A bibliometric analysis in gene research of myocardial infarction from 2001 to 2015

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Objectives: We aimed to evaluate the global scientific output of gene research of myocardial infarction and explore their hotspots and frontiers from 2001 to 2015, using bibliometric methods. **Methods:** Articles about the gene research of myocardial infarction between 2001 and 2015 were retrieved from the Web of Science Core Collection (WoSCC). We used the bibliometric method and Citespace V to analyze publication years, journals, countries, institutions, research areas, authors, research hotspots, and trends. We plotted the reference co-citation network, and we used key words to analyze the research hotspots and trends. **Results:** We identified 1853 publications on gene research of myocardial research from 2001 to 2015, and the annual publication number increased with time. Circulation published the highest number of articles. United States ranked highest in the countries with most publications, and the leading institute was Harvard University. Relevant publications were mainly in the field of Cardiovascular system cardiology. Keywords and references analysis indicated that gene expression, microRNA and young women were the research hotspots, whereas stem cell, chemokine, inflammation and cardiac repair were the frontiers. **Conclusions:** We depicted gene research of myocardial infarction overall by bibliometric analysis. Mesenchymal stem cells Therapy, MSCs-derived microRNA and genetic modified MSCs are the latest research frontiers. Related studies may pioneer the future direction of this filed in next few years. Further studies are needed.

1   **[Cover Page]**

3   **A Bibliometric Analysis in Gene Research of Myocardial Infarction from 2001 to 2015**

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19   **Running head: Bibliometric Analysis about MI Genetics Research**

Abstract

Background: We aimed to evaluate the global scientific output of gene research of myocardial infarction and explore their hotspots and frontiers from 2001 to 2015, using bibliometric methods.

Methods: Articles about the gene research of myocardial infarction between 2001 and 2015 were retrieved from the Web of Science Core Collection (WoSCC). We used the bibliometric method and Citespace V to analyze publication years, journals, countries, institutions, research areas, authors, research hotspots, and trends. We plotted the reference co-citation network, and we used key words to analyze the research hotspots and trends.

Results: We identified 1853 publications on gene research of myocardial research from 2001 to 2015, and the annual publication number increased with time. Circulation published the highest number of articles. United States ranked highest in the countries with most publications, and the leading institute was Harvard University. Relevant publications were mainly in the field of Cardiovascular system cardiology. Keywords and references analysis indicated that gene expression, microRNA and young women were the research hotspots, whereas stem cell, chemokine, inflammation and cardiac repair were the frontiers.

Conclusions: We depicted gene research of myocardial infarction overall by bibliometric analysis. Mesenchymal stem cells Therapy, MSCs-derived microRNA and genetic modified MSCs are the latest research frontiers. Related studies may pioneer the future direction of this filed in next few years. Further studies are needed.

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Introduction

46 Myocardial infarction (MI), a life-threatening condition, occurs when lack of blood flow,

47 causing the irreversible death of heart muscle. The incidence of MI has significantly increased in

48 the past few decades, and MI remains a leading cause of death worldwide. With the development

49 of genetic technology, gene researches have widely launched in MI. Researchers explore the

50 genetics about MI and apply gene therapy for better treatment efficacy. Many genes have been

51 identified an association with MI, such as PCSK9, TCF21(Braitsch et al. 2013; Kathiresan &

52 Myocardial Infarction Genetics 2008). Genome-wide association studies also have found 27

53 genetic variants that are associated with an increasing risk of MI(O'Donnell & Nabel 2011).

54 Although numerous papers focused on gene research of MI, there are limited attempts to analyze

55 them systematically.

56 There are several bibliometric studies focused on cardiovascular diseases research. Mark et al

57 performed a global bibliometric analysis from 1999 to 2008 to evaluate trends disaggregated by

58 country(Huffman et al. 2013). Publications has increased substantially in the past decade, but the

59 low-income countries with higher disease burdens still had a lower output. Bloomfield and AI-

60 Kindi confirmed this phenomenon separately by the bibliometric analysis from 52 African

61 countries and the Middle East(Al-Kindi et al. 2015; Bloomfield et al. 2015). Shuaib and et al.

62 focused on the citation frequency of top 100 cited cardiovascular articles(Shuaib et al. 2015).

