

The Heritability of Preterm Delivery

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OBJECTIVE: To study the heritability of preterm delivery.

METHODS: Women who delivered a singleton infant at less than 36 weeks of gestation were asked about their family history. Twenty-eight families were identified in which the proband had at least five first- or second-degree relatives with preterm delivery. An extensive genealogy database (GenDB) was constructed using more than 9,000 genealogy sources in the public domain (records before 1929). GenDB documents the relationships between more than 17.5 million ancestors and 3.5 million descendants of approximately 10,000 individuals who moved to Utah in the mid 1800s. This database was searched for the names, birth dates, and birthplaces of the four grandparents for each of the 28 probands. Pairwise coefficients of kinship were determined for the 93 preterm delivery grandparents identified, and for sets of 100 individuals born in the 1920s who were randomly selected from the population database.

RESULTS: Probands had a mean of 3.3 grandparents included in this database. The average coefficient of kinship for controls was 1.5×10^4 (standard deviation = 0.6×10^6). This measure agrees with previous calculations for the Utah population. The coefficient of kinship for familial preterm delivery grandparents was more than 50 standard deviations higher (3.4×10^5 [$P < .001$]).

CONCLUSION: This study confirms the familial nature of preterm delivery. On average, gravidae randomly selected from our population are 23rd degree relatives, while these preterm delivery probands are eighth-degree relatives. A genome-wide scan using these affected families is underway. (*Obstet Gynecol* 2005;106:1235-9)

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Despite recent advances in our understanding of the causes of preterm labor, preterm delivery is on the increase in the United States, and most preterm births are due to unknown causes.^{1,2} Evidence is mounting that genetic susceptibility may play a role in the etiologies of preterm delivery. Epidemiologic observations show that preterm births cluster in families,³ and there are significant ethnic/racial differences in the incidence of prematurity that cannot be solely explained by socioeconomic factors.^{4,5} A risk of preterm birth across generations has been reported; women who were born preterm themselves are more likely to deliver a preterm infant.⁶ Premature labor has a tendency to recur,⁵⁻⁷ and it occurs in association with certain genetic diseases. A twin study in Sweden has shown that both low birth weight and length of gestation are heritable.⁸ Lastly, various candidate genes have been studied to determine their role in the pathophysiology,⁹ and limited animal data suggest that genetic mechanisms can be important.¹⁰

Despite these suggestions that genes may play a role, studies on the genetics of premature delivery are limited. Population studies have been hampered by the inability to obtain accurate information on the length of gestation in past generations and the heterogeneous nature of this disorder.¹¹ A recent twin study in Australia estimated that the heritability was 17% for delivery before 38 weeks of gestation in the first pregnancy and 27% for premature delivery in any pregnancy.¹² An earlier study of the Old Order Amish suggested that prematurity is related to the maternal genotype.¹³ The present study is designed to estimate the heritability of preterm labor.

MATERIALS AND METHODS

After appropriate informed consent and using Institutional Review Board-approved protocols, 236 women who had delivered a singleton infant at less than 36 weeks of gestation at the University of Utah Hospital over a 4-month period were asked to participate in a study concerning the genetics of preterm labor. Sixteen women refused consent or were unable to provide consent. The 220 participants (93%) were



asked about their family history. Families were identified and labeled "Familial Preterm Delivery" if the probands reported five or more first- or second-degree relatives who also had a preterm delivery ($n = 28$). Ninety-eight percent of these affected relatives consented to answer questionnaires and allow review of medical records which confirmed preterm birth (although it was difficult to be certain of the exact gestational age from many of these records). Gestational ages were confirmed in the probands' deliveries by usual obstetric landmarks (when available), second-trimester ultrasonography, and neonatal assessment. Each proband was asked to provide a three-generation pedigree with particular attention to their grandparents' full name, birth date, birthplace, and maiden name (if any).

A large genealogy database was constructed using more than 9,000 genealogy data sources in the public domain (birth, death, and marriage records from before 1929). GenDB documents the relationships between more than 17.5 million ancestors and 3.5 million descendants of approximately 10,000 individuals who moved to Utah in the mid 1800s. GenMerge software (Pleiades Software Development, Inc., Salt Lake City, UT) was used to combine electronic data from the primary genealogy sources. This software uses a recur-

sive process to decide if two records are describing the same individual. Initially the software scans the database for inconsistent information (that is, a person is born before his parents). Matching algorithms find exact duplicates (same name, same birth date and place, same death date and place, same parent and offspring data). For each pair of duplicates, their genealogy data are combined, and the software recursively considers the relatives of the duplicates in overlapping portions of the genealogies. Inconsistencies are identified, and a weighted score is given for each common field in the records. Only the highest scores are considered "true" links, because names within families can be similar or identical because of historic naming conventions and because many birth or death places will be the same because relatives often live in close proximity to one another. The resulting database, constructed in SYBASE (Sybase, Dublin, CA), documents relationships between more than 17.5 million ancestors and 3.5 million descendants of the Utah founder population (Fig. 1). Using this resource, current Utah families can be linked across generations; in many instances pedigrees can be constructed including more than 15 generations.

