Maturitas 109 (2018) 104–111

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Review

Women-specific risk factors for heart failure: A genetic approach

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ARTICLE INFO

Keywords:
Heart failure
Reproductive factors
Genome-wide association studies
Genetic variant

ABSTRACT

Heart failure is a complex disease, which is presented differently by men and women. Several studies have shown that reproductive factors, such as age at natural menopause, parity and polycystic ovarian syndrome (PCOS), may play a role in the development of heart failure. Shared genetics may provide clues to underlying mechanisms; however, this has never been examined. Therefore, the aim of the current study was to explore whether any reproductive factor is potentially related to heart failure in women, based on genetic similarities. Conducting a systematic literature review, single nucleotide polymorphisms (SNPs) associated with reproductive factors, heart failure and its risk factors were extracted from recent genome-wide association studies. We tested whether there was any overlap between the SNPs and their proxies of reproductive risk factors with those known for heart failure or its risk factors. In total, 520 genetic variants were found that are associated with reproductive factors, namely age at menarche, age at natural menopause, menstrual cycle length, PCOS, preeclampsia, preterm delivery and spontaneous dizygotic twinning. For heart failure and associated phenotypes, 25 variants were found. Genetic variants for reproductive factors did not overlap with those for heart failure. However, age at menarche, gestational diabetes and PCOS were found to be genetically linked to risk factors for heart failure, such as atrial fibrillation, diabetes and smoking. Corresponding implicated genes, such as TNNI3K, ErbB3, MKL2, MTNR1B and PRKD1, may explain the associations between reproductive factors and heart failure. Exact effector mechanisms of these genes remain to be investigated further.

1. Introduction

Heart failure is a clinical syndrome characterised by a multitude of signs and symptoms, such as fatigue, shortness of breath, ankle swelling, oedema, and pulmonary crackles [1,2], which are caused by a structural or functional cardiac abnormality, resulting in decreased cardiac output and/or increased intracardiac pressures at rest or during stress [2,3]. The prevalence ranges between 1% and 2% in Western populations, and increases with age [2]. In fact, cardiovascular diseases, including heart failure, coronary heart disease, and stroke, are the leading cause of death globally [4], as well as in Europe [5]. Among different aspects of heart failure, such as epidemiological rates and risk factors, gender differences can be found. Mortality rates of heart failure are higher in women than in men, while the prevalence of heart failure in men is greater than in women [6]. Also the type of heart failure differs between the sexes; men suffer significantly more often from heart failure with reduced ejection fraction while the incidence rates of heart failure with preserved ejection fraction are almost 3-fold higher in women than in men [7]. Where hypertension is the most common cause of heart failure in women, heart failure in men often results from coronary artery diseases such as myocardial infarction [8]. These facts altogether suggest that aetiology of heart failure in women and men might differ. Perhaps women-specific reproductive factors play a role in the development of heart failure in women.

In the last decades, several studies have examined the relation between reproductive factors (e.g. age at menopause, parity and polycystic ovarian syndrome (PCOS)) and heart failure, as reviewed by Harvey et al., Wenger, and Bolijn et al. [6,9,10]. For example, regarding age at menopause, there is consistent evidence that women who reach menopause early (age < 45) have a significantly higher risk of heart failure compared to women with later menopause (age ≥ 45) [11–13]. This risk is increased by 20% [11], 40% [12] to 66% [13]. In contrast,

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https://doi.org/10.1016/j.maturitas.2017.12.016
Received 23 November 2017; Received in revised form 22 December 2017; Accepted 29 December 2017

no consensus has been achieved on the association between parity (number of births) and heart failure. Some studies [14,15], but not all [16], observed that risk of heart failure increased with higher parity. According to two separate studies, PCOS was not associated with heart failure [17,18]. However, mothers [17] and fathers [18] of women with PCOS had an elevated risk of other cardiovascular disease, i.e. stroke and myocardial infarctions.

The mechanisms underlying the potential associations between reproductive factors and heart failure remain unclear. A genetic approach could uncover the unsuspected underlying mechanisms causing heart failure. In the last decade, genome-wide association studies (GWAS) have made their entrance in common science [19]. Across the entire spectrum of cardiovascular diseases many genetic variations have been identified, including single nucleotide polymorphisms (SNPs) associated with disease as well as SNPs associated with risk factors [19]. Genetic overlap has even been found between these SNPs associated with risk factors and disease [20]. For example, some SNPs associated with LDL cholesterol are associated with coronary heart disease too [20]. Genetic factors also contribute to the development of heart failure, and several genomic regions are suggested to be associated with heart failure [21–24]. However, to our knowledge no prior studies have investigated the potential relation between reproductive factors and heart failure in women on a genetic basis. Therefore, the aim of the current study is to explore whether any women-specific reproductive factor is potentially related to heart failure or associated phenotypes based on genetic similarities, i.e. SNPs.

