Linking Preeclampsia and Cardiovascular Disease Later in Life:
Genetic Determinants

Yves Giguère MD, PhD, FRCPC
Axe de recherche sur la reproduction, la santé périnatale et la santé de l’enfant
Centre de recherche du CHUQ, Québec, Canada
Département de Biologie moléculaire, biochimie médicale et pathologie
Faculté de médecine
Université Laval

IFCC-OCD Conference
Paris
February 25-26, 2011

• Introduction
• Genetics of preeclampsia
• Linking preeclampsia and cardiovascular disease:
  • Review of the evidence
  • Clinical and metabolic factors
  • Genetic determinants
• Conclusion
PATHOPHYSIOLOGY OF PREECLAMPSIA

Maternal constitutional factors
  Genetic predisposition
  Immunological maladaptation
  Pre-existing vascular disease
  Environmental factors

Defective placentation (Stage 1)
  Placental ischemia
  Oxidative stress
  Cytotoxic factors (Stage 2)

Systemic maternal endothelial dysfunction

Vasospasm
Hypertension
Hypovolemia

Abnormal coagulation
Thrombosis

Endothelial damage
Increased permeability
Oedema
Proteinuria

PREECLAMPSIA
« DISEASE OF THE THEORIES »
PREECLAMPSIA AND CARDIOVASCULAR DISEASE
SHARE MANY RISK FACTORS

<table>
<thead>
<tr>
<th>PE</th>
<th>RISK FACTORS</th>
<th>CVD</th>
</tr>
</thead>
</table>
| ![PE Image]         | Elevated blood pressure  
Dyslipidemia  
Insulin resistance  
Diabetes  
Visceral obesity  
Inflammation | ![CVD Image] |

PREECLAMPSIA AND LONG-TERM RISK OF CARDIOVASCULAR DISEASE

- Women who suffered from PE are at higher risk to develop CVD later in life.

- Preeclamptic women tend to show the characteristics of the metabolic syndrome and have a 3 to 5-fold increased risk to develop the metabolic syndrome a few years later (Pouta et al 2004; Forest et al 2005; Girouard et al 2007).

- PE could therefore predict the risk for CVD later in life via a predisposition to develop metabolic syndrome.
• Introduction
• Genetics of preeclampsia
• Linking preeclampsia and cardiovascular disease:
  • Review of the evidence
  • Clinical and metabolic factors
  • Genetic determinants
• Conclusion

HOW MUCH GENETICS ??
**PREECLAMPSIA: HERITABILITY**

**Family study:**
- 312,310 Full sister pairs
- 26,748 Maternal half-sister pairs
- 32,757 Paternal half-sister pairs
- 51,684 Mother-daughter pairs

(Risk ↑ = 20-31%)

\[
\begin{align*}
PE &= 0.31 \\
GH &= 0.20 \\
PE+GH &= 0.28
\end{align*}
\]

PE+GH : 28 % heritability


**Twin studies:**

<table>
<thead>
<tr>
<th>Heritability estimates (h²) (mono vs dizygotic)</th>
<th>Initial studies: small and inconclusive</th>
</tr>
</thead>
<tbody>
<tr>
<td>266 monozyg / 146 dizyg pairs ¹</td>
<td>917 monozyg / 1199 dizyg pairs ²</td>
</tr>
</tbody>
</table>

\[
\begin{align*}
PE &= 0.22 \\
GH &= 0.20 \\
PE+GH &= 0.25
\end{align*}
\]

PE : 20-50 % heritability

HBP : 30 % heritability


SEARCH FOR A GENETIC MODEL OF PREECLAMPSIA

- Recessive monogenic
- Dominant monogenic with incomplete penetrance
- Complex trait
  - Many susceptibility genes
  - Involvement of fetal genes: mother – fetus interactions

GENETICS OF DISEASES

Complex Genetic Traits: gene(s) + environment

- Classical Mendelian Diseases
- Expected effect of each gene
- Number of Genes involved: 0, 1
WHY IS THE STUDY OF GENETIC PREDISPOSITION TO COMPLEX TRAITS COMPLEX?

