Renin Angiotensin System Polymorphisms and Pregnancy Complications

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Table of content

Abstract

Introduction: The renin angiotensin system (RAS) plays an important role in blood pressure regulation and salt-water homeostasis. Aberrant maternal circulating and uteroplacental RAS profiles have been implicated in pregnancy complications, in particular preeclampsia. Our primary aims were to determine associations of polymorphisms in the RAS genes including renin, angiotensinogen (AGT), angiotensin converting enzyme (ACE), angiotensin II type 1 receptor (AGT1R) and type 2 receptor (AGT2R) with pregnancy complications, including preeclampsia, small for gestational age (SGA) and spontaneous preterm birth (sPTB) and to identify potential gene-environment and gene-fetal sex interactions that may modify risks for these pregnancy complications. The secondary aims were to determine the association of RAS polymorphisms with maternal plasma RAS profile at 15 weeks' gestation, maternal blood pressure at 15 weeks' gestation and uterine and umbilical artery resistance at 20 weeks' gestation.

Methods: Healthy nulliparous women, their partners and babies (3234 trios) were recruited prospectively in Adelaide, Australia and Auckland, New Zealand. Data analyses were confined to 2121 Caucasian parent-infant trios, among which 123 had preeclampsia, 216 had SGA and 116 had sPTB. Uncomplicated pregnancies (n=1185) served as controls. DNA was genotyped by Sequenom MassARRAY. Maternal blood samples were taken at 15 weeks' gestation and measured for plasma prorenin, ACE, angiotensin II (ANG II) and angiotensin 1-7 (ANG 1-7) concentrations. Maternal blood pressure was measured at 15 weeks' gestation. Doppler sonography on the uterine and umbilical arteries was performed at 20 weeks' gestation. Mean uterine or umbilical artery resistance indices (RI) above the 90th percentile were considered abnormal.

Results: Maternal and neonatal *ACE A11860G* GG genotype was associated with elevated maternal plasma ACE concentration. Neonatal *renin T/G* and maternal *AGT M235T* were

associated with maternal plasma ANG 1-7 concentration. In female-bearing pregnancies, maternal *AGT1R A1166C* CC genotype was associated with an increased risk for abnormal uterine artery RI, whereas in male-bearing pregnancies, the *AGT M235T* TT genotype in mothers and neonates was associated with an increased risk for abnormal umbilical artery RI. In the Australian SCOPE cohort, maternal *ACE A11860G* GG genotype was associated with an increased risk for SGA and a reduction in customized birth weight centile compared with the AA or AG genotype. Interestingly, these associations were only observed in female-bearing pregnancies and in women with socio-economic index<34 or pre-pregnancy green leafy vegetable intake<1 serve/day. Furthermore, maternal, neonatal and paternal *AGT2R C4599A* was associated with preeclampsia in women with BMI≥25kg/m^2. In the same subset of women, paternal *AGT2R C4599A* and paternal *AGT2R A1675G* were associated with uterine artery bilateral notching. Finally, no significant associations, gene-environment interactions or gene-fetal sex interactions were found for sPTB.

Conclusion: The association of RAS polymorphisms with preeclampsia, SGA and abnormal uterine and umbilical artery RI indicates the involvement of the RAS in the pathogenesis of pregnancy complications, in particular preeclampsia and SGA. Furthermore, future genetic association studies into pregnancy complications should take account of fetal sex and appropriate environmental factors, otherwise genetic associations hidden by these factors may be left unrecognized.

Declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission for any degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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Abstracts arising from this thesis

1. S.D. Sykes, Y. Wang, **A. Zhou**, G.A. Dekker, C.T. Roberts, E.R. Lumbers, K.G. Pringle. Fetal sex alters the expression of the uteroplacental and maternal circulating renin-angiotensin systems; implications for maternal cardiovascular function and fetal outcome**.** *Gordon Research Seminar, 2012, USA*

2. C.T. Roberts, **A. Zhou**, S. Thompson, G.A. Dekker. Interactions between genes encoding renin-angiotensin system peptides and fetal sex in pregnancy complications. *International Federation of Placenta Associations 2011, Geilo, Norway.*

3. **A. Zhou**, S. Thompson, G. Heinemann, J. Zhang, G.A. Dekker, C.T. Roberts. Polymorphisms in RAS genes are associated with being born small for gestational age in an Australian cohort. *Renin Angiotensin System workshop, 2010, Melboune, Australia.*

4. **A. Zhou**, S. Thompson, R. Nowak, G. Heinemann, J. Zhang, G.A. Dekker, C.T. Roberts. Paternal renin angiotensin system polymorphisms are associated with pregnancy complications. *International Federation of Placenta Associations annual meeting, 2009, Adelaide, Australia.*

5. **A. Zhou**, S. Thompson, R. Nowak, G. Heinemann, J. Zhang, G.A. Dekker, C.T. Roberts. Renin angiotensin system polymorphisms in paternal genotypes are associated with pregnancy complications. *The Australian Society for Medical Research annual meeting, 2009, Adelaide, Australia.*

6. **A. Zhou**, S. Thompson, R. Nowak, G. Heinemann, J. Zhang, G.A. Dekker, C.T. Roberts. Renin angiotensin system polymorphisms are associated with pregnancy complications. *39th Society for reproductive biology annual meeting, 2008, Melbourne, Australia.*

7. **A. Zhou**, S. Thompson, R. Nowak, G. Heinemann, J. Zhang, G.A. Dekker, C.T. Roberts. Renin angiotensin system polymorphisms and pregnancy success. *ARC/NHMRC Research Network in Genes & Environment in Development annual meeting, 2008, Cairns, Australia.*

List of figures

List of tables

Abbreviations

ACE	Angiotensin converting enzyme
ACE2	Angiotensin converting enzyme 2
AGRF	Australian Genome Research Facility
AGT	Angiotensinogen
AGT1R	Angiotensin II type 1 receptor
AGT1R-AA	Angiotensin II type 1 receptor agonistic autoantibody
AGT1R-B2	Angiotensin II type 1 receptor-bradykinin B2 receptor heterodimer
AGT2R	Angiotensin II type 2 receptor
ANG 1-7	Angiotensin 1-7
ANG 1-9	Angiotensin 1-9
ANG I	Angiotensin I
ANG II	Angiotensin II
BMI	Body mass index
C.I.	Confidence interval
dBP	Diastolic blood pressure
DNA	Deoxyribonucleic acid
dNK	Decidual natural killer cell
ELISA	Enzyme-linked immunosorbent assay
EMT	Epithelial mesenchymal transition
EVT	Extravillous trophoblasts
FCS	Fetal Calf Serum
GDM	Gestational diabetes
GHT	Gestational hypertension
hAGT	Human angiotensinogen
hCG	Human chorionic gonadotropin
hrenin	Human renin
HUVEC	Human umbilical vein endothelial cells
IL-6	Interleukin-6
IUGR	Intrauterine growth restriction
NEP	Neutral endopeptidase 24.11
OR	Odds ratio
PAI-1	Plasminogen activator inhibitor-1
PCR	Polymerase chain reaction
PEP	Prolyl-endopeptidase
PIH	Pregnancy-induced hypertension
RAS	Renin angiotensin system
RI	Resistance index
RR	Relative risk
sBP	Systolic blood pressure
SCOPE	Screening for Pregnancy Endpoints
SEI	Socio-economic index
sFlt1	Soluble fms-like tyrosine kinase 1
SGA	Small for gestational age

SNP	Single nucleotide polymorphism
sPTB	Spontaneous preterm birth
VEGF	Vascular endothelial growth factor