CYTOKINE GENE POLYMORPHISMS AND PRETERM BIRTH: A REVIEW

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INTRODUCTION

- Preterm birth $\rightarrow$ responsible for neonatal mortality & significant increase in major complication
  70% have long term neurological & developmental deficits
- 40% $\rightarrow$ caused by an intrauterine infection
- Infection is predicted to promote the elaboration of cytokine & other mediators
- Cytokines $\rightarrow$ prostaglandin biosynthesis $\rightarrow$
  myometrial contractility $\rightarrow$ preterm labour & birth
Many lines of indirect evidence support a potential genetic basis for PTB;
- repetition of PTB
- ♀ born preterm are more likely to deliver preterm
- ♀ who deliver preterm subsequently have another PTB with the same partner

Genetic → immune hyper-responsiveness to an infectious → overproduction of cytokines
Activation of maternal/fetal HPA axis
- Maternal-fetal stress
- Premature onset of physiological initiators

Inflammation-infection
- Chorionic-decidua
- Systemic
  - IL-1
  - IL-6
  - IL-8
  - TNF
  - CSF
  - FasL

Decidual haemorrhage
- Abruptio
  - Thrombin
  - Thrombin RC

Pathological uterine Distention
- Multifetal pregnancy
- Polyhydramnion
- Uterine abnormally

CRH
E1-E3

Proteases

CRH (+)

Cervical change
Rupture of membrane

PTB

Uterine contraction

IL-1
IL-6
IL-8
TNF
CSF
FasL
Thrombin
Thrombin RC
PG synthesis, IL 8

Pathways of preterm birth resulting from PPROM or preterm labour
OBJECTIVE

To determine variation in the carriage of polymorphism in the genes that code for the synthesis of the cytokines in preterm birth.
METHOD

Types of studies
All case control and cohort studies measuring the association between gene polymorphisms that code for the synthesis of the cytokine & PTB with or without PPROM

Search strategy for identification of studies
PubMed was searched
Manual searches
Direct communication with other researchers
RESULTS

