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Pedigree-based Analysis of Inherited and Noninherited Risk Factors of Congenital Heart Defects

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ABSTRACT

Background: Although congenital heart defect (CHD) pedigrees are rare, they are generally taken as evidence of the existence of a genetic etiologic mechanism or environmental factors common to family members, or a combination of both. Therefore, the analysis of CHD pedigrees is important for bridging the gap in our knowledge of its etiology.
Aims: To assess the prevalence of CHD and evaluate the nongenetic factors in the CHD patients and healthy controls in the pedigrees.
Study design: Observational retrospective study.
Subjects: Twenty-three CHD pedigrees were involved in the prevalence statistics; thirty-nine CHD cases and fifty-two healthy controls in the CHD pedigrees were included in the family-based noninherited factors analysis.
Outcome measures: The three-degree relatives and overall CHD prevalence were calculated. Thirty-four noninherited risk factors were compared between the CHD and control groups, first by univariate analysis and later by multivariable logistic stepwise regression analysis.
Results: The CHD prevalence of the probands' relatives in all pedigrees was 8.0%, and it was 10.9%, 2.9% and 11.9% in first-, second- and third-degree relatives, respectively. The three risk factors, including maternal febrile illnesses (OR = 14.2, 95%CI: [1.5 - 133.7]), influenza (OR = 6.9 [2.0 - 23.6]) and air pollution (OR = 13.5 [2.6 - 70.5]), were strongly associated with a higher risk of CHD in our sample.
Conclusions: For the cluster and high prevalence of CHD in the collected pedigrees, our study confirms that genetic factors play a major role in the pathogenesis of CHD, while environmental factors, such as maternal febrile illnesses, influenza and air pollution, may also increase the burden of risk for CHD pathogenesis.
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1. Introduction

Congenital heart defects (CHDs) comprise the most common congenital disorder in newborns and are the most common cause of infant death from birth defects [1,2], accounting for one-third of all major congenital anomalies [3]. Worldwide, the incidence of CHD ranges from 1.9/1,000 to 50.0/1,000 live births [3,4]. In China, our recent work on neonatal screening for CHD using echocardiography has shown that the prevalence of CHD in live births is 26.6 per 1,000 [5], which ranks first of all birth defects [6]. With the tremendous success of contemporary surgical procedures and improved survival, many patients with complex cardiac lesions are reaching adult life [7]. However, despite the improved treatment and prognosis of these patients, CHD always poses substantial physiological, emotional and socioeconomic challenges for patients, families and society. Consequently, our insight into the etiology of heart malformations is not only a fundamental research endeavor; it is imperative in providing proper health care for this growing community [8].

A genetic component of CHD was initially implicated by their recurrence in families [9], and familial cases have been described for nearly all types of cardiac malformations [10]. Classic Mendelian transmission of CHD in some families has been described in the recent literature, and the pattern of inheritance may depend on the specific type of CHD [11]. In the past decade, molecular genetic studies have exploited these observations from families with multiple affected individuals and have provided insights into the genetic basis of several forms of CHD [12]. Chromosomal anomalies account for about 8% - 10% of presenting cases of CHD, and approximately 3% - 5% of CHD can be attributed to Mendelian syndromes in which a single mutation results in pathological consequences [13]. For the remaining cases of CHD, a paradigm of variable expressivity and penetrance is emerging, even with single-gene defects, suggesting an important role for secondary factors in CHD [14].

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Although relatively less information is available on the noninherited modifiable factors that may have an adverse effect on the fetal heart, the body of epidemiological literature on this topic has grown in the past decade [15]. Increasing numbers of studies have explored the association of maternal (and paternal) illnesses, nutritional deficiencies, drugs [16], and chemical exposures during embryonic and early fetal development with CHD [17]. So far, there are a handful of well-established nongenetic teratogens that greatly increase the chance of heart defects [18], including maternal diabetes, first trimester rubella infection and isotretinoin (Accutane) exposure [15]. Despite decades of international efforts to combat these factors, the compendium of nongenetic causes of CHD continues to increase and diversify [8]. An exploration of the contribution of noninherited risk factors that are potentially modifiable is particularly important in the context of the growing health burden of CHD [15].

Based on the previous background, we hypothesized that both genetic and environmental risk factors play critical roles in the pathogenesis of CHD in our collected CHD families. Therefore, we first estimated the prevalence of CHD in the relatives of the probands, as well as the distribution of the CHD subtypes, and subsequently performed a comprehensive analysis of the noninherited risk factors in CHD patients and healthy members in the pedigrees.

