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Original Investigation

Family Aggregation and Heritability of ESRD in Taiwan: A Population-Based Study

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Background: Aggregation of end-stage renal disease (ESRD) has been observed in families of European origin, as well as those of African origin. However, it is not well documented if this disease aggregates in Asian families. Furthermore, the contribution of genetic factors and shared environmental factors to family aggregation remains unclear.

Study Design: Population-based cross-sectional cohort study.

Setting & Participants: All 23,422,955 individuals registered in the Taiwan National Health Insurance Research Database in 2013. Among these, 47.45%, 57.45%, 47.29%, and 1.51% had a known parent, child, sibling, or twin, respectively. We identified 87,849 patients who had a diagnosis of ESRD.

Predictor: Family history of ESRD.

Outcomes & Measurements: ESRD and heritability defined as the proportion of phenotypic variance attributable to genetic factors.

Results: Having an affected first-degree relative with ESRD was associated with an adjusted relative risk of 2.46 (95% CI, 2.32-2.62). Relative risks were 96.38 (95% CI, 48.3-192.34) for twins of patients with ESRD, 2.15 (95% CI, 2.02-2.29) for parents, 2.78 (95% CI, 2.53-3.05) for offspring, 4.96 (95% CI, 4.19-5.88) for siblings, and 1.66 (95% CI, 1.54-1.78) for spouses without genetic similarities. Heritability in this study was 31.1% to 11.4% for shared environmental factors and 57.5% for nonshared environmental factors.

Limitations: This was a registry database study and we did not have detailed information about clinical findings or the definite causes of ESRD.

Conclusions: This whole population−based family study in Asia confirmed, in a Taiwanese population, that a family history of ESRD is a strong risk factor for this disease. Moderate heritability was noted and environmental factors were related to disease. Family history of ESRD is an important piece of clinical information.

INDEX WORDS: End stage renal disease (ESRD); family aggregation; environmental risk factors; family transmission; family history of ESRD; heritability; Taiwan; Asia; risk factor.

End-stage renal disease (ESRD) causes substantial medical and economic burdens all over the world. According to the US Renal Data System (USRDS) annual report, the incidence and prevalence of ESRD in Taiwan are among the highest in the world, with an unadjusted incidence rate of 450 per million people in Taiwan, compared with 359 per million people in the United States and 285 per million people in Singapore and Japan.[1] More than 80,000 Taiwanese patients currently require dialysis, and the number is increasing.[2]

Some Mendelian disorders may cause ESRD; these include polycystic kidney disease, Alport syndrome, and hereditary nephrotic syndrome. Other disorders such as diabetes mellitus, hypertension, long-term nonsteroidal anti-inflammatory drug use, and gouty nephropathy are also important risk factors. Family aggregation of ESRD is well established in some

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multicenter studies and in a few population-based studies.[3-6] Family members of individuals treated for ESRD have high rates of chronic kidney disease (CKD) or hypertension.[7,8] Familial clustering of diabetic nephropathy and kidney diseases has also been shown in previous studies.[9,10] Obtaining a family history of ESRD is important in clinical practice because it may help physicians identify patients at a high risk for CKD. Early diagnosis and treatment of CKD may slow the progression of this disease and reduce the incidence of ESRD. Family clustering of ESRD suggests that both genetic factors and shared environmental factors are important in the pathogenesis of this disease. Genetic factors for diabetic nephropathy and for CKD progression have been reported.[11,12] Despite evidence for the important role of genetic factors in the pathogenesis of CKD, and probably ESRD, the magnitude of a genetic contribution to CKD susceptibility is unknown. Using data from National Health Insurance (NHI), we conducted a study consisting of essentially the entire population of Taiwan in 2013. We used genealogy and linked health information stemming from this comprehensive database to determine familial clustering of ESRD by estimating the risks for ESRD according to specific affected kinships and to assess the relative contribution of genetic, shared, and unshared environmental factors to susceptibility for ESRD.

METHODS

Ethics Approval and Consent

This study was approved by the Institutional Review Board of the Chang Gung Memorial Hospital, Taoyuan, Taiwan (IRB no. 104-8043B), with waiver of informed consent because no identifiable information was used in this study.