- Complex traits:
  - heterogeneous disorders
  - Classification of cases difficult (study design)

- Interactions between genes and environment:
  - G and E background variable from population to population
  - Complex G - G and G - E interactions

- Modest gene effect size (Large-scale studies needed)

- Confusion between association and cause

- Observations need to be validated (repeat studies in independent samples)

- How to integrate susceptibility genes into risk algorithms

GENETIC STUDIES

<table>
<thead>
<tr>
<th>Linkage analysis</th>
<th>Genetic Association study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family pedigrees</td>
<td>Population-based</td>
</tr>
</tbody>
</table>

**Linkage analysis**
- Marker allele A1 cos segregates with disease

**Genetic Association study**
- Controls
- Cases
- Allele A6 is 'associated' with disease

LINKAGE STUDIES

**Advantages**
- Good for localising areas of disease risk across the genome
- Can be used to study multiple genetic markers simultaneously
- Can be used to diagnose genetic abnormalities (genes unidentified)

**Disadvantages**
- Need to identify a large number of families with several affected generations
- Can be less helpful for complex traits
- Useful for a limited number of disorders. (i.e. monogenic disorders, oligogenic disorders)
- Expensive, laborious, time-consuming, and less reliable than direct gene analysis

GENETIC ASSOCIATION STUDIES

**Advantages**
- Is more powerful for studying common diseases (small gene effects)
- Can be used to test of a specific marker in a particular gene (individual SNPs)
- Can be useful in investigating gene-gene or gene-environment interactions

**Disadvantages**
- Prone to confounding variables and the choice of controls is key for avoiding selection bias
- Cannot test causality, it can only measure statistical association
- Can be expensive and statistically complex if a large number of polymorphisms is tested
GENETICS OF PREECLAMPSIA

LINKAGE ANALYSES
- In specific genomic regions
- Genome-wide
- Discrepant findings
  - 7q36 may be involved (Australia)
  - 2p13 (Iceland, NZ)
  - 2q25, 9p13 (Finland)
  - 11q/22q, 12q (NL)
  - 13q (Australia, Norway)

Lachmeijer et al. *Eur J Hum Genet* 2001;

GENETICS OF PREECLAMPSIA

LINKAGE ANALYSES
Chromosomal localization of susceptibility regions
- 1q32.3-1q43
- 2p25, 2p13, 2q21.1-2q24.1, 2q23.3, 2q24.2, 2a32.1-2q35, 2q37-2q37.3
- 3q11.1-3q21.2
- 4q32, 4q34.2-4q34.3
- 5q15-5q21.1
- 6p22.3-6p21.1
- 7q34-7q36.3, 7q36
- 9p13, 9p11, 9q21.32-9q31.2, 9q34
- 10q22.1
- 11q13, 11q23-11q24
- 12q23.2
- 13q33.1-13q24
- 15q11, 15q22.32-15q26.1
- 18p11.2
- 22q13.1

GENETIC ASSOCIATION STUDIES

- Factor V (Leiden - A1691G)
- Prothrombin (PT) gene – G20210A
- Angiotensinogen gene (AGT) – M235T, T174M
- Angiotensin II type I receptor (AT1) – C1166A
- Methylenetetrahydrofolate reductase (MTHFR) – C677T
- Angiotensin converting enzyme (ACE) – I/D (intron 16)
- Plasminogen activator inhibitor (PAI-1) – 4G/5G
- Nitric oxide synthase NOS3 – eNO-CA, Glu298Asp
- Lipoprotein lipase (LPL) – N291S, D9N, S447X
- Apolipoprotein E (ApoE) – e2, e3, e4
- Glutathion S-transferase family of genes (GST) – Ile105Val
- Cytochrome P450 1A1 (CYP 1A1) – Ile462Val
- Glycoprotein IIIa (GPIIa) – C98T
- Microsomal epoxide hydrolase (EPHX) – Tyr113His
- Tumor necrosis factor-a (TNF- a) – G-308A, C-850T, T-4845G
- Interleukin-1 receptor antagonist (IL-1RA) – intron2
- Interleukin-10 (IL-10) – G-1082A, G-2849A
- CD14 receptor – C-260T
- Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) – A49G

And others...

