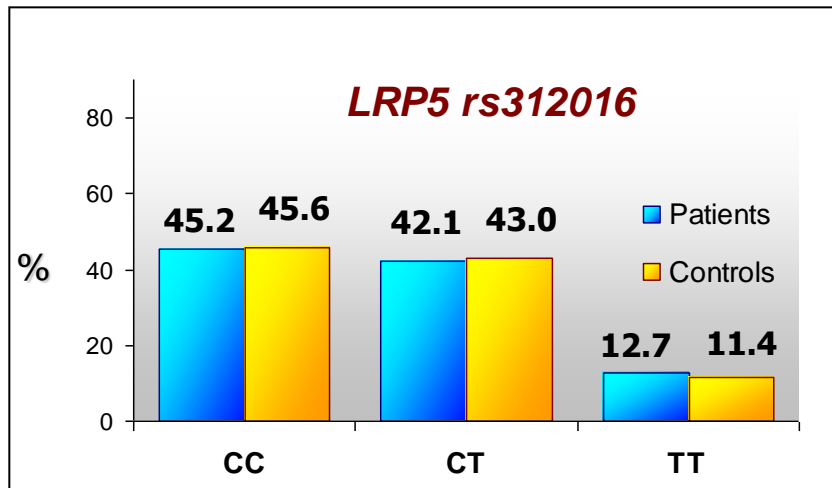
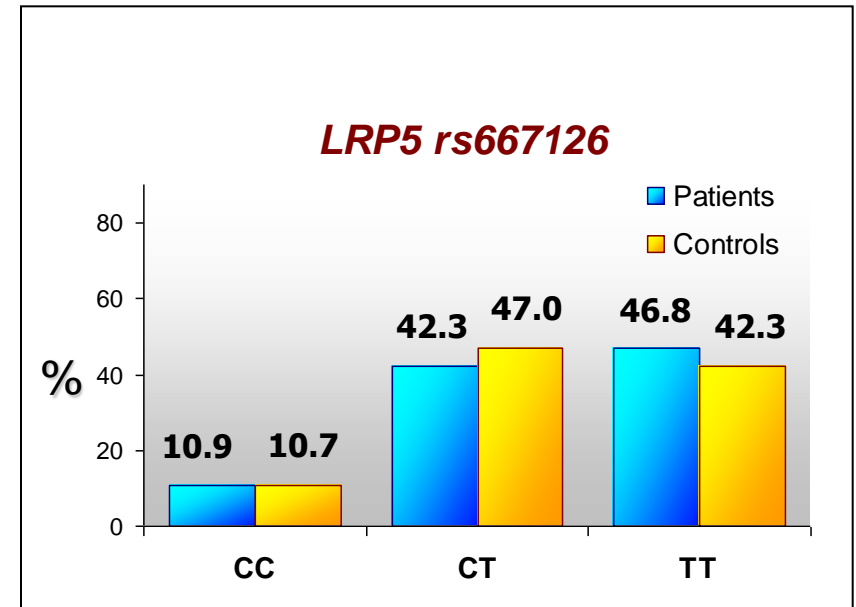
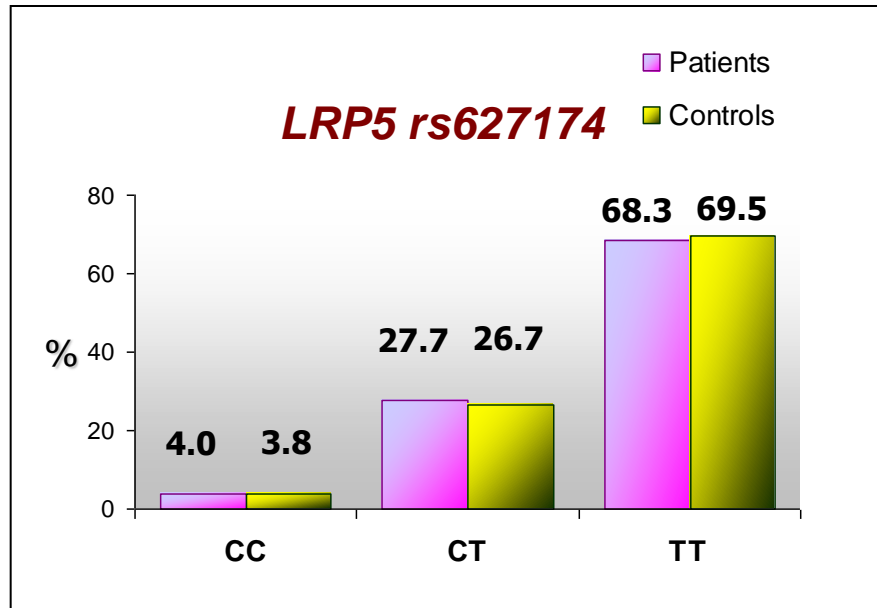


**Galora S et al, submitted**

**Department of Medical and Surgical  
Critical Care, University of Florence, Italy**



# Genotype distribution of polymorphisms of *LRP5* gene in AAA patients (n=423) and control subjects (n=423)



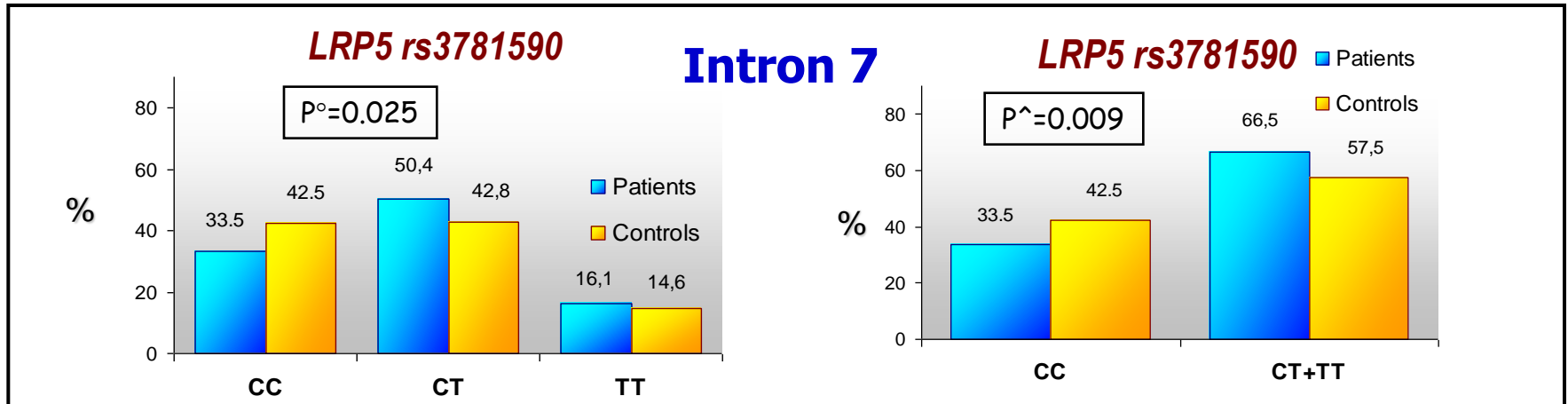
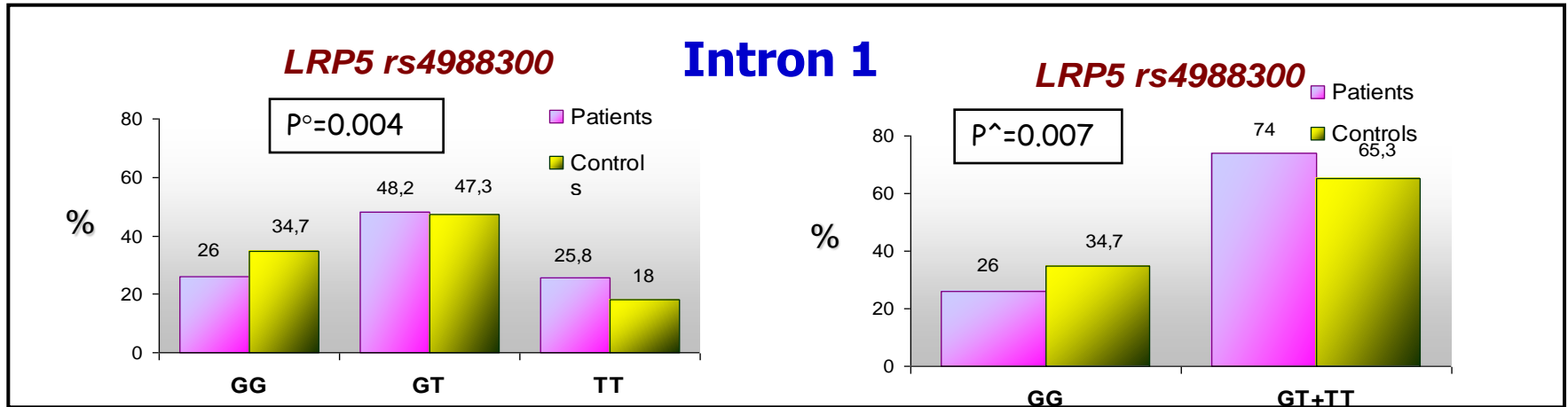
**Galora S et al, submitted**