68 Article

32 article
Relationship between PTB & gene polymorphism

16 article
PTB & cytokine

1: malaria
1: periodontal disease
3: frequency

excluded

3: multiple gestation
1: congenital anomaly & amniocentesis

7 article
met eligible criteria
<table>
<thead>
<tr>
<th>Author, year</th>
<th>Gene</th>
<th>Study design</th>
<th>Outcomes studied</th>
<th>Case</th>
<th>Control</th>
<th>Geographic area (City, country)</th>
<th>Ethnic groups</th>
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<tbody>
<tr>
<td>Roberts, 1999</td>
<td>TNF-α (-380)</td>
<td>Case-control</td>
<td>Preterm birth with or without PROM</td>
<td>55</td>
<td>110</td>
<td>Pennsylvania</td>
<td>African-American</td>
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<td>Genc, 2002</td>
<td>IL-1β IL-1RN*2</td>
<td>Case-control</td>
<td>Preterm birth with or without PROM</td>
<td>52</td>
<td>197</td>
<td>New York</td>
<td>African, European, non African-Hispanic</td>
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<tr>
<td>Simhan, 2003</td>
<td>IL-6</td>
<td>Case-control</td>
<td>Preterm birth with intact membrane</td>
<td>51</td>
<td>156</td>
<td>Pittsburgh</td>
<td>White, African-American</td>
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<tr>
<td>Genc, 2004</td>
<td>IL-1RN*2</td>
<td>Cohort</td>
<td>PPROM, Spontaneous preterm delivery</td>
<td>212</td>
<td></td>
<td>Boston</td>
<td>Black, Hispanic, White, other</td>
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<tr>
<td>Bessler, 2004</td>
<td>IL-1ra allele2</td>
<td>Cohort</td>
<td>Preterm delivery</td>
<td>65</td>
<td></td>
<td>Israel</td>
<td>Jewish, Arab</td>
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<td>Annels, 2004</td>
<td>IL-1 TNF IL-4 IL-6 IL-10 TNFRSF6 TGFB1 MBL2</td>
<td>Case-control</td>
<td>Preterm delivery</td>
<td>202</td>
<td>185</td>
<td>North Adelaide, Australia</td>
<td>White and European descent</td>
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<td>Macones, 2004</td>
<td>TNF</td>
<td>Case-control</td>
<td>PPROM, Spontaneous preterm delivery</td>
<td>125</td>
<td>250</td>
<td></td>
<td>African-American, Caucasian</td>
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<tr>
<td>NO</td>
<td>AUTHOR, YEAR</td>
<td>GENE</td>
<td>RESULT</td>
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</table>
| 1  | Roberts, 1999 | TNF-α (-380) | OR: 1.85 (0.92 – 3.54), p: 0.08  
PPROM + preterm delivery: term delivery = OR: 3.18 [1.33 – 7.83], p: 0.008 |
| 2  | Genc, 2002 | IL1B IL1RN*2 | Total study: No significant  
Subgroup analysis:  
**IL1B:**  
Carriage in African mother = OR: 3.5 [95%CI: 1.2 – 10.4, p: 0.020]  
Carriage in children of African descent was associated with PTB (p: 0.033)  
**ILRN*2:**  
PROM & subsequent PTB in the Hispanic descent: OR: 6.5 (1.25 – 37.7) p: 0.021 |
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<thead>
<tr>
<th></th>
<th>Author</th>
<th>IL-6/IL1RN/IL-1ra</th>
<th>Findings</th>
</tr>
</thead>
</table>
| 3 | Simhan, 2003 | IL-6              | CC variant = OR: 0.17 [0.04 - 0.74]  
No African-American women carried Racial disparity : p < 0.001   |
| 4 | Genc, 2004  | IL1RN*2, IL-1β    | IL1RN*2 was associated with an elevated vaginal pH in black and white women (p<0.001 & p<0.005)  
Reduced IL-1β response to gram (-) &/ GV (p<0.01), and a decreased rate of SPTB (0.02) |
| 5 | Bessler, 2004 | IL-1ra allele 2   | IL-1raA2 was higher in PTB (p:0.0095)  
IL-1RaA1 was lower (p:0.007)  
**IL-1ra A2 carrier**  
Arabic descent showed a carrier rate more compared with Jews (p:0.0375)  
Carrier rates between Adults Jewish and preterm Jewish = 23% : 24% = p:0.034  
**IL-1raA2 homozygotes**  
Preterm Jewish compared to adult (p<0.001)  
Arabic descent showed increased frequency of homozygous for IL-1ra A2 & heterozygous IL1ra (A1/A2) compared with Jewish (NS) |
<table>
<thead>
<tr>
<th>Year</th>
<th>Authors</th>
<th>Phenotype</th>
<th>IL-1 Components</th>
<th>Analysis</th>
<th>Results</th>
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<tbody>
<tr>
<td>6</td>
<td>Annels, 2004</td>
<td>Preterm &lt; 35 weeks</td>
<td>IL-1, IL-4, IL-6, IL-10, TNF, TGFB1</td>
<td>Univariate analysis</td>
<td>IL1B, IL-10, TNF, TGFB1 were associated with preterm (p &lt; 0.6)</td>
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<td>Multivariate analysis</td>
<td>NS</td>
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<td>PTB &lt; 29 weeks</td>
<td>IL-10, TNFA, IL-4, MBL2</td>
<td>Univariate analysis</td>
<td>IL-10 (ATA) = OR: 2.4, p: 0.04</td>
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<td>TNF AGG = OR: 3.4, p: 0.02</td>
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<td>IL4-590C allele = OR: 3.4, p: 0.02</td>
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<td>MBL2 = OR: 2.3, p: 0.03</td>
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<td>PPROM</td>
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<td>Univariate analysis</td>
<td>IL-10 and IL6</td>
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<td>Multivariate analysis</td>
<td>Homozygous IL-10 GCC = OR: 2.0, p:0.02</td>
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</tbody>
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<tr>
<th>Year</th>
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<th>TNF Components</th>
<th>Analysis</th>
<th>Results</th>
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<tbody>
<tr>
<td>7</td>
<td>Macones, 2004</td>
<td>Maternal carriers TNF allele 2 increased risk of SPB</td>
<td>TNF</td>
<td>Univariate analysis</td>
<td>TNF2 + BV = OR: 6.1 (1.9 - 21.0)</td>
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<td>Multivariate analysis</td>
<td>TNF2 without BV: OR: 1.7 (1.0 - 3.1)</td>
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<td>African American: OR: 2.5 (1.4 - 4.5)</td>
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<td>Caucasian: OR: 1.6 (0.5 - 5.2)</td>
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CONCLUSION

There was a relationship between preterm birth with polymorphisms of gene which involved in cytokine synthesis.

Not consistent & may vary depending on ethnicity and environmental factors.
Implications for research:

- Well-designed studies are required to evaluate the racial disparity, important sociodemographic & environmental factors such as nutritional, smoking, or socioeconomic status should be assessed.
- Other research also need to find the best method for prevention, prediction, and treatment of preterm birth.