GENETICS OF PREECLAMPSIA: CHALLENGES

- Preeclampsia is confined to pregnancy
- Which phenotype(s) to study?
  - Arbitrary clinical definitions
  - Constellation of signs and symptoms
  - Effect of other genetically determined phenotypes:
    - Obesity / Hypertension / Insulin resistance / Diabetes / Dyslipidemia
- What role for fetal genome?
  - Paternal contribution to the fetal genome
  - Maternal - fetal interactions
- Different genes may influence different stages
  - Biological plausibility ⇒ Clinical utility
GENETICS OF CARDIOVASCULAR DISEASE: CHALLENGES

Which phenotype(s) to study?
- Arbitrary clinical definitions
- Constellation of signs and symptoms
- Effect of other genetically determined phenotypes:
  - Obesity / Hypertension / Insulin resistance /
  - Diabetes / Dyslipidemia
- What role for epigenetics?
- Different genes may influence different stages
  - Biological plausibility ⇒ Clinical utility

• Introduction
• Genetics of preeclampsia

Linking preeclampsia and cardiovascular disease:
  - Review of the evidence
  - Clinical and metabolic factors
  - Genetic determinants

• Conclusion
LINK BETWEEN PE AND CARDIOVASCULAR DISEASE

PE  METABOLIC SYNDROME  CVD

Elevated blood pressure
Dyslipidemia
Insulin resistance
Visceral obesity

INFLAMMATORY RESPONSE

HYPERTENSIVE DISORDERS OF PREGNANCY AND CARDIOVASCULAR DISEASE

Evidence for a link ??
HYPERTENSIVE DISORDERS OF PREGNANCY
AND CARDIOVASCULAR DISEASE

Do changes observed in HDP persist or correlate with the occurrence of CVD risk factors or CVD later in life?

Retrospective studies: HDP and long-term cardiovascular risk factors and disease

- Chesley et al. 22-42 year follow-up (1980-85)
  - RR = 2.4 to develop type II diabetes
- Sibai et al. 7.2 year follow-up (Am J Obstet Gynecol, 1992)
  - 9.5% chronic hypertension
  - 25% chronic hypertension if recurrence of PE
  - From 7543 medical records
  - Death from CVD: RR = 1.43/1.90/2.61 (GH/PE/E)
- Hannaford 27 year follow-up (Heart 1997)
  - 23,000 women
  - Hypertension RR = 2.35 / Angina RR = 1.53 / MI RR = 2.24
Systematic reviews: HDP and long-term cardiovascular risk factors and disease

Bellamy et al. + meta-analysis (BMJ 2007)
- 198,252 women
- Hypertension RR = 3.70
- IHD RR = 2.16
- Stroke RR = 1.81
- Overall mortality RR = 1.49

McDonald et al. + meta-analysis (Am Heart J 2008)
- 116,175 women
- CD RR = 2.33
- Cerebrovascular disease RR = 2.03
- Peripheral arterial disease RR = 1.87
- CV mortality RR = 2.29

SEVERITY OF PREECLAMPSIA/ECLAMPSIA AND LONG-TERM CARDIOVASCULAR RISK FACTORS AND DISEASE

- McDonald et al. Systematic review and meta-analysis (Am Heart J 2008)
  - 116,175 women
  - CD vs severity of PE/E
    - Mild RR = 2.00
    - Moderate RR = 2.99
    - Severe RR = 5.36

- Mongraw-Chaffin et al. Prospective Study (Hypertension 2010)
  - 14,403 women
  - Cumulative CVD death survival
    - Early PE = 85.9%
    - Late PE = 98.3%
    - No PE = 99.3%
PROSPECTIVE STUDIES: HDP AND CARDIOVASCULAR RISK FACTORS

- Relatively few
- Generally small scale
- Individual risk factors: hypertension, insulin resistance, dyslipidemia…

PROSPECTIVE STUDY: LINKING HDP TO CVD RISK FACTORS IN QUÉBEC CITY

Women recruited N = 3799 (1989-1997)

HDP (N = 341; 9%) Normal pregnancy (N = 3235)

Observation study (2000-2002)

Women contacted (N = 244)

Women recruited (N = 168; 69%)

Women contacted (N = 280)