**Department of Medical and Surgical  
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# Genotype distribution of polymorphisms of *LRP5* gene in AAA patients (n=423) and control subjects (n=423)

Galora S et al, submitted



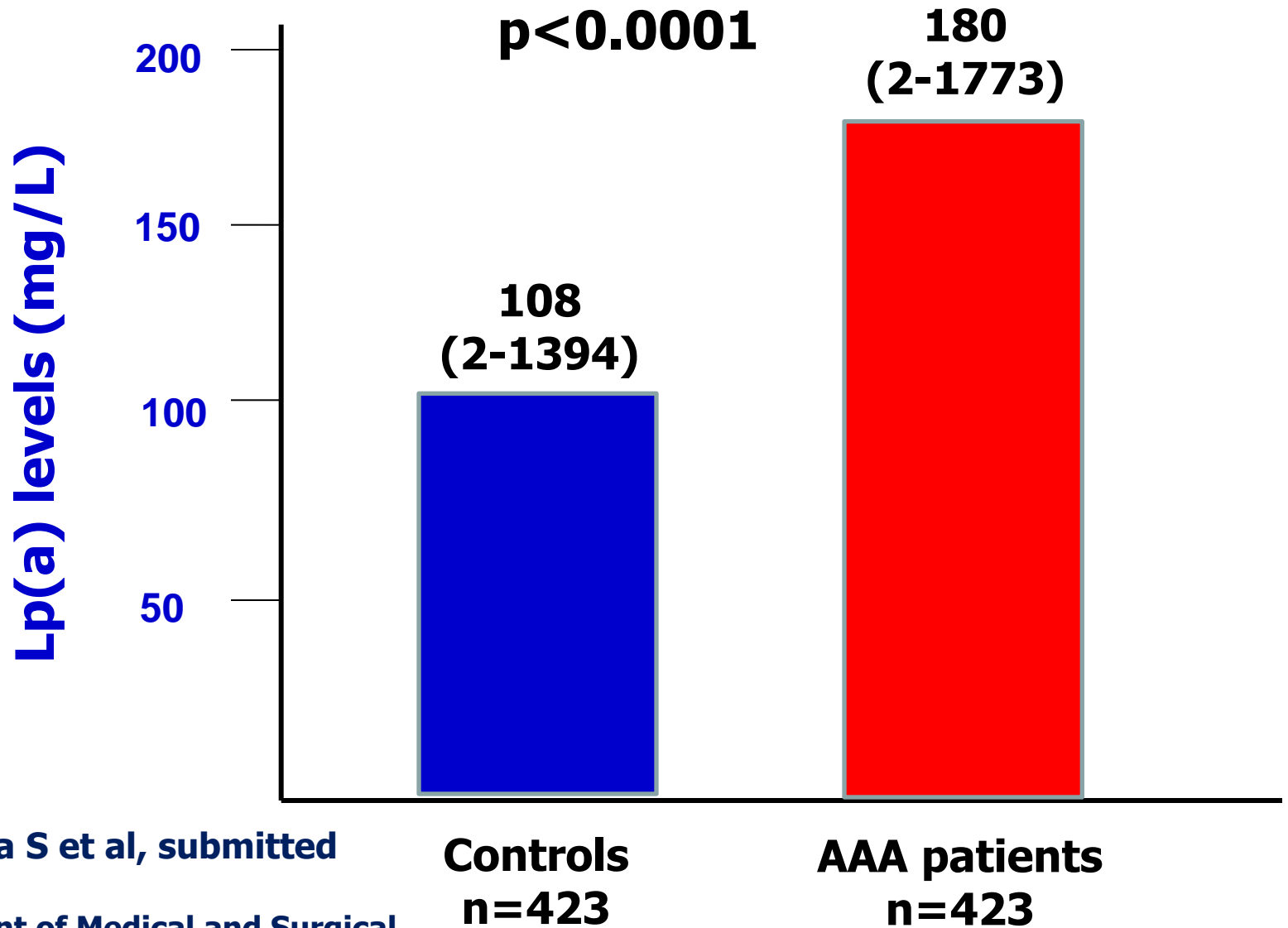
$p^{\circ}$  = according to the additive model;  $p^{\wedge}$  = according to the dominant model

# Odds ratio for the occurrence of AAA according to rs4988300 and rs3781580 LRP5 polymorphisms

| Variables                     | Univariable<br>Analysis | p     | Multivariable<br>Analysis* | p     |
|-------------------------------|-------------------------|-------|----------------------------|-------|
| LRP5<br>rs4988300<br>T allele | 1.52<br>(1.12-2.05)     | 0.007 | 1.62<br>(1.02-2.56)        | 0.040 |
| LRP5<br>rs3781590<br>T allele | 1.47<br>(1.11-1.96)     | 0.008 | 1.83<br>(1.17-2.85)        | 0.008 |

\* adjusted for age, gender, hypertension, diabetes mellitus, dyslipidemia, smoking habit, COPD (chronic obstructive pulmonary disease).