63 However, a global bibliometric analysis of the gene research of MI has not yet been performed.

64 Bibliometric analysis is a widely used quantitative method to examine the knowledge structure

65 and development in research fields(Guler et al. 2016). CiteSpace V is one of bibliometric

66   visualization tools for visualizing and analyzing emerging trends and transition patterns in

67   scientific literature, which is developed by Chaomei Chen in 2004(Chen 2004; Chen 2006; Chen

68   et al. 2010; Synnestvedt et al. 2005). Now it has been widely used to evaluate the productivity of

69   institutions, countries and authors; identify international collaborations and geographic

70   distributions; and explore research hotspots and frontiers in specified fields(Chen et al. 2014). In

71   the present study, we performed a bibliometric analysis of articles on the gene research of MI

72   indexed from 2001 to 2015, by using CiteSpace V to explore the research trend and hot spots.

73

Materials & Methods

75   We performed online retrieval from the Web of Science Core Collection (WoSCC) of Thomson

76   Reuters on Oct 1, 2016. We used the key words "myocardial infarction" and "gene" to retrieve

77   research articles or reviews between 2001 and 2015. We collected the following basic info for each

78   article: authors, title, abstract, institution, country/region, journal, keywords, and references. The

79   search queries were listed below in Supplementary Table 1.

80   Articles or reviews that meet the following criteria were included: (1) The time span is between

81   2001 and 2015. (2) Articles indexed in WoSCC. (3) Articles on gene research of MI, including

82   original research and reviews. (4) Articles with basic info. The following document were excluded:

83   (1) Meeting abstracts, proceedings, corrected articles, and repeated articles. (2) Unpublished

84   Documents without enough information for further analysis.

85   The downloaded data were analyzed based on Web of Science database literature analysis report

86   and export information function. Then we used CiteSpace V (64 bits) to analyze publication

87   outputs and construct knowledge maps. In addition, we also used software VOSviewer (version

88   1.6.6) for better network visualizations in some cases(Ozsoy & Demir 2017; van Eck & Waltman

89   2010). In this paper, Individual network was derived from the 50 most cited articles published in

90   a one-year time slice. TFIDF weighting was used to analyze the content of each cluster(Merigo &

91   Montserrat 2010). Finally, we also applied burst detection to investigate the growth rate of citations

92   or keywords(Lee et al. 2016).

93

Results

95   Based on the selection criteria, 1,853 publications about gene research of MI were indexed in

96   WOSCC from 2001 to 2015, and were included in the study. Much of publications were research

97   articles (1799, 97.1%), followed by review articles (54, 2.9%). English (98.4%) is primary

98   language used by scholars, while the remaining 1.6% of the publications were written in Russian,

99   Spanish, German and Portuguese. The number of publications (Supplementary Table 2) showed a

100   gradually increased trend over time which rose from 82 in 2001 to 164 in 2015 and peaked in 2015.

101   More than 494 scholarly journals have published articles on MI research. The 10 most active

102   journals are presented in Supplementary Table 3. They published 444 articles and accounted for

103   24.0% of all articles included in this study. Circulation published the highest number of articles

104   (66, 3.616%), followed by Atherosclerosis (60, 3.238%), Plos One (48, 2.590%), American

105   Journal of Physiology Heart and Circulatory Physiology and Journal of Molecular (42, 2.267%)

106   and Cellular Cardiology (42, 2.267%).

107   The 1,853 articles originated from 69 countries and territories (Table 1, Figure 1). The top 10

108   countries are composed of six European countries, two Asian countries and two North American

109 countries which accounted for 94.87% of the total number of publications. USA, China, Japan,

110 Germany and Italy were the most productive countries.

111 The 1,853 articles were published by more than 500 research institutions (Table 1, Figure 2).

112 The top 10 institutions with the greatest outputs in this area totally published 351 articles,

113 accounting for 18.94% of publications. The first major research echelon was led by Harvard

114 University, followed by Karolinska Institutet, University of Washington, University of Toronto,

115 and Leiden University.

116 Gene research of MI were distributed in more than 60 special research areas. Supplementary

117 Table 4 shows the top 10 research areas from 2001 to 2015. Cardiovascular System Cardiology

118 accounted for the largest number of publications (45.278%), followed by research experimental

119 medicine (11.387%), genetics heredity (10.362%), cell biology (9.498%), and hematology

120 (8.852%).

