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Molecular biology related to pre-eclampsia

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Abstract. Pre-eclampsia affects 3% of pregnancies and is a major cause of maternal and fetal morbidity and mortality. It is commoner in primigravidae and is characterised by abnormal placentation and endothelial dysfunction. Pre-eclampsia has a complex aetiology that is influenced by maternal and fetal genes in addition to environmental factors. Most genetic studies to date have focussed on maternal genes. There have been a large number of genetic linkage and association studies. While not all studies have consistent results for specific candidate genes/loci there are several genes in which the data are interesting in several studies, e.g. genes encoding the hereditary thrombophilias, elements of the renin–angiotensin system and HLA-G. Genome-wide scans have also identified a small number of chromosomal loci of interest, e.g. on chromosomes 2p13 and 10q22. However, most studies do not have sufficient power to definitively confirm or refute specific genes or loci of interest and few investigate the role of the fetal genotype. It is to be hoped that the larger, well-phenotyped DNA resources with maternal and fetal samples will overcome some of these problems. © 2005 Published by Elsevier B.V.

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1. Introduction

Pre-eclampsia is a multi-system disorder of pregnancy that is characterised by widespread maternal endothelial dysfunction [1,2]. It affects approximately 3% of primigravidae in the UK, and is a major cause of maternal and perinatal mortality worldwide. It is classically recognised by hypertension and proteinuria, but hepatic impairment is a frequent feature, and a smaller proportion of women develop thrombocytopaenia, haemolysis and the associated “haemolysis, elevated liver enzymes,

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low platelets" (HELLP) syndrome. The commonest causes for maternal death are adult respiratory distress syndrome and intracerebral haemorrhage. Fetal complications include intrauterine growth restriction (IUGR), placental abruption and in severe cases intrauterine death. Pre-eclampsia has a complex aetiology. The maternal features include a heightened inflammatory state [3] and endothelial damage [1,2]. Prior to the onset of clinically identifiable disease, women destined to develop pre-eclampsia show evidence of placental ischaemia and abnormal placentation that can also lead to IUGR and prematurity.

2. Studies of the genetic aetiology of pre-eclampsia

2.1. Evidence that the aetiology of pre-eclampsia has a genetic component

The maternal [4,5] and fetal [6] genotype both contribute to the risk of pre-eclampsia, but the pattern of inheritance is not clear. There have been two reports of concordance in monozygotic twins identified when recruiting affected family members for genetic studies [7,8] and a study of 917 monozygotic and 1199 dizygotic twins using the Swedish Twin Register and Swedish Medical Birth Register predicted a heritability of 0.54 (95% confidence interval 0–0.71) [9]. However, two studies have not found concordance in monozygotic twins [10,11].

2.2. Candidate gene studies

To date several genetic variants have been reported to be associated with pre-eclampsia in specific groups of patients. Examples include the hereditary thrombophilias [12,13], angiotensinogen [14–16], angiotensin II type I receptor [17] and genes that influence the immune response, e.g. HLA-G [18]. However, the list of candidate genes for pre-eclampsia is extensive, and different genes will confer susceptibility to maternal and fetal features of the condition [19].

Strategies that may be used to identify the genetic factors that play a role in the aetiology of pre-eclampsia include studies of rare pedigrees where the condition appears to be inherited in a Mendelian fashion, linkage studies using sib-pairs or other affected pedigree members and association studies using populations.

Examples of the use of apparently Mendelian pedigrees to identify genes that confer susceptibility to complex disorders include the demonstration of glucokinase mutations in maturity onset diabetes of the young (MODY) [20,21], and the demonstration of mutations in the beta subunit of the epithelial sodium transporter in Liddle syndrome, a familial form of hypertension [22]. While there are no reports of specific mutations in pre-eclampsia pedigrees, a mutation in the mineralocorticoid transporter can cause severe pregnancy-induced hypertension [23]. This mutation results in the receptor being activated by progesterone in addition to aldosterone. The association with pregnancy-induced hypertension is explained by the 100-fold increase in progesterone that occurs in pregnancy.

A large number of candidate genes have been investigated in pre-eclampsia and a full review of them all is beyond the scope of this article. The reader is referred to a recent comprehensive review [24]. A few examples of candidate gene studies will be considered in more detail.