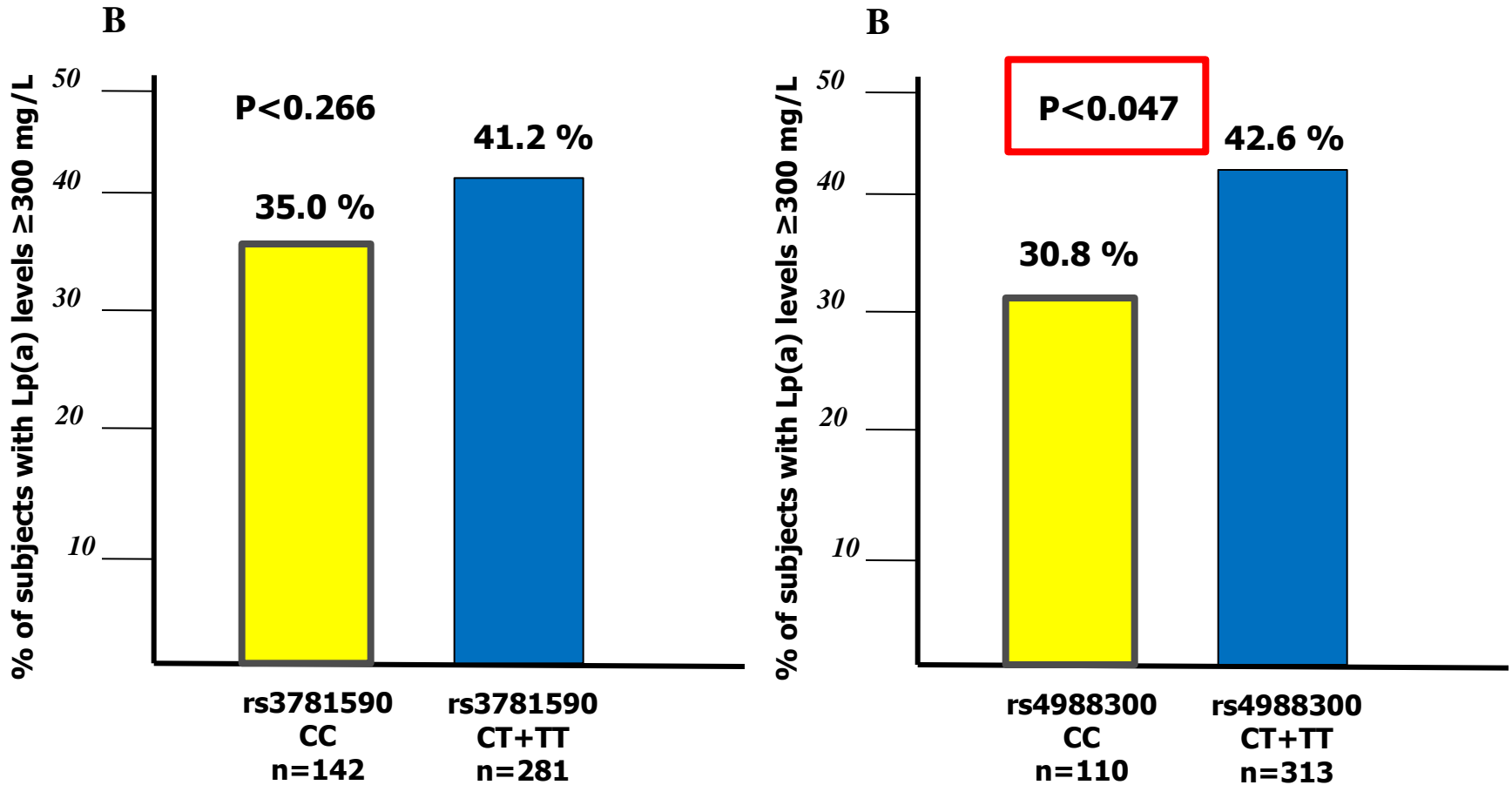
# Lp(a) levels in controls and AAA patients



Galora S et al, submitted

Department of Medical and Surgical  
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# Lp(a) levels in carriers of the rs4988300 and rs3781590 polymorphisms

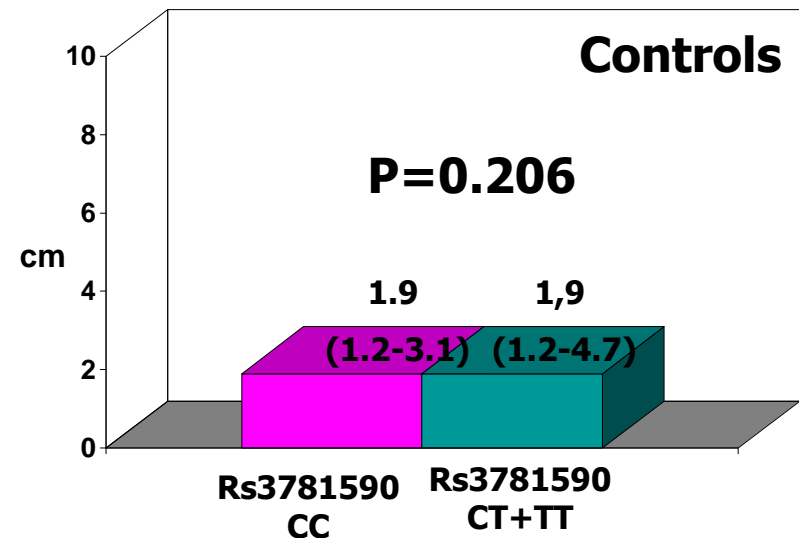
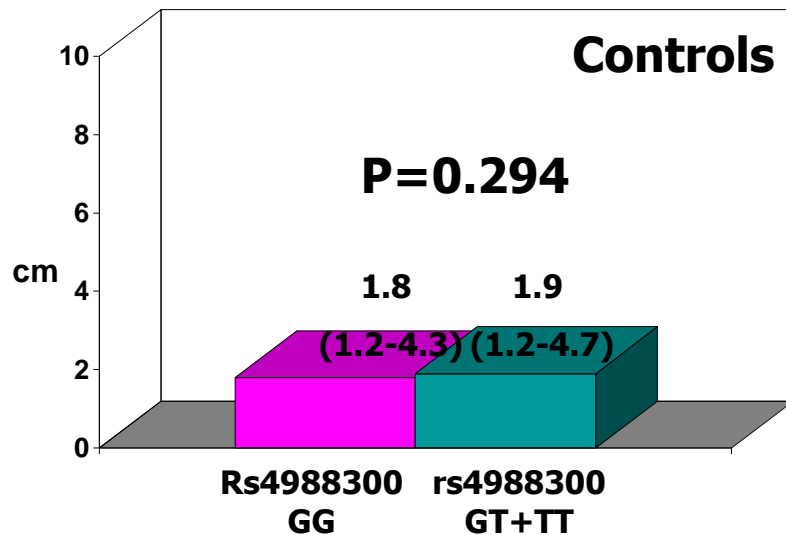
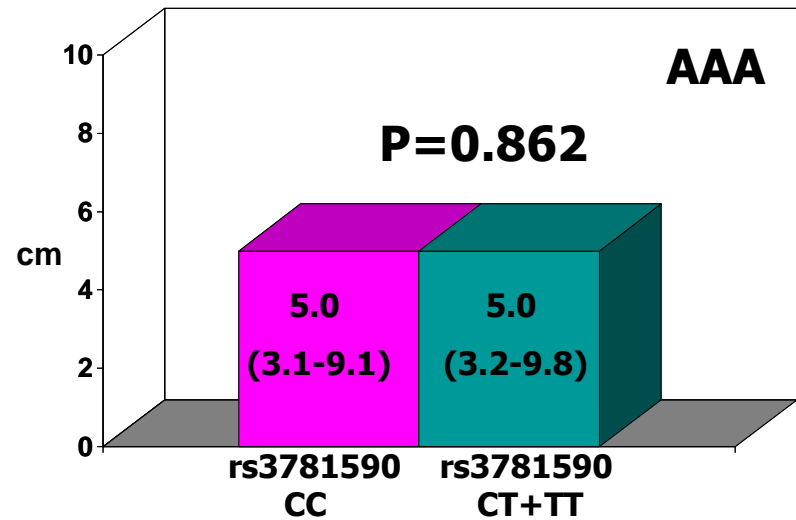
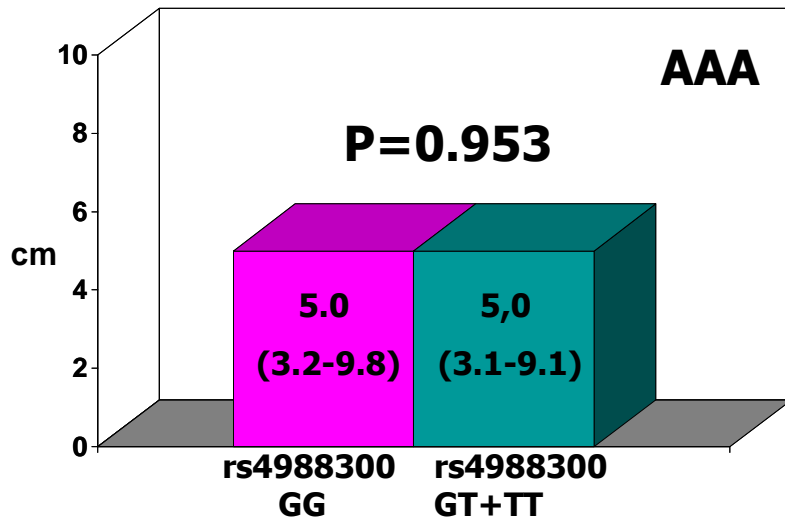


