CYTOKINE GENE POLYMORPHISMS AND PRETERM BIRTH : A REVIEW

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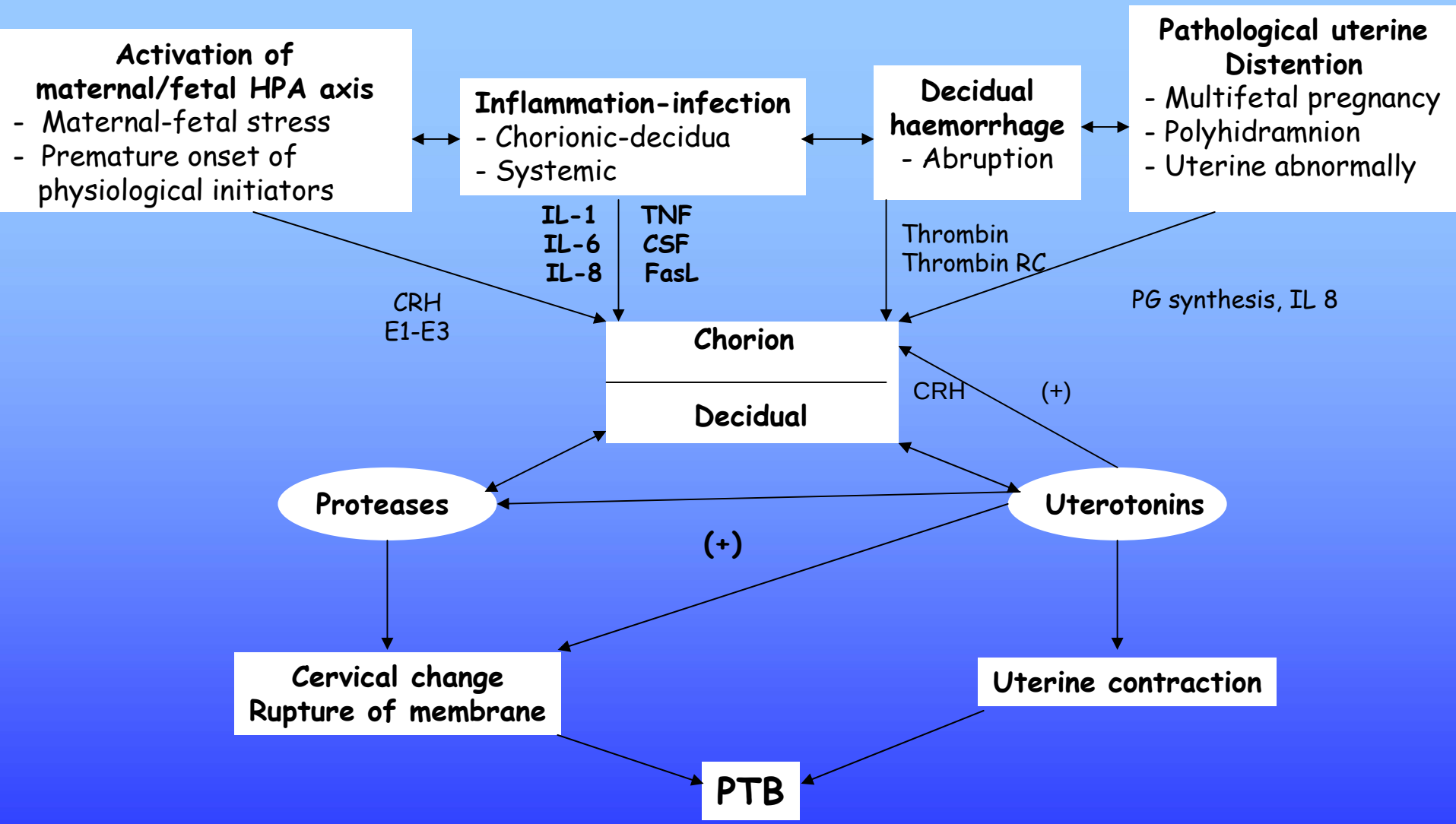
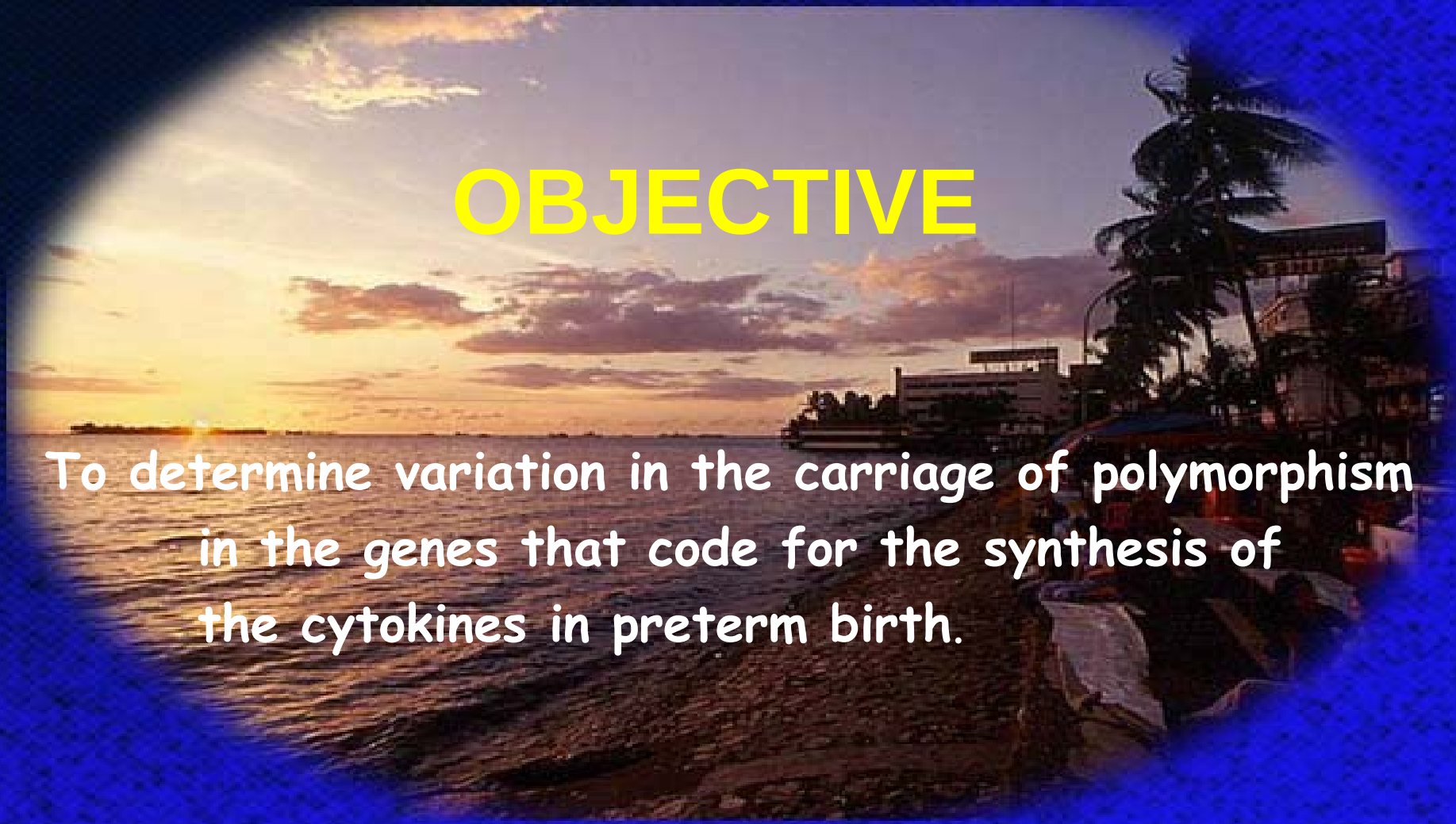
INTRODUCTION

