

Update on Genetics of Pre-eclampsia

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Over half of the familial predisposition to pre-eclampsia can be attributed to genetic factors in the mother and/or fetus. The search for genetic susceptibility variants has progressed through candidate gene studies, family-based linkage studies, and most recently genome-wide association studies (GWAS). It is unlikely that any single variant has a large effect on pre-eclampsia susceptibility; studies involving thousands of samples are required to detect variants with small effect size. These exceed the resources of most individual research groups, and collaborative approaches are likely to be more fruitful.

Collaboration has included meta-analysis of existing data, and recent publications offer some support to a role for thrombophilic polymorphisms in pre-eclampsia. A small number of GWAS have been published so far; the lack of replication of positive GWAS results in an independent population has been frustrating. This may be due to false positive results in the original GWAS, or lack of statistical power in the replication set. A further concern is that the pre-eclampsia syndrome is a common end-point to multiple pathologies with differing underlying genetic susceptibility, requiring ever larger sample sizes for their detection. In this climate, researchers should make every effort to record the phenotypic characteristics of their cohorts, to enable meta-analysis of independent GWAS results. The **InterPregGen** consortium of groups from Europe and Central Asia is conducting GWAS analysis of maternal and fetal genes in 13,000 pre-eclamptic pregnancies. This study will provide the opportunity to analyse maternal-fetal gene interactions in addition to their individual effects.

Developments arising from the ever-falling costs of DNA sequencing include deep sequencing to identify rare variants with large effect sizes. The era of whole genome sequencing is likely to supplant the GWAS approach, creating challenges for data analysis, but with the potential to provide greater insights into the genetic basis of pre-eclampsia.