**Galora S et al, submitted**

**Department of Medical and Surgical  
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# Effect of rs4988300 and rs3781590 *LRP5* polymorphisms on abdominal aortic diameters

Galora S et al, submitted





# LRP5 AAA ASSOCIATION STUDY CONCLUSIONS

- ❖ In conclusion, our data identified 2 LRP5 gene polymorphisms (rs4988300 and rs3781590) as **independent genetic markers of AAA**
- ❖ Present data suggest the need to confirm in larger populations the role of **these two markers** and of **LRP5** gene in the **aneurismal disease** in order to improve the understanding of its **pathophysiology** and **pathogenesis**

# COMMUNICATION AGENDA

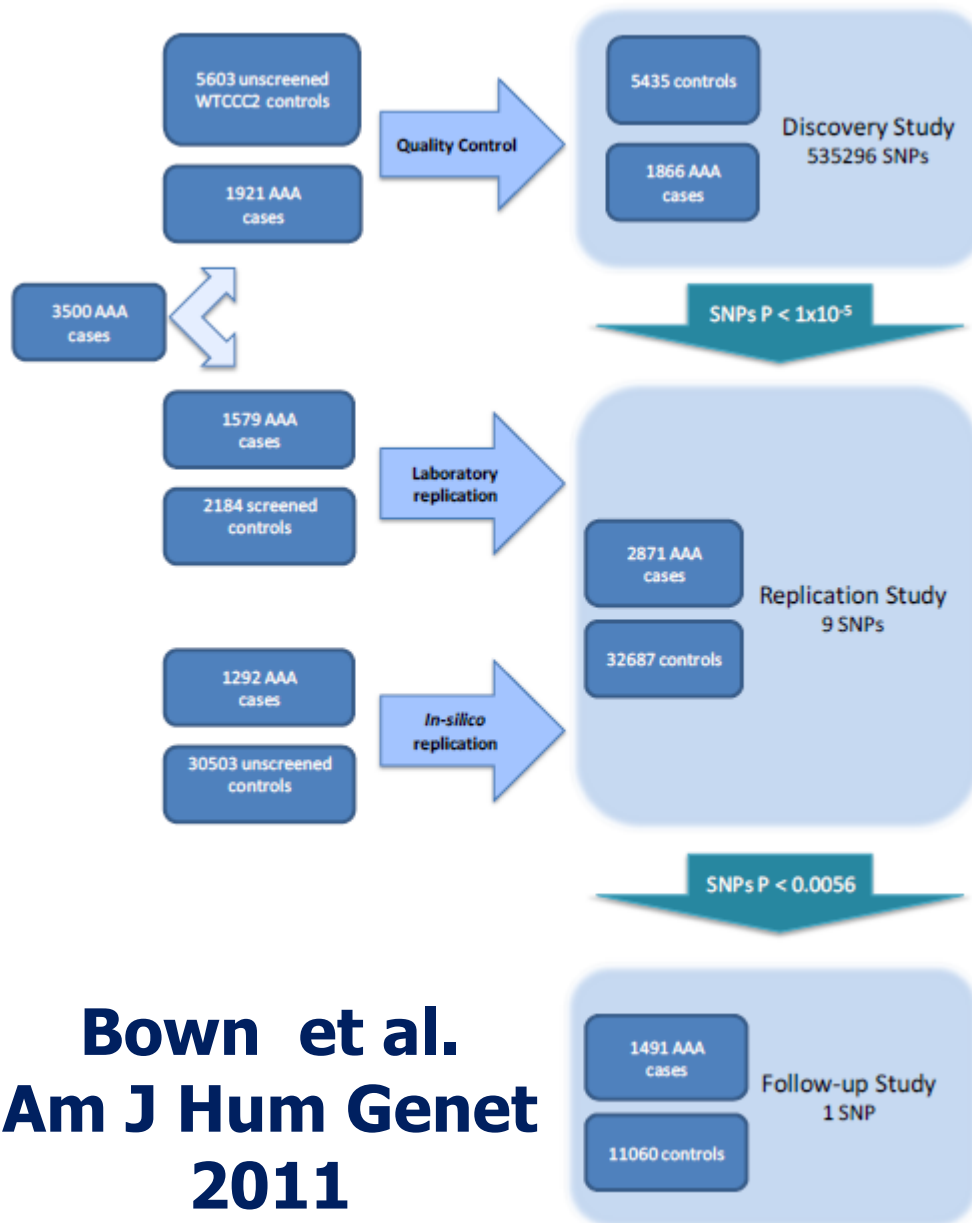


presentation of data on the role of polymorphisms in the low density lipoprotein receptor-related protein 5 gene (*LRP5*) as independent genetic markers of abdominal aortic aneurysm (AAA)



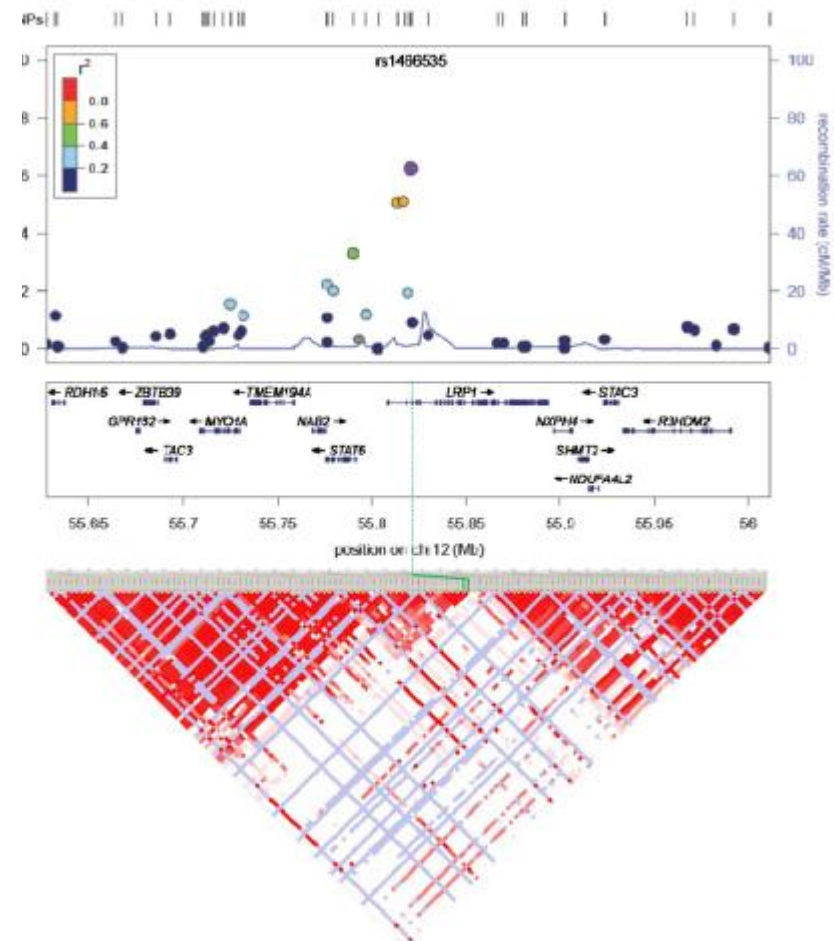
**brief summary of ongoing and published data obtained by our group in the same cohort of AAA patients and controls on the identification of other AAA genetic susceptibility factors, in order to point out a future challenge**

