



Gene Mutations and Pregnancy Induced Hypertension: A Meta-Analysis

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Learning Objectives ---- At the end of this presentation the learner will be able to:

1. Understand MTHFR C677T gene mutations in relation to pregnancy induced hypertension (PIH) in various race-ethnicity groups in the world. 2. Discuss potential epigenetic factors associated with PIH.



Objectives

To disseminate current evidence on population genome health and related epigenetic factors, through the meta-analyses of methylenetetrahydrofolate reductase (MTHFR) gene in pregnant women who developed hypertension.

Background

- PIH including preeclampsia, eclampsia are the leading causes of maternal and perinatal mortalities.
- Genetic and environmental factors contribute to its development.
- Many studies have reported the association between the MTHFR gene C677T polymorphism and risk of PE, but the results were inconclusive.

Methods

Cochrane, Embase, PubMed, and Web of Science on-line databases were searched using related key words.

Progression on Selection of Studies

Potentially relevant studies identified and screened for retrieval (n = 73)

- ◊ 16 meta-analyses
- ◊ 57 case control studies

9 studies excluded (not English):

- ◊ 2 meta-analyses
- ◊ 7 case control studies

Studies retrieved for more detail evaluations (n = 64)

- ◊ 14 meta-analyses
- ◊ 51 case control studies

14 meta-analyses included:
43 case control studies (16 overlapping; 8 without sufficient information)

51 case control studies:
14 papers without sufficient information; 4 papers not focus on pregnancy hypertension

Studies with sufficient information fulfilling all inclusion/ exclusion criteria (n = 52, 2 studies with 3 and 2 additional race groups, respectively)

Results

Pool Relative Risk of MTHFR 677 Gene Subtypes (57 studies)

Genotype (number of studies)	PIH Case N=6463 (n, %)	Control N=11213 (n, %)	RR (95% CI)
TT Overall (57)	822 (12.72)	1179 (10.51)	1.26 (1.11 – 1.40)***
White (24)	357 (11.86)	610 (9.69)	1.16 (1.01 – 1.34)*
Hispanic (4)	236 (21.91)	346 (23.63)	0.98 (0.85 – 1.13)
South American (4)	62 (16.40)	66 (11.89)	1.40 (1.01 – 1.93)*
East Asia (8)	153 (26.15)	163 (13.55)	1.82 (1.49 – 2.23)***
South Asia (5)	16 (2.78)	31 (3.12)	0.96 (0.51 – 1.84)
Middle Eastern (6)	53 (8.31)	38 (7.29)	1.16 (0.77 – 1.74)
Africa (6)	20 (2.70)	2 (0.26)	5.82 (2.06 – 16.5)***
CT Overall (57)	2437 (37.71)	4402 (39.25)	1.00 (0.96 – 1.04)
White (24)	1254 (41.66)	2614 (41.53)	1.01 (0.96 – 1.07)
Hispanic (4)	464 (43.08)	629 (42.96)	1.03 (0.94 – 1.13)
South American (4)	173 (45.77)	258 (46.49)	0.94 (0.81 – 1.08)
East Asia (8)	272 (46.50)	69 (4.56)	0.96 (0.86 – 1.07)
South Asia (5)	97 (16.87)	200 (20.12)	0.77 (0.61 – 0.98)*
Middle Eastern (6)	244 (38.24)	185 (35.51)	1.06 (0.92 – 1.24)
Africa (6)	142 (19.16)	152 (19.44)	1.07 (0.88 – 1.30)
CC Overall (57)	3204 (49.57)	5632 (50.22)	0.96 (0.93 – 1.00)
White (24)	1399 (46.48)	3069 (48.76)	0.96 (0.91 – 1.01)
Hispanic (4)	377 (35.00)	489 (33.40)	0.98 (0.88 – 1.08)
South American (4)	143 (37.83)	231 (41.62)	0.96 (0.81 – 1.13)
East Asia (8)	160 (27.35)	451 (37.49)	0.74 (0.64 – 0.86)***
South Asia (5)	462 (80.35)	763 (76.76)	1.06 (0.95 – 1.17)
Middle Eastern (6)	341 (53.45)	298 (57.20)	0.94 (0.85 – 1.04)
Africa (6)	579 (78.14)	628 (80.31)	0.95 (0.91 – 1.00)

CI = Confidence Interval; P value = * <0.05 , ** <0.001

East Asia

Relative risk meta-analysis plot (fixed effects)

Xt Xc Nt Nc

18 11 34 102 Japan Yoshida 2007

34 32 99 192 Japan Watanabe 2001

12 33 89 182 Japan Kobashi 2000

16 40 51 318 Japan Sohda 1997

18 9 62 51 China Shen 2009

17 11 25 53 China Wang 2008

20 9 33 40 China Zhang 2007

18 18 39 102 China Li 2000

Africa

Relative risk meta-analysis plot (fixed effects)

Xt Xc Nt Nc

15 0 29 44 Egypt Ibrahim 2012

2 0 42 100 Tunisia Kai 2011

2.14 (1.26, 3.51)

1.50 (0.75, 3.09)

1.25 (1.24, 4.50)

2.05 (1.07, 4.09)

2.11 (1.19, 3.69)

White

Relative risk meta-analysis plot (fixed effects)

Xt Xc Nt Nc

14 32 234 643 Finland Hiltunen 2009

12 6 121 106 Finland Jääskeläinen 2006

4 7 109 96 Finland Laihuri 2000

31 143 232 1699 Denmark Lykke 2012

Germany Muettel 2008

UK Prasimutino 2002

UK O'Shaughnessy 1999

UK Camilleri 2004

UK (Mixed) Camilleri 2004

Netherlands Lachmeijer 2001

Netherlands Zutterel 2000

Netherlands Demarte 2004

Slovak Milisnova 2011

Germany (Croatia) Prasimutino 2004

Hungary Rigó, Jr. 2000

Hungary Nagy 2007

Austria Stoenek 2007

Italy Grandone 1997

Spain Alba-Rallo 2005

Australia Kaiser 2000

USA Power 2003

USA Powers 1999

USA Kim 2001

USA Univestine 2001

combined [fixed]

Conclusion

- ✓ MTHFR 677 homozygous (TT) mutation genotype was significantly associated with increased risk of developing PIH ($p < 0.001$).
- ✓ MTHFR 677TT subtype was a significant risk of PIH in White race (RR= 1.16, $p < 0.05$), South American (RR=1.40, $p < 0.05$), East Asian (RR= 1.82, $p < 0.001$) and in Africa (RR=5.82, $p < 0.001$).
- ✓ Lifestyle factors, body mass index (BMI) before pregnancy (Kg/M²) was an important predictor for the development of PIH.
- ✓ Normal weight (BMI < 25) was protective against the development of PIH and preeclampsia (RR = 0.75, $p < 0.0001$); whereas, overweight (BMI = 25-29, RR = 1.52, $p < 0.0001$) and obesity (BMI > 30, RR = 1.80, $p < 0.0001$) were associated with increased risk of developing PIH and preeclampsia (376 cases and 2294 controls in 2 studies of Caucasian women).

TT + CT subtypes by Country-Race for Case and Control groups (# of studies; # of subjects)