121 The 1853 articles were written by more than 11225 authors. The top 10 authors publishing

122 articles were listed in Supplementary Table 5. Hamsten Anders from Karolinska Institutet, Psaty

123 BM and Schunkert H published the most articles (25 records) and accounted for 1.349 % of all

124 published articles. We also analyzed author citations,by using Citespace V, and constructed co-

125 citation maps to evaluate the scientific relevance of publications. As shown in Figure 3, the largest

126 nodes were Pfeffer MA (179 citations), Ridker PM (143 citations), Frangogiannis NG (125

127 citations) and Libby P (119 citations), indicating their important role in MI research. Additionally,

128 there were 7 large citation clusters in Figure 3.

129 In the present study, we used CiteSpace V to construct a knowledge map of keyword co-

130 occurrence with 147 nodes and 947 links (Figure 4) and identified the top 20 keywords in

131   publications from 2001 to 2015 (Supplementary Table 6), according to frequency and citation

132   counts. The top keywords were 'myocardial infarction', 'coronary artery disease', 'heart failure',

133   'expression', 'polymorphism', 'atherosclerosis', and 'gene expression'.

134   We used CiteSpace V to detect burst keywords. Burst keywords are considered as indicators of

135   research frontiers or emerging trends over time. Figure 5 shows the top 20 keywords with the

136   strongest citation bursts. The strongest ones include cytokine, angiotensin converting enzyme,

137   genetics, mutation and mesenchymal stem cell. The recent burst of keywords were microRNA,

138   mesenchymal stem cell, oxidative stress and gene therapy.

139   We constructed a co-cited reference map and explored changes associated with the key clusters

140   of articles. The network contains 491 nodes and 1374 links. The Modularity Q was 0.7863 and the

141   Mean Silhouette was 0.3218 (Figure 6). There were initially 71 clusters, and we filtered out small

142   clusters with low silhouette. To learn more about the development of a cluster in a certain period,

143   we also construct a reference co-citation time-view map (Figure 7). According to the citation

144   frequency and centricity, we selected hotspot references in each period of time.

145

146   **Discussion**

147   When considered with the impact of a journal, we found that the top 10 active journals all had

148   an IF >3.0, and more than 33.3% (3/10) of the top 10 active journals had an IF >10 which account

149   for 7% of the total number of included publications, including Circulation (IF2015=17.047),

150   Journal of the American College of Cardiology (IF2015=17.759) and Circulation Research

151   (IF2015=11.551). When compared with the high-IF rate of all MI articles (7.5%), gene research

152   of MI was still intensively published in high-IF journals.

153   The United States was the leading country in gene research of MI over the past 15 years, and

154   China was the only developing country in the leading group, demonstrating its significant progress

155   in the life sciences during the past 15 years. Our study is not the first investigation showing the

156   pioneer countries in scientific output. These results were roughly consistent with previous

157   cardiovascular disease bibliometric studies(Huffman et al. 2013). A 2017 study showed that the

158   USA has the highest number of strong citation links with other countries, and China has highest

159   growth(Gal et al. 2017). Although the number of publications from Latin America, Africa, and the

160   Middle East increased in the past decade, these low- and middle-income countries with higher

161   disease burdens still lag behinds developed countries, which are needed more target research

162   investments and international collaboration(Al-Kindi et al. 2015; Bloomfield et al. 2015;

163   Colantonio et al. 2015; Jahangir et al. 2011).

164   In Figure 3, the color of nodes indicated how new the associated reference was. Cool colors

165   referred to old researches, warm colors new researches(Chen et al. 2012). Consequently, Ridker

166   PM (in the bottom) and Pfeffer MA (in the top) represents the basis of MI research. The former

167   concentrates on clinical associations, such as hyperhomocysteinemia, atherosclerosis and so

168   on(Libby et al. 2011; Zee et al. 2007). The latter hammers focus on the pathophysiology, such as

169   changes of the renal function(Verma et al. 2007). In the middle of Figure 3, warm-color nodes and

170   linkages, leaded by Frangogiannis NG and Libby P, indicated that transcriptome was new

171   directions(Fiedler et al. 2011; Ounzain et al. 2015). Young women label appeared twice in warm-

172   color clusters, contacting closely with genotype, which may have indicated young MI women may

173   be associated with genetics variants. Some articles found that young women with acute myocardial

174   infarction have more comorbidity and higher in-hospital mortality than young men(Gupta et al.