# Genome wide association study and replication



**Bown et al.**  
**Am J Hum Genet**  
**2011**

## Abdominal Aortic Aneurysm Is Associated with a Variant (rs1456535) in Low-Density Lipoprotein Receptor-Related Protein 1

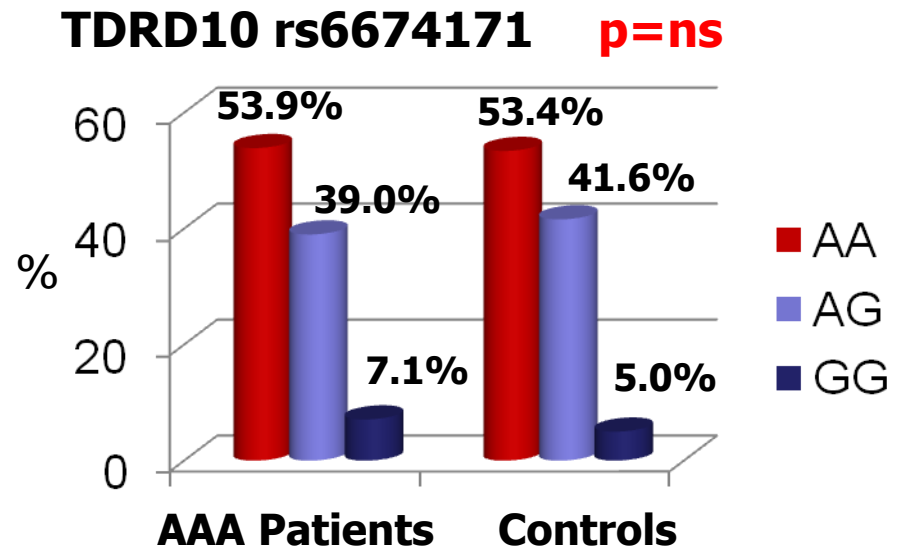
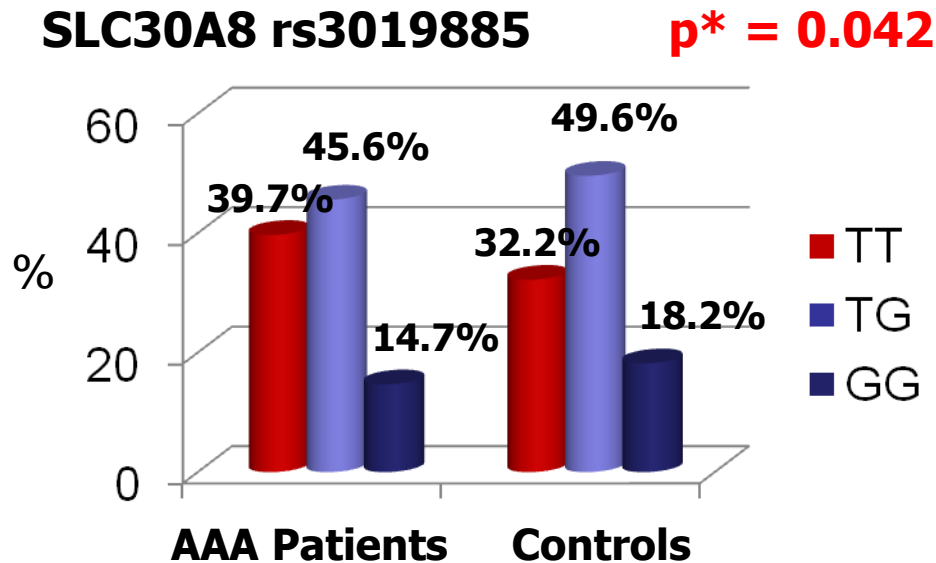
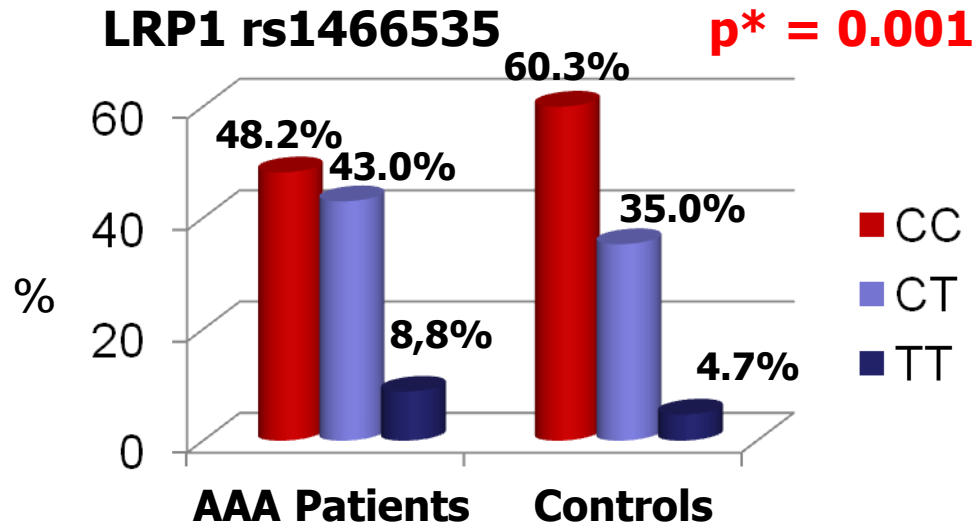