- Preterm birth → responsible for neonatal mortality & significant increase in major complication
  70% have long term neurological & developmental deficits
- 40% → caused by an intrauterine infection
- Infection is predicted to promote the elaboration of cytokine & other mediators
- Cytokines → prostaglandin biosynthesis → myometrial contractility → 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



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

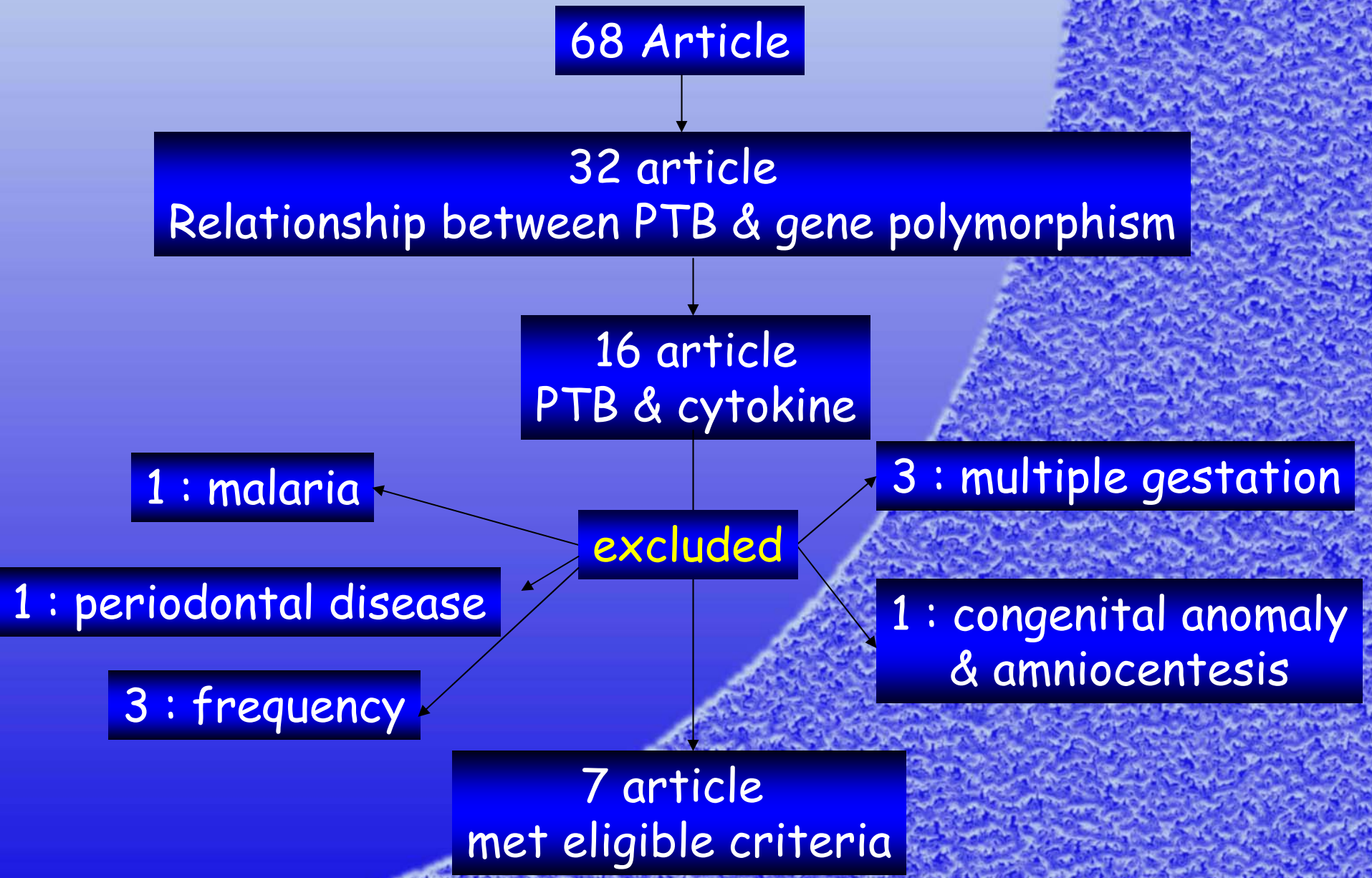

68 Article
32 article
Relationship between PTB & gene polymorphism
16 article
PTB & cytokine
1 : malaria
3 : multiple gestation
excluded
1 : periodontal disease
1 : congenital anomaly
& amniocentesis
3 : frequency
7 article
met eligible criteria

Table 1. Study characteristics

Author, year	Gene	Study design	Outcomes studied	Case	Control	Geographic area (City, country)	Ethnic groups
Roberts, 1999	TNF-α (-380)	Case-control	Preterm birth with or without PROM	55	110	Pennsylvania	African-American
Genc, 2002	IL-1β IL-1RN*2	Case-control	Preterm birth with or without PROM	52	197	New York	African, European, non African-Hispanic
Simhan, 2003	IL-6	Case-control	Preterm birth with intact membrane	51	156	Pittsburgh	White, African-American
Genc, 2004	IL-1RN*2	Cohort	PPROM, Spontaneous preterm delivery	212		Boston	Black, Hispanic, White, other
Bessler, 2004	IL-1ra allele2	Cohort	Preterm delivery	65		Israel	Jewish, Arab
Annels, 2004	IL-1 TNF IL-4 IL-6 IL-10 TNFRSF6 TGFB1 MBL2	Case-control	Preterm delivery	202	185	North Adelaide, Australia	White and European descent
Macones, 2004	TNF	Case-control	PPROM, Spontaneous preterm delivery	125	250		African-American, Caucasian

Table 2. Result

NO	AUTHOR, YEAR	GENE	RESULT
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 associatied with PTB (p: 0.033) **ILRN*2 :** PROM & subsequent PTB in the Hispanic descent: OR: 6.5 (1.25 – 37.7) p: 0.021