175   2014). Young women with MI more often have a family history of premature MI, which was

176   addressed in a study of 398 families in which 62 vascular biology genes were evaluated. Single

177   nucleotide polymorphisms in several thrombospondin genes were significantly associated with

178   familial premature MI(Topol et al. 2001).

179   The topics involved in gene research of MI can been delineated in the keywords assigned to

180   each article. Keywords provide a reasonable description of research hotspots, whereas burst words

181   represent new research frontiers(Chen et al. 2014). Adjacent keywords are often assigned to the

182   same articles. For example, in Supplementary Table 6, 'coronary artery disease', 'atherosclerosis',

183   'myocardial infarction', and 'heart failure' are closely related to coronary artery disease, and are

184   different pathophysiology stages of CHD. Gene expression is the synthesis process of gene product

185   which leads to the appearance in the phenotype. There are many gene products being associated

186   with MI, such as microRNA, SDF1 and so on(Boon & Dimmeler 2015; Bromage et al. 2014).

187   Burst words can be detected by CiteSpace, which represent words that are cited frequently in a

188   period of time. As shown in Figure 5, the top 4 burst keywords were as follow, mesenchymal stem

189   cell, oxidative stress, injury, and microRNA. Combined with those keywords with red lines in

190   Figure 4 for further analysis, mesenchymal stem cells (MSCs) transplantation, microRNA and

191   cardiac repair are forefronts of research in recent years. MSCs is a kind of non-hematopoietic stem

192   cell with low immunogenicity, which has become the main cell for MI regenerative therapy(Chou

193   et al. 2014). Many studies showed that MSCs transplantation therapy could have infarct-limiting

194   and cardiac repair effects after MI by revitalizing the cardiac stem cell and revascularization(Russo

195   et al. 2014; Shafei et al. 2017). Paracrine effect of MSCs could be mediated by extracellular

196   vesicles, such as MSCs-derived exosomal microRNA(Huang et al. 2015; Wen et al. 2012). Genetic

197   modified MSCs has been a therapeutic hotspot target for MI, which can promote secretion of

198   paracrine factors to enhance the therapeutic effect(Karpov et al. 2017).

199   As is shown in Figure 6 and Supplementary Table 7, Cluster 0, 1, 4, and 5 play an important

200   role. Cluster 0 (basic-fibroblast growth factor | gene expression profiles) was the largest while

201   Cluster 1 (system biology / cell survival) and Cluster 4 (inflammation / young women) have the

202   most burst cited-articles. The nodes and linkages of Cluster 2 (Chemokine / atherogenesis) and

203   Cluster 5 (cardiac repair) are painted on warm color, and indicated they are the latest research,

204   which is better visualized in Figure 7. Besides the same warm colors, Cluster 2 and Cluster 5 have

205   related overlapping each other, indicating relevance from aspect of literature metrology.

206   Upregulation of chemokines is a hallmark of the inflammatory following MI(Cavalera &

207   Frangogiannis 2014). Some researchers have suggested that chemokines may be potential

208   therapeutic targets to promote wholesome cardiac repair in MI patients(Cavalera & Frangogiannis

209   2014). It just so happens that "young women" appear once again in the Cluster 4 echoing with the

210   previous keywords analysis, hint a hotspot in the gene research of MI(Spatz et al. 2015).

211   There are some limitations in our bibliometric study. The primary source of input data for

212   CiteSpace is the WoSCC, which is more advanced at getting detailed data (e.g. journal sources,

213   author, country and institution information). So, our analysis was performed only with publications

214   in the WoSCC without using multiple search engines (Pubmed, Ovid, Scopus And Google Scholar

215   et al. are not included). In addition, a linguistic bias may exist because most publications in the

216   WosCC were in English.

217

Conclusions

219   In summary, we depicted the scientific output of gene research of myocardial infarction by

220   bibliometric analysis overall. Mesenchymal stem cells Therapy, MSCs-derived microRNA and

221   genetic modified MSCs are the latest research frontiers. Related studies may pioneer the future

222   direction of this filed in next few years. Further studies are needed.