Women recruited (N = 168; 60%)
### PREVALENCE OF THE METABOLIC SYNDROME

#### NCEP III criteria

<table>
<thead>
<tr>
<th></th>
<th>Hypertensive n (%)</th>
<th>Normotensive n (%)</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist circumference &gt; 88 cm</td>
<td>54 (32%)</td>
<td>24 (14%)</td>
<td>2.8 (1.7 ; 4.9)</td>
<td>0.0001</td>
</tr>
<tr>
<td>HDL-C &lt; 1.3 mmol/L</td>
<td>89 (53%)</td>
<td>64 (38%)</td>
<td>1.8 (1.2 ; 2.8)</td>
<td>0.006</td>
</tr>
<tr>
<td>TG ≥ 1.7 mmol/L</td>
<td>27 (16%)</td>
<td>17 (10%)</td>
<td>1.7 (0.9 ; 3.3)</td>
<td>NS</td>
</tr>
<tr>
<td>BP ≥ 130/85 mmHg</td>
<td>39 (23%)</td>
<td>15 (9%)</td>
<td>3.0 (1.6 ; 5.7)</td>
<td>0.0006</td>
</tr>
<tr>
<td>FBG ≥ 6.1 mmo/L</td>
<td>12 (7%)</td>
<td>4 (2%)</td>
<td>3.2 (1.0 ; 0.0)</td>
<td>0.04</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>32 (19%)</td>
<td>11 (7%)</td>
<td>3.4 (1.6 ; 6.9)</td>
<td>0.0006</td>
</tr>
</tbody>
</table>

Forest et al. Obstet Gynecol, 2005

### PREVALENCE OF THE METABOLIC SYNDROME

#### Modified WHO criteria

<table>
<thead>
<tr>
<th></th>
<th>Hypertensive n (%)</th>
<th>Normotensive n (%)</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting insulin &gt; 75e perc. or FBG ≥ 6.1 and &lt; 7.1 mmol/L or FBG ≥ 7.1 mmol/L</td>
<td>58 (35%)</td>
<td>30 (18%)</td>
<td>2.4 (1.5 ; 4.0)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Waist circumference &gt; 80 cm</td>
<td>87 (52%)</td>
<td>52 (31%)</td>
<td>2.4 (1.5 ; 3.7)</td>
<td>0.0001</td>
</tr>
<tr>
<td>HDL-C &lt; 1.0; TG &gt; 2 mmol/L</td>
<td>35 (21%)</td>
<td>26 (15%)</td>
<td>1.4 (0.8 ; 2.5)</td>
<td>NS</td>
</tr>
<tr>
<td>BP ≥ 140/90 mmHg</td>
<td>22 (13%)</td>
<td>2 (1%)</td>
<td>12.5 (2.9 ; 54.1)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>33 (20%)</td>
<td>8 (5%)</td>
<td>4.9 (2.1 ; 10.9)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Forest et al. Obstet Gynecol, 2005
### PREVALENCE OF THE METABOLIC SYNDROME

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Cases (n=168)</th>
<th>Controls (n=168)</th>
<th>Adjusted OR*</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCEP III</td>
<td>32 (19%)</td>
<td>11 (7%)</td>
<td>2.5 (1.1-5.9)</td>
<td>0.03</td>
</tr>
<tr>
<td>OMS (modified; EGIR)</td>
<td>33 (20%)</td>
<td>8 (5%)</td>
<td>3.6 (1.4-9.0)</td>
<td>0.006</td>
</tr>
<tr>
<td>IDF</td>
<td>43 (26%)</td>
<td>15 (9%)</td>
<td>3.1 (1.5-6.4)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

* Adjusted for age, tobacco, alcohol, exercise, oral contraceptives, familial history (chronic hypertension, gestational hypertension, diabetes, cardiovascular disease), and BMI at the index pregnancy. Girouard et al. Hypertension 2007

### LINKS BETWEEN GENETICS OF HDP AND CVD

Genes involved in the inflammatory process associated with the metabolic syndrome represents good candidates for:
- Contributing to the identification of women at risk of PE
- Bridging PE to long term cardiovascular risk

8 polymorphisms from 6 genes:
- Tumor necrosis factor (TNF-\(\alpha\); -308G>A, -857C>T)
- Tumor necrosis factor receptors (TNFRI 36A>G, TNFRII 676T>G)
- Interleukin-1a (IL-1a 4845G>T)
- Interleukin-6 (IL-6 -174C>G)
- Interleukin-10 (IL-10; -1082A>G, -2849G>A)
METHODOLOGY

Case-control study
(from a cohort of 9272 pregnant women)

307 nulliparous women whose pregnancy was complicated by a PE (freq. = 3.3%)
603 controls with normal pregnancies
matched for:
- Maternal age
- Pre-pregnancy body mass index
- Year of delivery

- Genotyping by ASO-PCR (allele specific oligonucleotide – polymerase chain reaction)
- Comparison of the genotypes, individually and jointly, via odds ratio after logistic regressions (p < 0.01; Trend: p < 0.05)
- Haplotype analyses using EM algorithm (Arlequin, v3.0)