2. Methods

2.1. Study population

Between August 2012 and June 2013, Twenty-three CHD pedigrees were invited to participate in our study in the Cardiac Center at the Children's Hospital of Fudan University, Shanghai, China. Cases with extra-cardiac anomalies, trisomy 21, 22q11 deletion or other chromosomal anomalies were excluded.

Our trained staff obtained an accurate three-generation pedigree from each proband at the time of recruitment, detailing the presence or absence of CHD in each family member. When the probands' CHD relatives were distant, a more detailed family history was recorded until it contained all CHD patients. Genealogical trees were drawn by Cyrillic (version 2.02). First-degree relatives were defined as parents or siblings; second-degree relatives as grandparents or uncles/aunts; third-degree relatives as cousins; and distant relatives as relatives beyond three lineal generations.

Since the prevalence of CHD in the distant relatives was difficult to describe, we firstly calculated the prevalence of CHD in the three-degree relatives of the 23 pedigrees. Then we analyzed the phenotype of all the fifty-three CHD cases comprising the probands, three-degree and distant relative. Finally, thirty-nine cases and fifty-two healthy controls from the pedigrees participated in the noninherited risk factor study. All the subjects were Chinese Han.

All study protocols were reviewed and approved by Huashan Institutional Review Board. Written consent was obtained from the parents before the study commenced.

2.2. Phenotype ascertainment

The phenotypes of the probands and their CHD relatives who were hospitalized in our hospital were confirmed by review of all available medical records, including echocardiography, electrocardiography, cardiac catheterization and/or operative notes. For all the other available members in the recruited pedigrees, the diagnoses were made by medical history taking, physical examination, electrocardiography, chest radiography, abdominal ultrasound and echocardiography at the Children's Hospital of Fudan University.

2.3. Classification of CHDs in probands and relatives

Subjects with heart defects were classified into the following 17 heart phenotypes on the basis of the classification used by Botto et al. [19] and Øyen et al. [20] in a hierarchical fashion: (1) heterotaxia; (2) conotruncal heart defect (CTD); (3) atrioventricular septal defect (AVSD); (4) anomalous pulmonary venous return (APVR); (5) left ventricular outflow tract obstruction (LVOTO); (6) right ventricular outflow tract obstruction (RVOTO); (7) isolated atrial septal defect (ASD); (8) isolated ventricular septal defect (VSD); (9) ASD and VSD; (10) complex defects; (11) conotruncal heart defect plus AVSD; (12) septal defect plus LVOTO; (13) septal defect plus RVOTO; (14) isolated patent ductus arteriosus (PDA) among infants born at term; (15) isolated PDA in preterm infants; (16) unspecified; and (17) all other specified heart defects. This classification algorithm for CHDs was based on anatomical, developmental and epidemiologic evidence.

The affected relatives of probands were classified by the concordance or discordance of their defects with the probands'. Lesions were considered concordant when the affected relative had a same phenotype referring to the above classification; otherwise, they were classified as discordant.

2.4. Noninherited risk factor measurements

A family-based case-control study was conducted to find differences in risk factors between CHD cases and healthy subjects both from the CHD pedigrees. A standard questionnaire contained risk factors from both mother and father:

1) Multivitamin; folic acid.
2) Maternal illnesses and conditions, including: diabetes; hypertension; anemia; hyperhomocysteinemia; phenylketonuria; febrile illnesses; influenza; other infections; obesity; epilepsy; endemic and epidemic diseases.
3) Maternal therapeutic drug exposures, including: antibiotics; lithium and sedatives/hypnotics; contraceptives; and traditional Chinese medicine.
4) Maternal nontherapeutic drug exposures, including: caffeine; alcohol; cigarette smoking and passive smoking.
5) Maternal environmental exposures, including: herbicides, pesticides and rodenticides; air pollution; chemical substances; noise; cooking with coal or wood; hair dye; prolonged use of a computer; wearing radiation protection clothing; living in a newly decorated house; contact with pets; and close proximity to a high-voltage wire.
6) Maternal sociodemographic characteristics, including: age; pregnancy history, including abortion within six months before pregnancy; threatened abortion during pregnancy; severe pregnancy reaction; and maternal stress.
7) Paternal sociodemographic characteristics, including: paternal age; obesity; alcohol; cigarette smoking; radiation and chemical substances.

2.5. Statistical analysis

The age of the subjects was presented as the mean ± standard deviation (SD). The prevalence of CHD was calculated for the first-, second- and third-degree relatives. When applicable, prevalence was calculated using data from all relatives with a class, that is, those born before and after the probands.

For the risk factor analysis, the association between exposures and CHD risk were first analyzed using Pearson's chi-square tests or Fisher's exact tests. Then, multivariate logistic stepwise regression analysis of the previous suspected variables was performed, and an odds ratio (OR) and 95% confidence interval (CI) were reported.

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