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Figure 1

Map of countries and territories of groups that published articles on the gene research of myocardial infarction during 2001–2015.

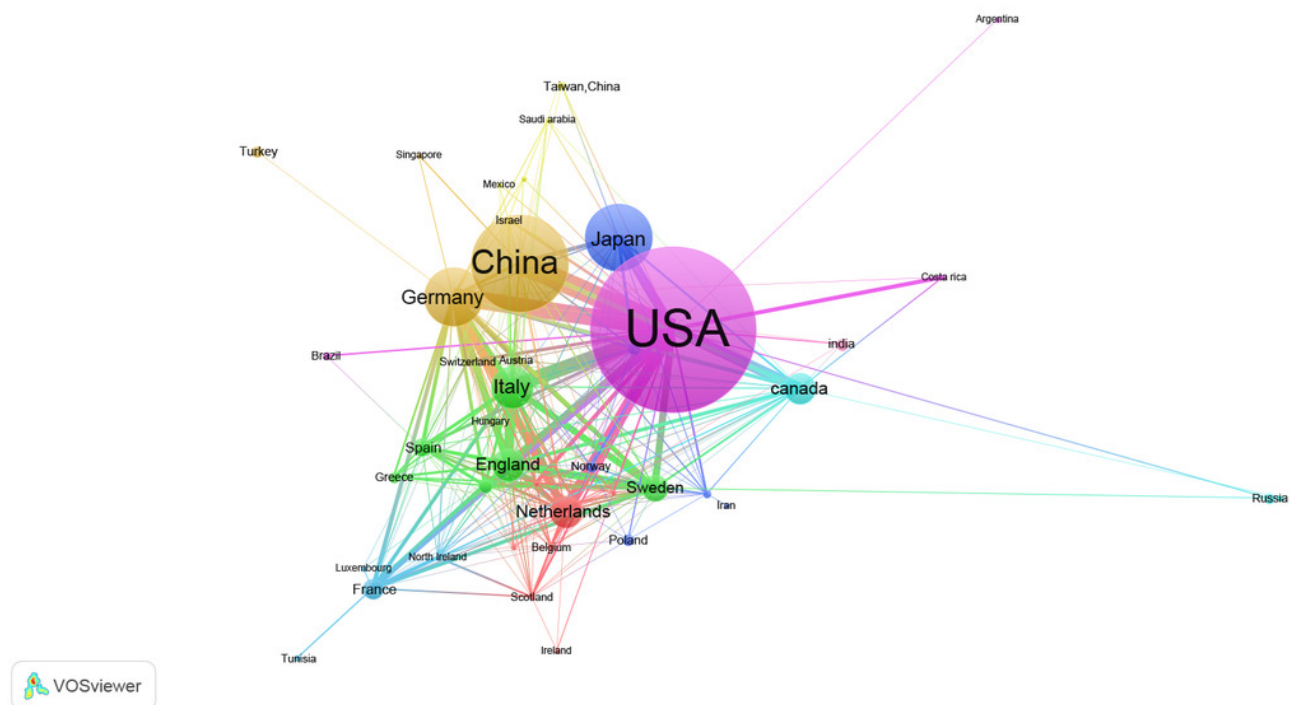



Figure 2

Institutions that published articles on the gene research of myocardial infarction during 2001–2015.

