Genetic influences on premature parturition in an Australian twin sample

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We investigated possible genetic influences on women's liability to preterm birth, using data from a large sample of Australian female twin pairs. In a 1988–90 questionnaire survey, both members of 905 parous twin pairs (579 monozygotic and 326 dizygotic) reported on whether deliveries had been more than two weeks preterm. Tetrachoric twin pair correlations for first birth were $r_{MZ} = 0.20 \pm 0.11$ and $r_{DZ} = -0.03 \pm 0.14$, and for any birth were $r_{MZ} = 0.30 \pm 0.08$ and $r_{DZ} = 0.03 \pm 0.11$. Best-fitting models to data contained only additive genetic influences and individual environmental effects. Heritability was 17% for preterm delivery in first pregnancy, and 27% for preterm delivery in any pregnancy. In the former case, however, we could not reject a model without genetic influences. Although our data did not allow for differentiation of the varying aetiologies of premature parturition, results from this exploratory analysis suggest that further investigation of genetic influences on specific reasons for preterm birth is warranted.


Keywords: Preterm birth, pregnancy outcome, twins, genetics

The risk of preterm birth has been found to be higher for women who were themselves born prematurely, suggesting a repeating pattern across generations. The relevance of genetic influences on prematurity had been highlighted by an earlier study using Old Order Amish records in Lancaster County, Pennsylvania, which suggested that prematurity was mostly related to the maternal genotype.

In order to explore the possibility of genetic influences on a woman's liability to preterm births we have examined self-reported, retrospective data on prematurity birth provided by a large number of Australian, female twin pairs. These twins are members of the Australian National Health and Medical Research Council Twin Registry, and participated in a health and lifestyle survey conducted between 1988 and 1990. Responses to this survey were obtained from both members of 1624 female monozygotic (MZ) and dizygotic (DZ) twin pairs aged 25 and older, for a pairwise response rate of 82%. The study questionnaire included questions on their menstrual cycles and reproductive events, including specific obstetric factors relating to each delivery.

Premature delivery (preterm birth) was defined in the questionnaire as delivery 'over 2 weeks early', rather than the standard definition of curtailment of pregnancy before the 37th week of gestation. We did not ask for number of weeks gestation. We investigated parous twins' independent reports of premature delivery of first baby, and also reports of whether any birth was premature using the >2 week criterion. Premature births may have been spontaneous or induced, vaginal deliveries or performed by Caesarean section. Data were also available on these items, but analyses are not presented here.

Twin pair matrices of tetrachoric correlations, and corresponding asymptotic covariance matrices, were computed separately for MZ and DZ twin pairs, using the Windows version of PRELIS 2.20. These correlations apply appropriately to dichotomous categorical data where the underlying distribution is assumed to be continuous and normally distributed. Genetic models were fitted by the method of asymptotic least squares to estimate the contributions of additive genetic, shared and non-shared environmental effects, using Mx. We proceeded by systematically testing the significance of dropping parameters in turn. In addition to the likelihood ratio $\chi^2$ test (LR), the Akaike Information Criterion (AIC, measured as $\chi^2-2df$) was used as an additional indicator of fit. On the grounds of parsimony the model with the least number of parameters that offered a fit not significantly worse than the full model was chosen. Data analysis methods are described more fully elsewhere.
Both members of 905 parous twin pairs (579 MZ pairs and 326 DZ pairs) answered the question concerning prematurity of their first and any subsequent birth. Ages of parous twins ranged from 25 to 87 years, and mean age was 43.94 ± 0.25 years. Mean ages of MZ twins (44.09 years) and DZ (43.71) twins did not differ significantly. The prevalence of premature first birth in the sample was 9.4% of individuals in MZ pairs and higher at 12.9% in the DZ twins, giving an overall prevalence of 10.7%. Premature parturition relating to any birth using the >2 week criterion was reported by 17.3% of individuals in MZ pairs and 21.6% of twins in DZ pairs. The percentage of nulliparae was the same (26%) for both MZ and DZ individuals.

Non-parametric one-way median score tests showed that parous MZ and DZ twins did not differ significantly on median total pregnancies. However, they did differ on median number of full-term (vs aborted) pregnancies (P < 0.05) and of offspring (P < 0.01), the latter median being higher for DZ twins (3) than for MZ twins (2). This suggested a higher prevalence of multiple births in the DZ twins. The median number of preterm babies reported by DZ twins was significantly higher than for MZ twins (P < 0.05), consistent also with a higher rate of multiple births.

The ratio of MZ to DZ twin pair correlations (>2:1) shown in Table 1 suggests that genetic influences may be operating on premature parturition. For both prematurity variables, using the AIC as the indicator, best-fitting most parsimonious models contained only additive genetic variation (A) and individual environmental effects (E). For having had a premature delivery for any birth, the best fitting model (AIC = −0.924) included a heritability of 27%. A model including non-additive genetic influences resulted in a better fit than a model containing only A and E. However, the (maternal) twin pair correlations. This might suggest that the heritability we have observed is occurring in the spontaneous rather than the indicated preterm deliveries, but to test this hypothesis would require a very large sample indeed. It would be fascinating to know whether, for example, there is a genetic contribution to factors such as cervical incompetence per se. Nevertheless, our data do suggest that genetic influences may be important in influencing preterm birth, and further investigation of this hypothesis may well be warranted.

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References