# Replication study data by Bown et al, 2011

| Chr | Gene   | SNP<br>(alleles)    | Risk<br>allele | Discovery Study<br>(1866 AAA, 5435 controls) |                     |                        | Laboratory replication<br>(1579 AAA, 2184 controls) |                     |      | Netherlands in-silico replication dataset<br>(840 AAA, 2791 controls) |                     |        | Iceland in-silico replication dataset<br>(452 AAA, 27712 controls) |                     |       | Combined<br>Replication P<br>value | Combined<br>Discovery and<br>replication P<br>value |
|-----|--|---------------------|----------------|--|---------------------|------------------------|---|---------------------|------|---|---------------------|--------|--|---------------------|-------|------------------------------------|---|
|     |  |                     |                | FA/FC  | OR<br>(95% CI)      | P                      | FA/FC   | OR<br>(95% CI)      | P    | FA/FC   | OR<br>(95% CI)      | P      | FA/FC  | OR<br>(95% CI)      | P     |                                    |   |
| 1   | <i>TDRD10</i>                                  | rs6674171<br>(A/G)  | G              | 0.214/0.181                                  | 1.23<br>(1.12-1.35) | 9.32x10 <sup>-6</sup>  | 0.200/0.194   | 1.04<br>(0.93-1.16) | 0.55 | 0.230/0.201   | 1.12<br>(1.03-1.22) | 0.0002 | 0.192/0.177  | 1.20<br>(0.90-1.61) | 0.22  | 0.037                              | 1.15x10 <sup>-5</sup>                               |
| 2   | <i>AC016912.2</i><br>(processed<br>transcript) | rs7565770<br>(A/C)  | A              | 0.585/0.539                                  | 1.21<br>(1.12-1.31) | 1.78x10 <sup>-6</sup>  | 0.548/0.529   | 1.08<br>(0.98-1.19) | 0.13 | 0.470/0.454   | 1.07<br>(0.96-1.20) | 0.24   | 0.486/0.473  | 1.05<br>(0.93-1.19) | 0.44  | 0.20                               | 2.61x10 <sup>-5</sup>                               |
| 2   | <i>MYT1L</i>                                   | rs4853946<br>(A/G)  | A              | 0.555/0.539                                  | 1.19<br>(1.10-1.28) | 6.41x10 <sup>-6</sup>  | 0.524/0.519   | 1.02<br>(0.92-1.12) | 0.71 | 0.536/0.547   | 0.96<br>(1.06-0.87) | 0.42   | 0.552/0.555  | 0.99<br>(1.01-0.97) | 0.22  | 0.84                               | 2.73x10 <sup>-4</sup>                               |
| 8   | <i>SLC30A8</i>                                 | rs3019885<br>(G/T)  | T              | 0.510/0.449                                  | 1.27<br>(1.18-1.37) | 1.24x10 <sup>-10</sup> | 0.462/0.422   | 1.08<br>(0.99-1.19) | 0.09 | 0.577/0.553   | 1.1<br>(0.99-1.23)  | 0.086  | 0.539/0.572  | 0.87<br>(0.76-1.00) | 0.045 | 0.010                              | 2.32x10 <sup>-10</sup>                              |
| 9   | <i>C9orf92</i>                                 | rs7044238<br>(C/T)  | C              | 0.375/0.335                                  | 1.19<br>(1.11-1.29) | 9.60x10 <sup>-6</sup>  | 0.345/0.351   | 0.98<br>(0.88-1.08) | 0.64 | 0.669/0.656   | 1.06<br>(0.94-1.19) | 0.32   | 0.644/0.629  | 1.07<br>(0.92-1.24) | 0.37  | 0.52                               | 4.26x10 <sup>-4</sup>                               |
| 12  | <i>LRP1</i>                                    | rs1466535<br>(C/T)  | C              | 0.679/0.634                                  | 1.22<br>(1.13-1.32) | 9.99x10 <sup>-7</sup>  | 0.679/0.653   | 1.12<br>(1.02-1.23) | 0.02 | 0.677/0.648   | 1.14<br>(1.02-1.28) | 0.026  | 0.610/0.583  | 1.12<br>(0.98-1.28) | 0.10  | 0.0042                             | 2.86x10 <sup>-9</sup>                               |
| 13  | <i>GPC6</i>                                    | rs2892667<br>(A/G)  | G              | 0.327/0.287                                  | 1.21<br>(1.12-1.31) | 2.32x10 <sup>-6</sup>  | 0.292/0.308   | 0.93<br>(0.84-1.03) | 0.17 | 0.301/0.299   | 1.01<br>(0.92-1.11) | 0.84   | 0.329/0.334  | 0.98<br>(1.09-0.88) | 0.72  | 0.60                               | 1.73x10 <sup>-4</sup>                               |
| 14  | <i>BMP4</i>                                    | rs2071047<br>(C/T)  | C              | 0.628/0.587                                  | 1.19<br>(1.10-1.28) | 6.05x10 <sup>-6</sup>  | 0.591/0.593   | 0.99<br>(0.90-1.09) | 0.65 | 0.618/0.633   | 0.93<br>(1.05-0.83) | 0.23   | 0.642/0.632  | 1.06<br>(0.90-1.25) | 0.48  | 0.57                               | 3.51x10 <sup>-4</sup>                               |
| 19  | <i>ZNF665</i>                                  | rs11666426<br>(C/T) | C              | 0.442/0.400                                  | 1.19<br>(1.11-1.29) | 5.73x10 <sup>-6</sup>  | 0.404/0.413   | 0.96<br>(0.88-1.06) | 0.41 | 0.615/0.610   | 1.03<br>(0.91-1.17) | 0.64   | 0.655/0.644  | 1.09<br>(0.96-1.23) | 0.36  | 0.47                               | 3.36x10 <sup>-4</sup>                               |

Bown MJ et al., Am J Hum Genet 2011

Genotype distribution of polymorphisms of *LRP1*, *SLC30A8* and *TDRD10* genes in AAA patients (n=423) and control subjects (n=423)



$p^*$  = according to dominant model

Unpublished data



## Univariate logistic regression analysis

**rs3019885 SLC30A8 = OR=0.73  
(95% CI 0.54-0.98), p=0.042**  
**rs1466535 LRP1 = OR=1.65  
(95%CI 1.24-2.20), p=0.001**

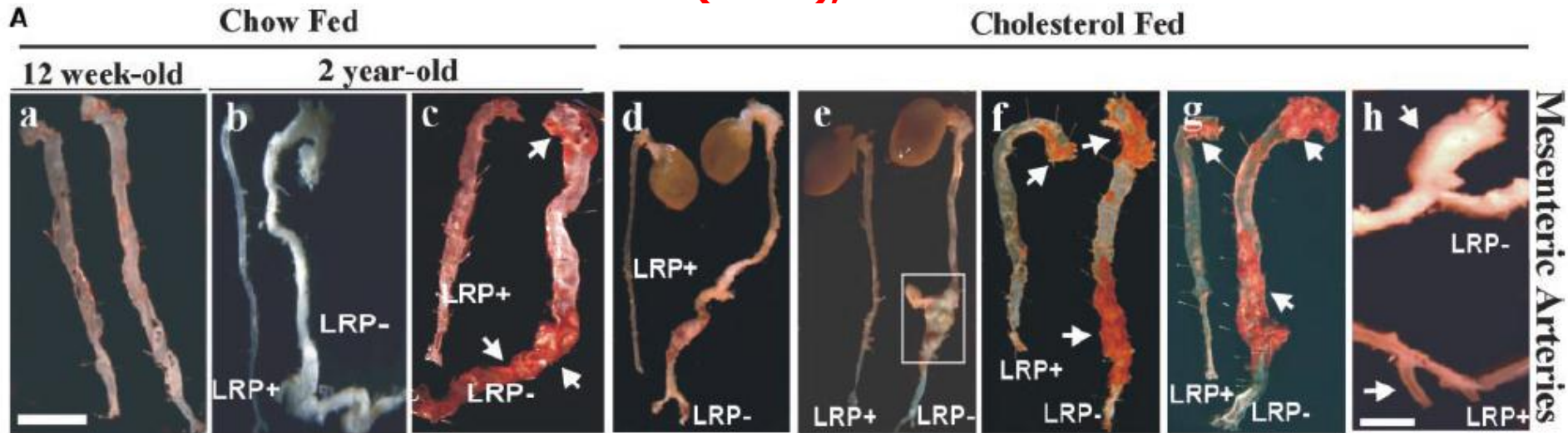
## Multiple logistic regression analysis

| VARIABLES                 | OR (95% CI)            | P           |
|---------------------------|------------------------|-------------|
| <b>LRP1</b>               |                        |             |
| <b>rs1466535 T Allele</b> | <b>1.85 (1.2-2.84)</b> | <b>0.01</b> |
| Age                       | 0.99 (0.97-1.01)       | 0.39        |
| Gender                    | 1.21 (0.58-2.53)       | 0.61        |
| Hypertension              | 3.08 (1.99-4.76)       | <0.0001     |
| Dyslipidemia              | 4.86 (2.94-8.04)       | <0.0001     |
| Diabetes                  | 0.67 (0.32-1.40)       | 0.29        |
| Smoking habit             | 2.91 (1.65-5.11)       | <0.0001     |
| COPD                      | 13.01 (8.19-20.68)     | <0.0001     |

Adjusted for traditional cardiovascular risk factors and chronic obstructive pulmonary disease (COPD)

**Unpublished data**

## Boucher et al. (2003), in animal model



### Accelerated formation of atherosclerotic lesions and aortic dilatation and aneurysm in LDLR<sup>-</sup>; smooth muscle-specific LRP1<sup>-</sup> mice.

Inactivation of LRP1 in vascular SMCs of mice causes PDGFR over-expression and abnormal activation of PDGFR signaling, resulting in disruption of the elastic layer, SMC proliferation, aneurysm formation, and marked susceptibility to cholesterol-induced atherosclerosis.