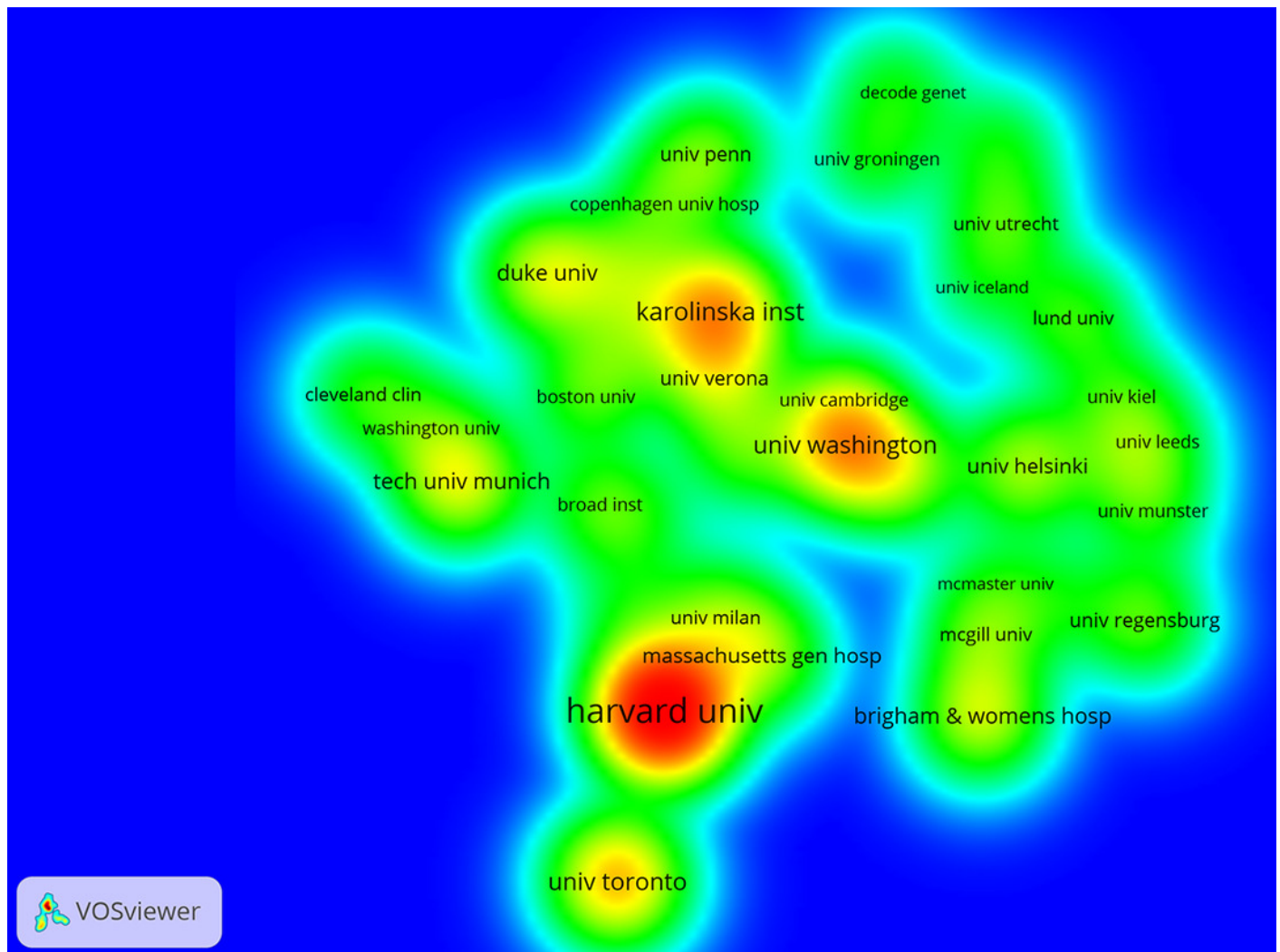



Figure 3

Co-citation map of authors who published articles on the gene research of myocardial infarction during 2001–2015