The database was searched for the four grandparents for each of our familial preterm delivery probands.

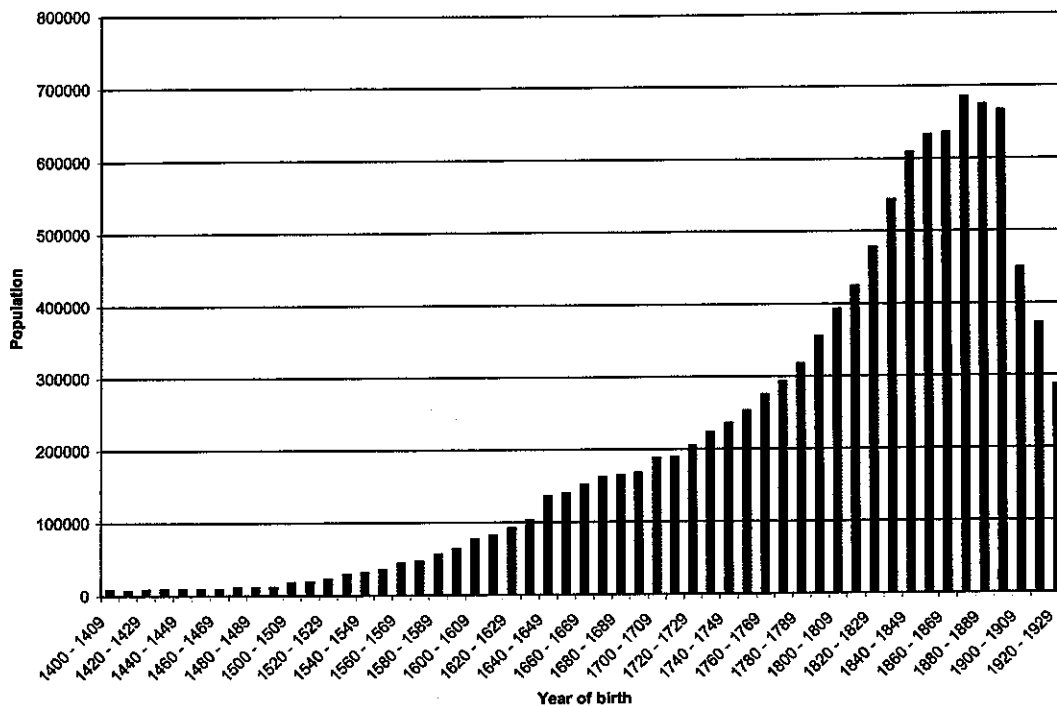


Fig. 1. Distribution of birthdates for individuals in the GenDB database. The database describes the relationship between 21 million ancestors of present families in Utah.

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For 93 of the 112 grandparents, exact matches for the name, maiden name, birth date, and birth places provided by the probands were found in GenDB. Pairwise coefficients of kinship were determined¹⁴ for the 93 preterm delivery grandparents identified in GenDB and for 1,000 randomly selected sets of 100 individuals born in the 1920s. The coefficient of kinship quantifies the degree of relatedness between two individuals. This coefficient is defined as the probability that randomly selected homologous genes from two individuals are identical by descent from a common ancestor. Thus, kinship calculations are based on searching for paths of common descent; each pair of individuals contributes an exponent of 1/2 to the total kinship. Siblings have a coefficient of kinship of 0.25; first cousins have a coefficient of kinship of 0.0625; and *n*th degree relatives have a coefficient of kinship equal to (0.5)^{*n*}. In this study, the mean coefficient of kinship¹⁵ for the familial preterm delivery probands was calculated by considering all possible unique pairings of the grandparents of the familial preterm delivery probands from the 28 families.

RESULTS

Forty-two percent of the 220 patients interviewed reported that their mother had one or more preterm deliveries. Because of the large average family size in Utah, women who delivered prematurely had an average of 1.2 sisters who are also parous; the rate of preterm delivery in these sisters was reported as 35%. We did not attempt to confirm the diagnosis unless the proband reported five or more first- and second-degree relatives who delivered prematurely.

Through this effort, we identified 28 families with an apparent familial predisposition to preterm delivery (as evidenced by five close relatives with preterm delivery confirmed by medical records). Based on the available medical records, we tried to characterize the affected pregnancies for known predispositions to preterm delivery (intraamniotic infection, indicated delivery, premature rupture of the membranes, cervical factors, placental inflammation/ischemia, excessive and premature uterine contractions). Unfortunately, the clinical data sets were usually incomplete (especially for the relatives who delivered at other institutions). Sixteen of the 28 probands were clinically classified as "idiopathic" preterm delivery (Table 1). The mean gestational age at delivery for the familial preterm delivery probands was 30.2 weeks of gestation (range 23.5–35.5).