### Bown et al. (2011), in human

**T allele is associated with a reduced LRP1 gene expression**, by altering a SREBP-1 binding site than influencing LRP1 enhancer activity at the locus.

**Table 2. Effect of rs1466535 Genotype on LRP1 Expression**

| Tissue                      | Number | CC versus TT<br>Fold-Change (95% CI) |
|-----------------------------|--------|--------------------------------------|
| Aortic adventitia           | 133    | 1.19 (1.04–1.36)                     |
| Aortic intima media         | 138    | 1.17 (0.96–1.42)                     |
| Mammary artery intima media | 89     | 1.24 (0.99–1.56)                     |
| Liver                       | 212    | 0.99 (0.91–1.07)                     |

# Polymorphisms of genes involved in extracellular matrix remodeling and abdominal aortic aneurysm

Table I. Polymorphisms investigated

| <i>Gene symbol and chromosome position</i> | <i>Ensemble gene ID</i> | <i>dbSNP ID</i>                   | <i>Common polymorphism name</i> | <i>Position in gene region</i>               |
|--|-------------------------|-----------------------------------|---------------------------------|--|
| MMP1<br>11q22-q23                          | ENSG00000196611         | rs1799750                         | −1607G/GG                       | 5' near gene                                 |
| MMP2<br>16q13-q21                          | ENSG00000087245         | rs2285053<br>rs243865<br>rs243866 | −735C/T<br>−1306C/T<br>−1575G/A | 5' near gene<br>5' near gene<br>5' near gene |
| MMP3<br>11q22.3                            | ENSG00000149968         | rs3025058                         | 5A/6A                           | 5' near gene                                 |
| MMP9<br>20q12-q13                          | ENSG00000100985         | rs3918242                         | −1562C/T                        | 5' near gene                                 |
| MMP10<br>11q22.3                           | ENSG00000166670         | rs486055                          | A180G<br>Lys53Arg               | exon 2                                       |
| MMP12<br>11q22.2-11q22.3                   | ENSG00000110347         | rs2276109                         | −82A/G                          | 5' near gene                                 |
| MMP13<br>11q22.3                           | ENSG00000137745         | rs2252070                         | −77A/G                          | 5' near gene                                 |
| TIMP1<br>Xp11.3-p11.23                     | ENSG00000102265         | rs4898                            | C434T<br>Phe124Phe              | exon 5                                       |
| TIMP3<br>22q12.1-q13.2                     | ENSG00000100234         | rs9619311                         | −1296T/C                        | 5' near gene                                 |
| ELN<br>7q11.1-q21.1                        | ENSG00000049540         | rs2071307                         | G1355A<br>Ser422Gly             | exon 20                                      |

ID, Identification number.

**Saracini C et al., J Vasc Surg 2012**

**Table III. Genotype distribution and allele frequency of the 12 investigated polymorphisms in AAA patients and control subjects**

| SNP                 | Genotypes (%)      |                 |                 | Minor allele frequency | Genotypes (%)              |                 |                 | Minor allele frequency | P                     |
|---------------------|--------------------|-----------------|-----------------|------------------------|----------------------------|-----------------|-----------------|------------------------|-----------------------|
|                     | Patients (n = 423) |                 |                 |                        | Control subjects (n = 423) |                 |                 |                        |                       |
| MMP1<br>rs1799750   | AA(26.0)           | AG(49.1)        | GG(24.9)        | G = .495               | AA(24.8)                   | AG(51.3)        | GG(23.8)        | G = .495               | 1                     |
| MMP2<br>rs2285053   | CC(71.2)           | CT(27.2)        | TT(1.6)         | T = .152               | CC(74.6)                   | CT(23.1)        | TT(2.2)         | T = .138               | .524 <sup>c</sup>     |
| rs243865            | CC(64.9)           | CT(31.0)        | TT(4.1)         | T = .196               | CC(56.3)                   | CT(37.6)        | TT(6.1)         | T = .249               | .023 <sup>c</sup> ←   |
| rs243866            | GG(67.2)           | GA(29.5)        | AA(3.3)         | A = 0.180              | GG(61.8)                   | GA(33.4)        | AA(4.7)         | A = 0.215              | .296 <sup>c</sup>     |
| MMP3<br>rs3025058   | 5A/5A<br>(26.5)    | 5A/6A<br>(54.7) | 6A/6A<br>(18.8) | 6A = 0.462             | 5A/5A<br>(21.9)            | 5A/6A<br>(50.8) | 6A/6A<br>(27.3) | 6A = 0.572             | .013 <sup>b</sup> ←   |
| MMP9<br>rs3918242   | GG(73.9)           | GA(23.1)        | AA(3.0)         | A = 0.146              | GG(72.5)                   | GA(23.9)        | AA(3.6)         | A = 0.156              | .159 <sup>a</sup>     |
| MMP10<br>rs486055   | CC(95.4)           | CT(4.3)         | TT(0.3)         | T = .024               | CC(94.9)                   | CT(4.8)         | TT(0.3)         | T = .027               | 1                     |
| MMP-12<br>rs2276109 | AA(78.1)           | AG(19.1)        | GG(2.9)         | G = .124               | AA(76.9)                   | AG(21.1)        | GG(1.9)         | G = .125               | .719 <sup>b</sup>     |
| MMP-13<br>rs2252070 | AA(34.8)           | AG(43.9)        | GG(21.4)        | G = .433               | AA(40.0)                   | AG(45.9)        | GG(14.1)        | G = .371               | .023 <sup>b</sup> ←   |
| TIMP1<br>rs4898     | TT(100.0)          | CT(0.0)         | CC(0.0)         | C = .000               | TT(96.8)                   | CT(3.2)         | CC(0.0)         | C = .016               | <.0001 <sup>a</sup> ← |
| TIMP3<br>rs9619311  | TT(41.9)           | CT(44.4)        | CC(13.7)        | C = .359               | TT(46.1)                   | CT(44.1)        | CC(9.8)         | C = .318               | .264 <sup>b</sup>     |
| ELN<br>rs2071307    | GG(39.9)           | GA(43.8)        | AA(16.3)        | A = 0.382              | GG(31.3)                   | GA(51.8)        | AA(16.9)        | A = 0.428              | .022 <sup>c</sup> ←   |

AAA, Abdominal aortic aneurysm; SNP, single nucleotide polymorphism.

P values were adjusted by using the false discovery rate (FDR) multiple-testing correction.

<sup>a</sup>P = according to the additive model.

<sup>b</sup>P = according to the recessive model.

<sup>c</sup>P = according to the dominant model

**Saracini C et al., J Vasc Surg 2012**

# Odds ratio for the occurrence of AAA according to rs243865 MMP2, rs3025058 MMP3, rs2252070 MMP13, and rs2071307 ELN polymorphisms

**Saracini C et al., J Vasc Surg 2012**

Table IV. Odds ratios for the occurrence of AAA according to rs243865 MMP2, rs3025058 MMP3, rs2252070 MMP13, and rs2071307 ELN polymorphisms

| <i>Variables</i>               | <i>Univariate analysis</i> | <i>P</i> | <i>Multivariate analysis<sup>a</sup></i> | <i>P</i> |
|--------------------------------|----------------------------|----------|--|----------|
| MMP2 rs243865<br>T allele      | 0.7 (0.52-0.93)            | .013     | 0.55 (0.34-0.85)                         | .007     |
| MMP3 rs3025058<br>5A allele    | 1.61 (1.13-2.33)           | .007     | 1.82 (1.04-3.12)                         | .034     |
| MMP13 rs2252070<br>GG genotype | 1.65 (1.11-2.46)           | .013     | 2.14 (1.18-3.86)                         | .012     |
| ELN rs2071307<br>A allele      | 0.69 (0.51-0.92)           | .012     | 0.64 (0.41-0.99)                         | .046     |

AAA, Abdominal aortic aneurysm; COPD, chronic obstructive pulmonary disease.