RESULTS

General characteristics of the study sample

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Preeclampsia (n = 307)</th>
<th>Control (n = 603)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>27 ± 5</td>
<td>27 ± 5</td>
</tr>
<tr>
<td>Pre-pregnancy BMI, kg/m2</td>
<td>24.6 ± 5</td>
<td>23.9 ± 5</td>
</tr>
<tr>
<td>Gestation at delivery, wk</td>
<td>36.3 ± 4</td>
<td>38.1 ± 3*</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>2 717.0 ± 944.0</td>
<td>3 178.0 ± 756.0*</td>
</tr>
<tr>
<td>Eclampsia, %</td>
<td>2</td>
<td>...</td>
</tr>
<tr>
<td>HELLP syndrome, %</td>
<td>13</td>
<td>...</td>
</tr>
<tr>
<td>Severe preeclampsia, %†</td>
<td>45</td>
<td>...</td>
</tr>
<tr>
<td>Preeclampsia without any other complications, %</td>
<td>40</td>
<td>...</td>
</tr>
</tbody>
</table>

Data are presented as mean ±SD or percentages, as indicated. BMI indicates body mass index.
*P < 0.0001
†Excluding HELLP syndrome and eclampsia cases; severe PE diagnosed as a BP ≥ 160/110 mmHg and proteinuria ≥ 2g/24 h

Laroche al. under review
**Comparisons of genotype distribution of cytokine gene polymorphisms between PE cases and controls**

<table>
<thead>
<tr>
<th>Polymorphisms</th>
<th>Controls (n = 603)</th>
<th>Cases (n = 307)</th>
<th>Odds ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IL-1α 4845G&gt;T</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GG</td>
<td>305 (250/54)</td>
<td>166</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>GT/TT</td>
<td>294 (168/126)</td>
<td>138 (108/30)</td>
<td>0.86 (0.65-1.14)</td>
<td>0.328</td>
</tr>
<tr>
<td><strong>IL-6 -174C&gt;G</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>205 (140/65)</td>
<td>93</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>CG</td>
<td>302 (160/142)</td>
<td>160</td>
<td>1.17 (0.86-1.59)</td>
<td>0.389</td>
</tr>
<tr>
<td>GG</td>
<td>94 (53/41)</td>
<td>53</td>
<td>1.24 (0.82-1.88)</td>
<td>0.359</td>
</tr>
<tr>
<td><strong>IL-10 -1082A&gt;G</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td>224 (127/97)</td>
<td>100</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>AG</td>
<td>247 (140/107)</td>
<td>140</td>
<td>1.27 (0.93-1.74)</td>
<td>0.158</td>
</tr>
<tr>
<td>GG</td>
<td>118 (56/62)</td>
<td>63</td>
<td>1.20 (0.81-1.71)</td>
<td>0.418</td>
</tr>
<tr>
<td><strong>IL-10 -2849G&gt;A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GG</td>
<td>366 (217/149)</td>
<td>183</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>GA/AA</td>
<td>222 (190/32)</td>
<td>119 (100/19)</td>
<td>1.07 (0.81-1.43)</td>
<td>0.685</td>
</tr>
<tr>
<td><strong>TNF-α -857C&gt;T</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>487 (314/94)</td>
<td>220</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>CT/TT</td>
<td>108 (77/31)</td>
<td>80 (77/3)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td><strong>TNFRI 36A&gt;G</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td>236 (135/101)</td>
<td>95</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>AG/GG</td>
<td>361 (257/104)</td>
<td>207 (162/45)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td><strong>TNFRII 676T&gt;G</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TT</td>
<td>353 (205/148)</td>
<td>170</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>TG/GG</td>
<td>247 (218/29)</td>
<td>131 (115/16)</td>
<td>1.00</td>
<td></td>
</tr>
</tbody>
</table>

Women who were carrying the at-risk TNF-α -857T allele were at increased risk of PE (OR = 1.64; CI<sub>95</sub> = 1.18-2.28) as well as those who were carrying the TNFRI 36G allele (OR = 1.42; CI<sub>95</sub> = 1.06-1.91)

**At risk genotype:**
- TNF-α -857T (T) or TT
- TNFRI 36G (G) or GG

Laroche al. under review
In combination analysis, the presence of two at-risk genotypes for TNF-a and TNFRI genes increased PE risk to 2.26 (CI95 = 1.43-3.57; \( P = 0.0007 \)) compared to those without any at-risk genotype.