More than 93% of the 28 familial preterm delivery probands have one or more of their grandparents included in the GenDB database (mean 3.3 grandparents

Table 1. Characteristics of Familial Preterm Delivery Index Cases

Characteristic	
No. of probands with familial preterm delivery	28
Median number of affected first- or second-degree relatives (range)	6 (5–10)
No. of probands with "idiopathic" preterm delivery	16
Mean gestational age in weeks at delivery (range)	32.3 (23.5–35.5)
Percentage of probands' grandparents in GenDB	93.3
Mean no. of four grandparents included	3.3

included out of four). The average kinship coefficient for controls was 1.5×10^6 (standard deviation = 0.6×10^6), consistent with previous calculations for the Utah population. The coefficient of kinship for familial preterm delivery grandparents was more than 50 standard deviations higher (3.4×10^5 [$P < .001$]).

DISCUSSION

This study confirms the familial nature of preterm delivery and the likelihood of a major gene effect in preterm labor. If a preterm delivery is influenced by heritable factors, then the trait should be more common in relatives as their kinship coefficient increases. Likewise, if genes contribute to the prevalence of preterm delivery in a population, the coefficient of kinship should be higher in cases than in controls. We show that controls from the early 1900s were roughly 19th-degree relatives on average. Therefore, gravidae randomly selected from our present population are on average 23rd-degree relatives four degrees further removed. By considering only the pair of grandparents for each pair of preterm delivery probands with the nearest common ancestor, familial preterm delivery probands are eighth-degree relatives on average.

Obviously, the calculated mean coefficient of kinship will vary depending on how cases are selected. We focused on familial clusters because our long-term aim is to discover the genes involved. Limited analysis of patients who delivered prematurely and reported no family history of preterm delivery shows that these probands often link into these extended pedigrees as well (data not shown).

Many of the families currently living in Utah and most of the subjects in this study are descendants of the approximately 10,000 people who moved to Utah to found the Church of Jesus Christ of Latter Day Saints (or Mormon Church). These pioneers were generally unrelated individuals, and as a group they



are genetically representative of a Northern European population.¹⁶ Due to a continued influx of immigrant workers and converts to the Mormon religion from around the world, the Utah population does not have unusual levels of inbreeding.¹⁷ Due to the Latter Day Saints church proscriptions against consumption of tobacco and alcohol and relatively low rates of sexually transmitted diseases and substance abuse, this population may have a lower rate of environmental triggers for premature labor. In 2002, the preterm birth rate was 10.5% in Utah.¹⁸

The families do not appear to group into a single family lineage. In several instances, three or more of the 28 families do cluster as descendents of a common ancestor. This implies that founder effects (alleles associated with the disease which are identical by descent occur in many individuals in the population). In several instances, probands share common ancestors with other probands on both their maternal and paternal sides, giving us an opportunity to look for polygenic effects as the associated genes are discovered.

Analysis of these affected families suggests that one or more relatively common alleles act as "major genes" conferring susceptibility to preterm delivery. It is unlikely that any particular genotype is necessary for the disease to occur; rather, "preterm delivery genes" act as a susceptibility loci that lower a woman's threshold for delivering prematurely. Whereas genetic risk factors are stable through the mother's and child's life spans, they are easier to observe than other transient factors such as cervical shortening or fetal inflammation which can only be observed proximate to the delivery. Because ultimately genetic and environmental factors operate on the same critical molecular pathways, the present study suggests that greater systemic research into the genetics of preterm delivery is warranted.

Mutant genes in any of dozens of pathways could affect a woman's risk of delivering prematurely.⁹ Every ligand, every receptor, every amplification cascade, and every aspect of the programmed responses that orchestrate the pathophysiologic response is under the control of the genes of either the mother or the fetus. Until recently, preterm birth would quite likely cause the death of the neonate, suggesting that predisposing alleles may arise frequently as new mutations. Many new alleles will be "private" mutations, affecting one woman or only a handful of women; however, any mutation identified that affects an individual patient's risk may give us new insights into the normal mechanism of labor or lead to a treatment that is applicable to all women. A more exciting outcome from genetic studies of pre-

term delivery would be the discovery of a common predisposing mutation that might allow predictive testing of obstetric patients or suggest a treatment that is widely applicable.

Uncovering genetic contributions to the pathogenesis of preterm delivery poses a complex challenge. The "phenotype" is clearly heterogeneous, variable, and nonspecific.¹⁹ We hope to discover important predisposition genes by studying this large population. Relatively complete and accurate knowledge of the ancestral histories of many of our research subjects should help us sort out the genetic heterogeneity and map predisposing genes using identity-by-descent methods.²⁰ Once preterm delivery is understood at a molecular level and genetic determinants can be examined directly, the clinical classification as well as the diagnosis and treatment of preterm delivery are likely to be redefined.

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