2. Methods

2.1. Search methods and article selection

A search for known GWAS signals for women-specific, reproductive factors and heart failure, including associated phenotypes, was initially performed in the GWAS Catalog [25], using the terms: *Age at menarche, age at menopause, breastfeeding, fertility, gestational diabetes, gravidity, hypertensive pregnancy disorders, maternal age, menstrual cycle duration and regularity, menopausal complaints, miscarriage, parity, polycystic ovarian syndrome, preeclampsia, preterm delivery, reproductive duration, heart failure, cardiac function, cardiac structure* and *cardiomyopathy*. Because the GWAS Catalog is not entirely up-to-date, PubMed was searched for published articles on GWAS of reproductive factors or heart failure including associated phenotypes, using the same terms and some additional key words: *genome-wide association study*; *genome-wide association studies*; and *genetics*. The PubMed search was limited in the following features: study design (GWAS or large-scale gene-centric); language (English); species (human); and age (≥ 18). GWAS aiming to find associations with any of the abovementioned traits were selected when they met the following inclusion criteria: (1) the study population described patients of European ancestry; and (2) the study was the most recent published GWAS on that specific trait. When two studies on the same trait were published in the same year; both studies were included. Concerning the outcome (heart failure and cardiomyopathy); more GWAS were included; because the most recent studies had not incorporated earlier GWAS results.

2.2. Data extraction

The following study characteristics were extracted from the articles: study design, number of patients in the first stage, number of patients in the replication stage(s), used *p*-value, and rs-numbers of SNPs that authors claimed to be significantly associated with the trait.

2.3. Data analysis

Using the single nucleotide polymorphisms annotator SNiPa [26], proxies of all extracted SNPs were determined with the 1000 Genomes, Phase 3 v 5 data set. Search options were set at: Genome Assembly, GRCh37; Population, European; Genome Annotation, Ensembl 887; and r^2 threshold, 0.8. All SNPs were included as proxies for themselves, and aliases of proxies were incorporated as well.

To compare SNPs associated with reproductive factors and SNPs associated with heart failure, lists with retrieved SNPs, their proxies and their aliases of a reproductive factor and of heart failure were merged on rs-numbers, using R [27]. In addition, all genetic associations collected in the GWAS Catalog were downloaded until September 2017 to explore whether any of the SNPs or their proxies associated with reproductive factors matched SNPs associated with established risk factors of heart failure [28]. The entire GWAS Catalog was compared to the proxies we found for reproductive factors, again using R. The results were searched for traits regarding established and possible risk factors of heart failure, i.e. *anaemia, atrial fibrillation, blood pressure, chronic obstructive pulmonary disease, coronary artery disease, chronic kidney disease, depression, diabetes, heart rate, hypertension, left bundle block, left ventricular hypertrophy, obesity, sleep-disordered breathing, smoking,* and *valvular heart disease* [29–31].

For all SNPs the nearest gene, as reported by the authors, was retrieved from the articles. The gene ontology consortium [32] and the database of ensembl.org [33] were then consulted to study gene functions and thereby possible underlying mechanisms of heart failure. Additionally, when a gene appeared to have a cardiac function, a PubMed search on the particular gene was conducted to study the underlying mechanism more thoroughly.

3. Results

Initially 86 studies and 933 articles were identified in the GWAS Catalog and on PubMed, respectively. Of these 1019 studies, 17 met the inclusion criteria (see Fig. 1 for a flowchart of the article selection). Ten studies reported GWAS findings on reproductive factors, i.e. age at menarche [34], age at natural menopause [35], breast feeding duration [36], gestational diabetes [37], menstrual cycle length [38], PCOS [39,40], preeclampsia [41], preterm delivery [42], and spontaneous dizygotic twinning [43]. Seven studies reported GWAS findings on echocardiographic traits of cardiac structure and function [44], dilated [45,46] and hypertrophic cardiomyopathy [47], and heart failure [48–50]. In total, 546 SNPs were extracted as significantly associated with reproductive factors or heart failure, of which the majority, 389, was associated with age at menarche. More comprehensive study details are presented in Table 1.

3.1. Comparison of genetic variants

When comparing the genetic variations discovered in these GWAS, none of the SNPs for reproductive factors were associated with heart failure or its associated phenotypes echocardiographic cardiac structure and function, dilated and hypertrophic cardiomyopathy at the genome-wide significance level.

With regard to the entire GWAS Catalog, both age at menarche, as well as gestational diabetes and PCOS were found to be genetically linked to risk factors for heart failure. First, considering age at menarche, proxies of menarche SNPs were associated with atrial fibrillation (menarche SNP: rs2723065), cardiac function (i.e. QT interval and pulse pressure; rs1704528, rs2723065), coronary artery disease (rs11556924), type 1 diabetes (rs1131017), type 2 diabetes (rs7576624, rs9972653), fasting glucose-related traits (rs17085563), obesity and obesity-related traits such as body mass index, waist circumference and weight (rs10136330, rs10138913, rs1040070, rs10933, rs11209943, rs112991346, rs13322435, rs1428120, rs16917237, rs29941, rs395962, rs4804025, rs4897178, rs506589, rs7132908, rs7359336, rs7576624, rs758747, rs79541760, rs9972653), and smoking behaviour (rs16917237). The menarche SNP associated with atrial fibrillation, rs2723065, is upstream the CEP68