

Abstract 28

FAMILIAL GENETIC PREDISPOSITION TO MENOPAUSAL AGE IS A MUCH MORE POTENT CONTRIBUTANT TO FXPOI (POF) THAN THE *FMR1* PREMUTATION

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Normal menopausal age distribution is characterised by being approximately Gaussian, with age limits varying between 40 and 60 years, with a variance of ~ 11 years within all populations studied and a high heritability of ~ 60-70% amongst first degree relatives. This implies that each family has it's own position within the population distribution determined by it's genetic predisposition to menopausal age. The only common environmental factor known to reduce menopausal age is smoking, but this explains <5% of the variance. The number of genes determining menopause is unknown, but recent SNP association studies on >5000 menopausal women have detected several loci that explain only 5% of the total variance despite having a high allele frequency or relative contribution to the phenotype. Depressingly, this suggests that hundreds of loci are probably involved in determining predisposition to menopausal age. 10 years ago the association between *FMR1* premutation and occurrence of menopause before 40 years was noted, although ~80 of premutation carriers became menopausal within the normal range. The *FMR1* premutation appears to give the largest reduction in age of menopause of any known genetic factor apart from a few extremely rare recessive mutations mainly resulting in primary ovarian agenesis. In this study we have compared the menopausal age of carriers with that of normal sisters and shown that, although the menopausal age of the carrier is **always** lower than that of their normal sibling(s), the position of the carrier within the population menopausal distribution is predominantly determined by the genetic predisposition of the family and not the *FMR1* premutation. Familial differences in genetic predisposition to menopause are the major confounders in predicting the effect of *FMR1* repeat length on menopausal age. Indeed, the majority of instances of FXPOI occur in families with a low age predisposition to menopause; it is the combination of a low menopausal age predisposition with a *FMR1* premutation that is the most frequent cause of menopause below 40 years. The converse is also true that *FMR1* premutation carriers from families with a high menopausal age predisposition are much less likely to exhibit premature infertility. An additional modification of the menopause phenotype could also arise by skewing of X-chromosome inactivation modulating *FMR1* expression, although opinions differ on its relevance. We present a model embodying familial predisposition to menopause, *FMR1* repeat length and skewing of X-inactivation in presumed decreasing order of relevance. It is likely that this model is appropriate for calculating the specific contribution of all genetic determinants to menopause and not just *FMR1* premutations. These considerations strongly suggest that counselling for the risk of premature infertility by *FMR1* carriers, as recommended by the American College of Obstetrics and Gynaecology, only achieves useful predictive value when information on familial predisposition obtained from the menopausal age of earlier generations is incorporated into the risk estimate; this emphasises the necessity of collecting the reproductive history of all FXS female family members at every available opportunity. The alternative approach of predicting menopausal predisposition from genetic profiles, is being thwarted by the extremely slow progress and exorbitant cost of population based association analyses being currently used. An alternative method based on the greatly reduced genetic and phenotypic variability within families and called intrafamilial association analysis, which potentially is much more efficient and cheaper than population based studies, is described in Abstract 97.