<sup>a</sup>Adjusted for age, gender, hypertension, diabetes mellitus, dyslipidemia, smoking habit, and COPD.

**Adjusted for age, gender, hypertension, diabetes mellitus, dyslipidemia, smoking habit, and chronic obstructive pulmonary disease (COPD)**



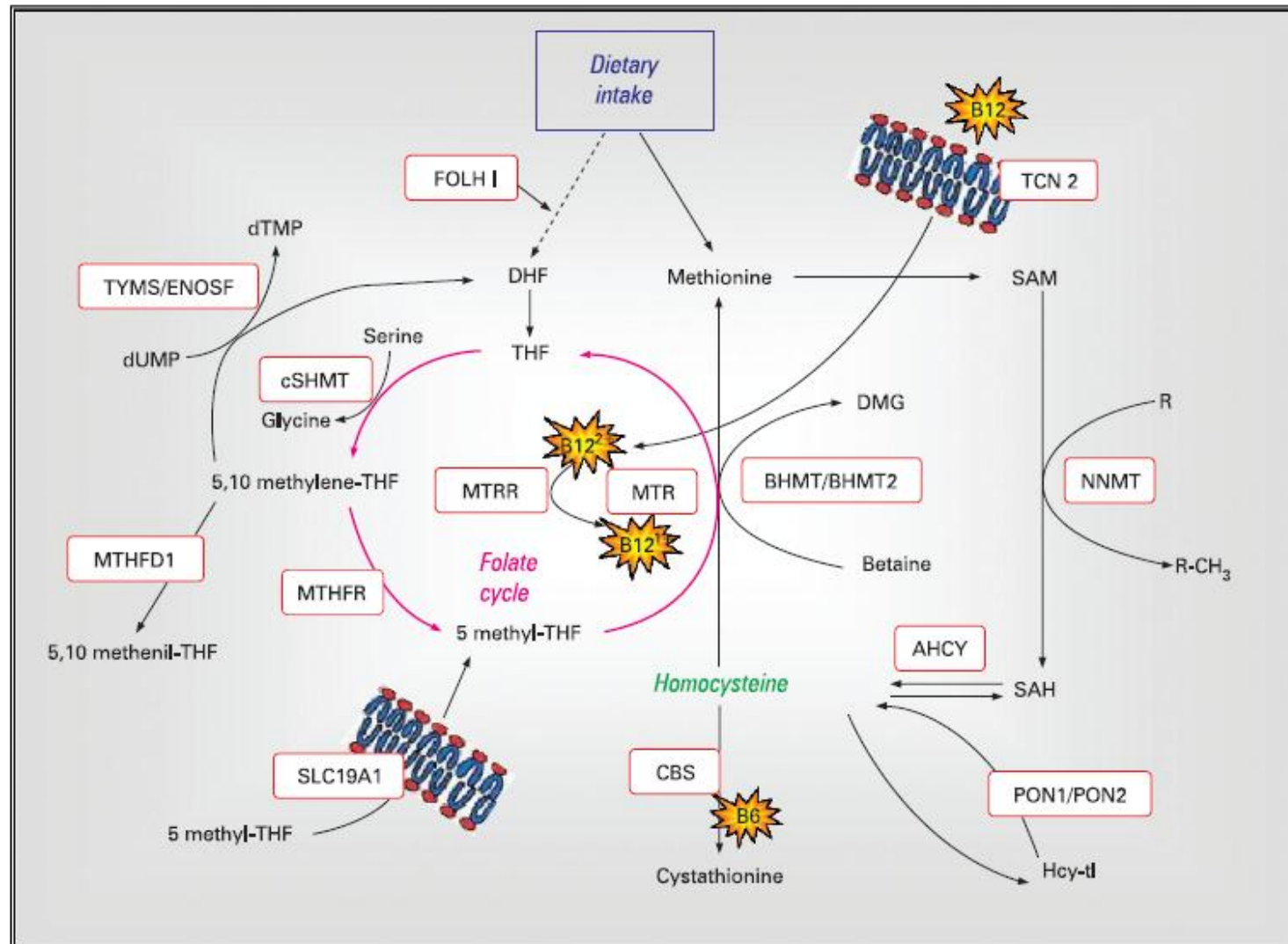
**J Med Genet 2008**

## Regulation of: Homocysteine levels

# DNA methylation

## Genetic stability

# Gene expression



# **Odds ratio for the occurrence of AAA according to rs8003379 MTHFD and rs326118 MTRR polymorphisms**

**Giusti et al., J Med Genet 2008**

| <b>Variables</b>                        | <b>Multivariable<br/>Analysis*</b> | <b>P</b>          |
|---|------------------------------------|-------------------|
| <b>MTHFD<br/>rs8003379<br/>T allele</b> | <b>0.41<br/>(0.26-0.65)</b>        | <b>&lt;0.0001</b> |
| <b>MTRR<br/>rs326118<br/>T allele</b>   | <b>0.47<br/>(0.29-0.77)</b>        | <b>0.003</b>      |

\* adjusted for age, gender, hypertension, diabetes mellitus, dyslipidemia, smoking habit, COPD (chronic pulmonary obstructive disease).

# Combination of genetic risk conditions

| Polymorphisms |        |               | OR (95%CI)       | p       |
|---------------|--------|---------------|------------------|---------|
| rs4988300     | LRP5   | (T allele)    | 1.62 (1.02-2.56) | 0.040   |
| rs3781590     | LRP5   | (T allele)    | 1.83 (1.17-2.85) | 0.008   |
| rs1466535     | LRP1   | (T allele)    | 1.85 (1.20-2.84) | 0.010   |
| rs243865      | MMP2   | (CC genotype) | 1.81 (1.17-2.94) | 0.007   |
| rs3025058     | MMP3   | (5A allele)   | 1.82 (1.04-3.12) | 0.034   |
| rs2252070     | MMP13  | (GG genotype) | 2.14 (1.18-3.86) | 0.012   |
| rs2071307     | ELN    | (GG genotype) | 1.56 (1.01-2.44) | 0.046   |
| rs8003379     | MTHFD1 | (GG genotype) | 2.44 (1.54-3.85) | <0.0001 |
| rs326118      | MTRR   | (GG genotype) | 2.13 (1.30-3.45) | 0.003   |

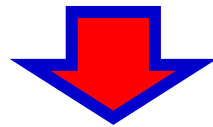
**The condition of having  $\geq 6$  genetic risk factors determines a risk of AAA:**

**OR=6.32 (3.46-11.52),  $p<0.0000000001$**

**adjusted for age, gender, hypertension, diabetes mellitus, dyslipidemia, smoking habit, COPD (chronic pulmonary obstructive disease)**

**In conclusion, our data suggest the need**

- ❖ **to confirm in larger and well characterized populations the 9 reported associations**
- ❖ **to concentrate our effort in studying the role of these markers and other markers in the same genes as well as in other genes emerged from “candidate gene studies” or “genome wide association studies (GWAS)” or “massive parallel sequencing” in the aneurismal disease in order to improve the understanding of its pathophysiology and pathogenesis**



- ❖ **The identification of numerous genetic susceptibility factors is fundamental to design and develop gene-based clinical studies in the future to validate diagnostic or prognostic scores based on clinical, imaging, biochemical, and multiple genetic information to be applied in the everyday clinical practice**

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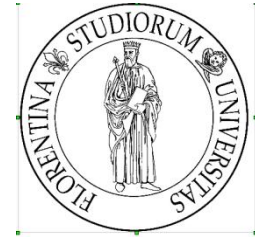
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