Oestrogen receptor genetics: a needle that cuts through many haystacks?

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This editorial refers to 'The association of oestrogen receptor α-haplotypes with cardiovascular risk factors in the British Women’s Heart and Health Study'† by D.A. Lawlor et al., on page 1597

Oestrogen is known to affect multiple aspects of human health, including complex traits such as cardiovascular disease, cancer, fracture risk, arthritis, behaviour and Alzheimer’s disease. Oestrogen receptor α (ESR1), one of two known oestrogen activated transcription factors, is expressed throughout many tissues. It can regulate gene expression by both oestrogen-dependent and oestrogen-independent mechanisms that result in direct or indirect activation of transcription of a wide range of genes. Most of the hundreds of reports of ESR1 genetics published since 1990 have been in areas of cancer biology, bone mineral density, or fracture risk. In the past 3 or 4 years, however, there have been a handful of interesting reports of association of ESR1 polymorphism with cardiovascular disease, its established risk factors, or in relation to response to hormone replacement therapy.1–6 This recent literature, which was both particularly intriguing and inconclusive among women, provided a strong rationale for the investigation by Lawlor et al.7 These authors carried out a cross-sectional analysis of 3404 women from the British Women’s Heart and Health Study. The women were in their 60s or 70s, from 23 towns across Britain; characterization included incident and prevalent coronary heart disease, its risk factors, and use of hormone replacement.

Two single nucleotide polymorphisms from the first intron of ESR1 were genotyped in participant DNA samples. The polymorphisms, c454-397T>G and c454-351A>T, are a few hundred basepairs from the start of exon 2 and have sometimes been described by the name of the detecting restriction enzyme, PvuII or XbaI, or their reference ID numbers, rs2234693 and rs9340799, respectively. The ESR1 gene is large, encompassing some 300 kb of DNA, and includes 8 exons. The first intron of a gene, like the promoter, usually contains a larger number of regulatory sequences than other introns.8 Although an intronic polymorphism cannot directly alter the sequence of amino acids it can alter expression, splicing, or binding of regulatory proteins. One of the two studied ESR1 polymorphisms, which have been examined in many previous studies, may alter transcription factor binding and affect expression level of the ESR1 protein.5,6 However, association studies cannot prove that the relationship is causal and some of the hundreds of other polymorphisms that have been catalogued in ESR1, rather than the genotyped ones, may be the cause of any observed phenotypic variation.

In contrast to some previous studies, the British Women’s Heart and Health Study provided no evidence of association of ESR1 genotypes or haplotypes with cardiovascular disease, its risk factors, or with response to hormone replacement;2,3,5,6 it did, however, identify evidence of a relationship between genotype and chance of taking hormone replacement. The authors tested but found no support for the possibility that this result was driven by differences in social class that might have affected hormone replacement use. From prior studies, the authors hypothesized that the T–A haplotype (made up of c454-397T and c454-351A) would be associated with phenotypes of decreased oestrogen response. This might correspond to more menopausal symptoms that would lead to greater use of hormone replacement. A corresponding trend was observed, with 10, 12, and 13% of individuals with 0, 1, or 2 copies of the T–A haplotype having been past users of hormone replacement (P = 0.02). A similar pattern was observed among current hormone replacement users (P = 0.05). Lawlor et al. note that although these results are not adjusted for multiple testing the consistency seen across both past and current users provides support that the association is real.

An interesting consideration is how such an ESR1 association with hormone replacement use might underlie association of ESR1 genotypes with multiple other hormone-dependent phenotypes. This would have implications for studies which either do not adjust for this variable, or fail to match the case and control populations appropriately. In the report by Lawlor et al.,7 a greater percentage of hormone replacement users, than non-users, were homozygous for the T–A haplotype. Thus, if hormone replacement were to increase the frequency of cardiovascular disease, we might expect to observe a higher frequency of T–A homozygotes among post-menopausal women with cardiovascular disease. This has in fact been observed in the
Rotations of Lawlor et al.⁷ have not been found in some other large studies might be due to differences in the various cohorts, for example, age, diet, or national differences in hormone replacement use.

Results from one or a few association studies may be false positives or may provide evidence that is significant enough to be highly probable of replication in future analyses in other similar cohorts.⁹,¹⁰ A study of over 7000 White men in five cohorts from four countries has provided evidence after adjustment for established cardiovascular risk factors that the CC genotype at ESR1 c454-397T>C is associated with increased risk of myocardial infarction among men (OR = 1.44; P < 0.0001).⁴,⁶,¹¹ There are also unreplicated reports, from studies again involving men, of concordant findings for risk of both stroke and venous thrombosis.¹²,¹³ Interaction with age¹¹ may account for a report of no association with myocardial infarction among relatively young subjects.¹⁴ To date, no replication of significant cardiovascular findings have been published from studies of women.²–⁶,¹³–¹⁵ though data from thousands of women support association of ESR1 polymorphism with fracture risk.¹⁶ One might in some ways expect that oestrogen, and thus the oestrogen receptor variant, would have a larger role in women than among men. However, factors such as menopausal, contraceptive, and hormone replacement status all complicate and potentially confound the study of oestrogen genetics among women. This requires that greater numbers of women be studied and awareness that any finding may be specific to a certain sub-group. It should be mentioned that in women there is already tolerance or accommodation of differences in oestrogen levels throughout the menstrual cycle and this might result in a greater capacity to buffer potential effects of oestrogen receptor variation.

Future studies will need to further examine the spectrum of variation across the ESR1 gene and to establish whether any significant association results can be replicated both within and between ethnic groups. The sample sizes should be large enough to test for the panoply of gene–gene and gene–environment interactions that may potentially be involved at the interface of ESR1 variation and human cardiovascular disease risk.

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References