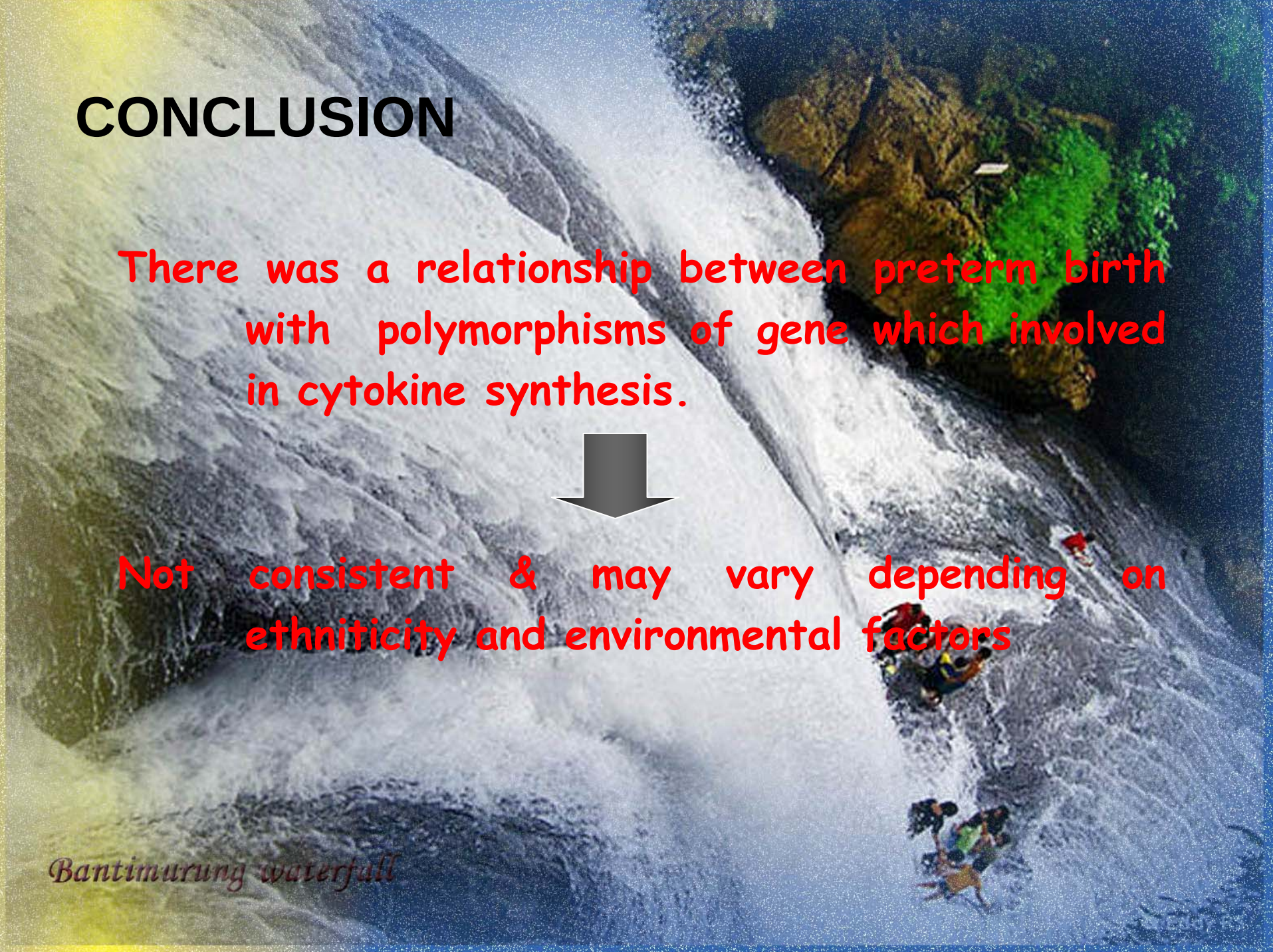
3	Simhan, 2003	IL-6	CC variant = OR: 0.17 [0.04 – 0.74] No African-American women carried Racial disparity : p < 0.001
4	Genc, 2004	IL1RN*2 IL-1ß	IL1RN*2 was associated with an elevated vaginal pH in black and white women (p<0.001 & p<0.005) Reduced IL-1ß response to gram (-) &/ GV (p<0.01), and a decreased 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 Jewis (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)

6	Annels, 2004	IL-1 IL-4 IL-6 IL-10 TNF TGFB1 TNFRSF6 MBL2	**Preterm < 35 weeks** **Univariate analysis** IL1B, IL-10, TNF, TGFB1 were associated with preterm (p <0.6) **Multivariate analysis** NS **PTB < 29 weeks** **Univariate analysis** IL-10, TNFA, IL-4, MBL2 **Multivariate analysis** IL-10 (ATA) = OR: 2.4, p: 0.04 TNF AGG = OR: 3.4. p: 0.02 IL4-590C allele = OR: 3.4, p: 0.02 MBL2 = OR : 2.3, p: 0.03 **PPROM** Univariate analysis IL-10 and IL6 Multivariate analysis Homozygous IL-10 GCC = OR; 2.0, p:0.02
7	Macones, 2004	TNF	Maternal carriers TNF allele 2 increased risk of SPB: OR: 2.7 (1.7 – 4.5) TNF2 + BV = OR: 6.1 (1.9 – 21.0) TNF2 without BV : OR: 1.7 (1.0 – 3.1) African American : OR: 2.5 (1.4 – 4.5) Caucasian : OR: 1.6 (0.5 – 5.2)

CONCLUSION

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

Not consistent & may vary depending on ethniticity and environmental factors



Implications for research :

- Well-design studies are required → to evaluate the racial disparity, important sociodemographic & environmental factor 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

Thank You