When we combined TNF-a -857C>T, TNFRI 36A>G and IL-1a 4845G>T, the association was even stronger: the presence of three at-risk genotypes, compared to the absence of at-risk genotypes was associated to a four-fold risk of PE (OR = 4.13; CI95: 2.16 – 7.89; \( P = 0.00002 \))
Finally, the addition of IL-10 -2849G>A polymorphism, known to decrease the intensity of the suppression of the inflammatory cascade initiated by IL-1a and TNF-a, resulted in a 7.2-fold risk of PE (CI95: 2.47 – 20.99; P = 0.0003)

Polymorphism combinations

At-risk genotype: TNF-a -857CT or TT; TNFRI 36AG or GG; IL-1a 4845GG; IL-10 -2849GA or AA

Laroche al. under review
**LINK BETWEEN PE AND CARDIOVASCULAR DISEASE**

**PE**  
Elevated blood pressure  
Dyslipidemia  
Insulin resistance  
Visceral obesity  

**METABOLIC SYNDROME**

**CVD**

**INFLAMMATORY RESPONSE**

---

**AGT HAPLOTYPES AND RISK OF PREECLAMPSIA**  
G1035A – Thr174Met – Met235Thr

GENETICS OF PREECLAMPSIA
QUEBEC CITY STUDY

- Proinflammatory cytokines: TNF-α, TNFRI, TNFRII, IL-1α, IL-6, IL-10...
- Blood pressure control: AGT, ACE, AGTR1, NOS3, TACR3, TGFβ1, EDN1, ECE1B...
- Thrombophilia / coagulation: MTHFR, F5, F2, F7, F13A1, B-fibrinogen, TAFI, PAI-1...
- Lipid metabolism / thermogenesis: LPL, HL, HSL, APOC3, APOE, CETP, APM1, LEPR, SRB1, LDLR, LRPAP1, IRS1, PPAR-γ, PPAR-α, ADRB3...
- Reactive oxygen species generation / antioxidant system: GSTP1, GSTM1, EPHXI, APOB, HFE, CAT, CYP1A1, MnSOD, PON1...
- Immunity / placentation: HLA-G...
- Angiogenic factors: VEGF, FLT1, PI GF, ENG...

- Introduction
- Genetics of preeclampsia
- Linking preeclampsia and cardiovascular disease:
  - Review of the evidence
  - Clinical and metabolic factors
  - Genetic determinants
- Conclusion
THE QUEBEC CITY STUDY

- The prevalence of metabolic syndrome and known cardiovascular risk factors are increased in women with a past history of HDP
- We found a dose-effect of a four-locus combination associated with a 7-fold increased risk of PE
- The involvement of this combination in PE susceptibility will need to be confirmed in an independent study sample
- Genetic determinants validated in independent study samples could eventually be integrated in multivariate risk models including clinical and biochemical markers and environmental factors

CONCLUSIONS AND PERSPECTIVES

- Large-scale studies using complementary approaches (including the study of fetal genome) are required to determine the genes responsible for preeclampsia and identify women at risk of PE and/or CVD
- A genetic predisposition contributing to an alteration in the inflammatory response leading to endothelial dysfunction could explain, at least in part, the close relationship between PE and risk of metabolic syndrome/CVD
- Genetic markers associated with PE/CVD could eventually be integrated into multivariate risk models including clinical and biochemical markers and environmental factors
# Acknowledgments

<table>
<thead>
<tr>
<th>Jean-Claude Forest</th>
<th>François Rousseau</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jacques Massé</td>
<td>Pierre De Grandpré</td>
</tr>
<tr>
<td>Jean-Marie Moutquin</td>
<td>Francine Déchêne</td>
</tr>
<tr>
<td>Joël Girouard</td>
<td>Mélanie Maltais</td>
</tr>
<tr>
<td>Marc Charland</td>
<td>Monique Longpré</td>
</tr>
<tr>
<td>Sébastien Lévesque</td>
<td>Suzanne Côté</td>
</tr>
<tr>
<td>Nathalie Bernard</td>
<td>Myia-A Marcotte</td>
</tr>
<tr>
<td>Patrice Savard</td>
<td>Aziz Aris</td>
</tr>
<tr>
<td>Mélissa Laroche</td>
<td>JM Roberts/RB Ness</td>
</tr>
<tr>
<td>Mylène Badeau</td>
<td></td>
</tr>
</tbody>
</table>