Study Population

This study investigated a cohort of all individuals registered in the Taiwan NHI Research Database in 2013. Data from the registry for NHI beneficiaries, registry of patients with catastrophic illnesses, and data sets of ambulatory care expenditures and details of ambulatory care orders are all part of the NHI Research Database. The database is anonymous, but the encrypted personal identification remains unique within the database to ensure valid internal linkages. Individuals without valid insurance status were excluded from analysis. The NHI program is a mandatory single-payer social health insurance system, and the coverage rate was >99.5% in 2013.[13]

Methods of identifying first-degree relatives in the NHI Research Database have previously been reported.[14-16] In brief, the registry of beneficiaries contains identifiers of the relationships between the insured person (who paid the insurance fee) and his or her dependents. Only blood relatives (parents, grandparents, children, and grandchildren) and spouses are eligible to be claimed as dependents of an insured person. This procedure follows the civil registration rules, which generally require a birth certificate issued by the medical facility that delivered the child or DNA parentage testing for those who were not born in medical facilities as proof to register a child as one's dependent. This allowed us to establish family relationships (parents, offspring, full siblings, twins, and spouses) using the identifiers and unique personal identification numbers of parents, grandparents, children, grandchildren, and spouses. In general, parent-offspring relationships and spouses could be identified directly. Full siblings of an individual were identified if they had the same parents. Twins were full siblings with the same date of birth (±1 day), but twin zygosity could not be determined from the database. To establish correlations among people from the same family, individuals were grouped into families according to their relationships.

Identifying ESRD

The Ministry of Health and Welfare in Taiwan has a list of catastrophic illnesses. These illnesses include cancer, chronic mental illness, chronic kidney failure requiring kidney dialysis, and congenital conditions and may incur large medical expenditures, as well as large copayments. Any insured individual with a certificate proving a catastrophic illness is exempt from such copayments. The issuance of catastrophic illness certificates requires a prior review by at least 2 specialists and a careful examination of medical records, laboratory studies, and imaging studies.

In this study, all cases of dialysis patients were obtained from the Registry of Catastrophic Illness Database, a subset of the NHI Research Database. The diagnostic codes are based on the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*). Patients enrolled in this study were diagnosed as having ESRD based on *ICD-9-CM* code 585. Patients with diagnoses of autosomal dominant polycystic kidney disease (ADPKD) or autosomal recessive polycystic kidney disease (ARPKD; *ICD-9-CM* codes: 753.12, 753.13, and 753.14) were excluded in our main analyses.

Statistical Analysis

The prevalence of ESRD was calculated for the general population and for individuals with affected first-degree family members. Relative risks (RRs) for ESRD were calculated as the adjusted prevalence ratios between first-degree relatives of an individual with ESRD and the general population. The RR estimated in this study was essentially the same as the relative recurrence risk according to its original definition by Risch.[17] The Cox proportional hazards model is a well-recognized statistical technique to handle censored survival data and estimate instantaneous hazards ratios based on varying follow-up time. Breslow[18] adapted the Cox models to estimate prevalence rate ratios in a cross-sectional study by applying an equal follow-up time for all individuals. This method has been proved to produce consistent estimates for prevalence ratios close to true parameters.[19,20] A marginal model was used in this study to handle intrafamilial clustering; this model focuses on the mean population hazard function.[21,22] We calculated RRs for individuals with an affected first-degree relative of any kinship and also for individual kinship (parent, offspring, sibling, and twin). Because the kinship and sex of the affected relative may influence familial risk, we created models separately according to the kinship and sex of affected relatives (mother, father, daughter, son, sister, brother, twin sister, and twin brother). We excluded twins from the sibling analyses. In addition to first-degree relatives, we estimated RRs for spouses. The RR was estimated for the number of affected first-degree kinships (father, mother, son, daughter, brother, and sister). In this model, we compared the risk for ESRD in individuals with 1 or 2 affected first-degree relatives with the risk in the general population. The RR was adjusted for age, sex, family size, and socioeconomic status.

Heritability

Heritability was defined as the proportion of phenotypic variance attributable to genetic factors; the theoretical definition of familial transmission is the proportion of genetic and shared environmental contributions. Both familial transmission and heritability can be calculated using the polygenic liability model.[23-25]