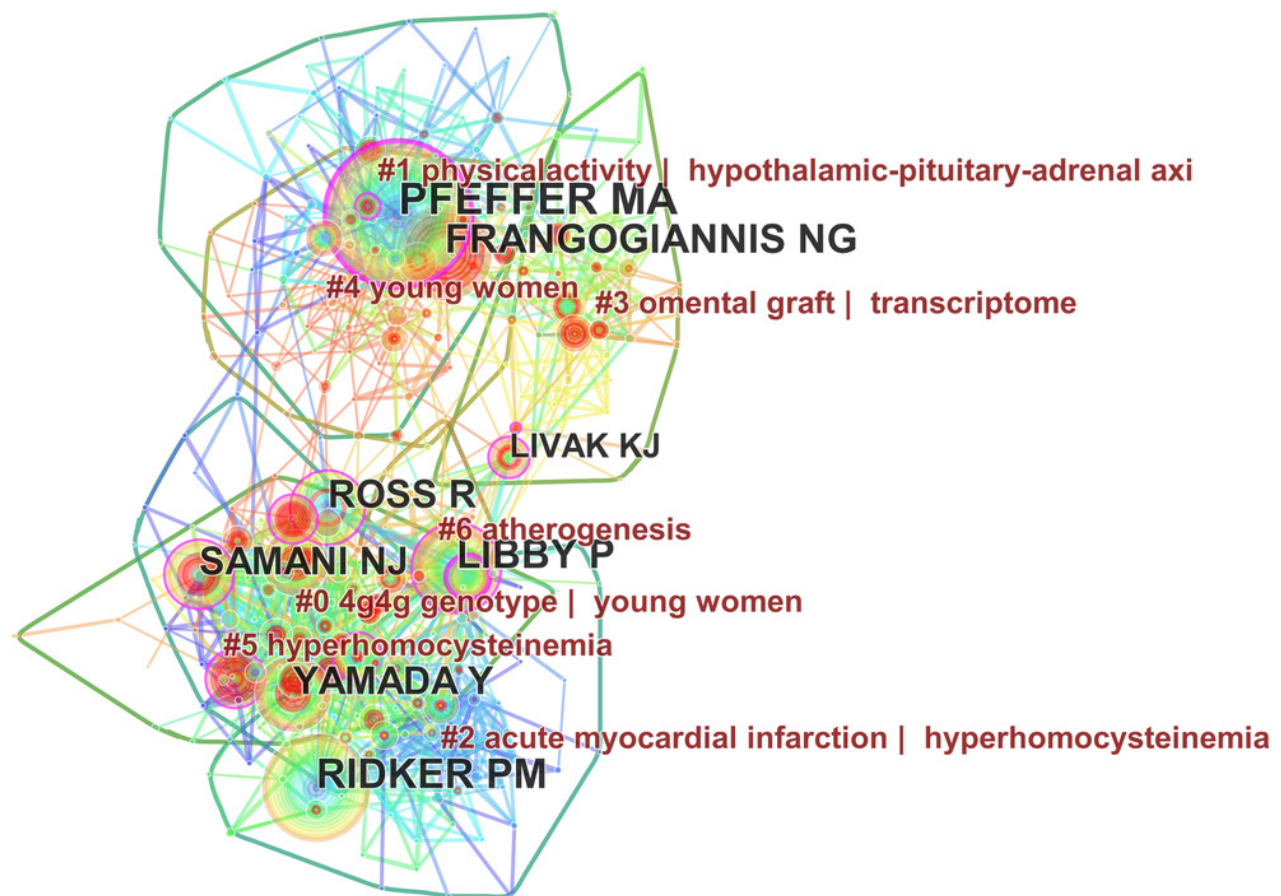



Figure 4

Keywords networks based on articles on the gene research of myocardial infarction during 2001–2015

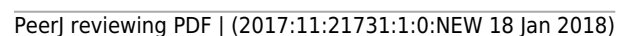



Figure 5

Top 20 keywords with the strongest citation bursts on the gene research of myocardial infarction during 2001–2015

Top 20 Keywords with the Strongest Citation Bursts

Keywords	Year	Strength	Begin	End	2001-2015
cytokine	2001	13.4142	2002	2006	
angiotensin converting enzyme	2001	13.0615	2001	2006	
genetics	2001	11.665	2006	2009	
mutation	2001	10.4072	2001	2004	
mesenchymal stem cell	2001	9.8746	2011	2015	
injury	2001	9.8208	2012	2015	
endothelial growth factor	2001	9.7786	2008	2010	
oxidative stress	2001	9.5117	2012	2015	
microrna	2001	9.1851	2013	2015	
haplotype	2001	9.0539	2006	2009	
congestive heart failure	2001	9.0239	2003	2005	
stem cell	2001	8.908	2010	2012	
cardiac function	2001	8.888	2010	2015	
rat	2001	8.3051	2001	2005	
infarction	2001	8.1902	2001	2005	
remodeling	2001	8.1658	2005	2007	
gene therapy	2001	7.9672	2011	2013	
nitric oxide synthase	2001	7.6665	2006	2007	
gene	2001	7.5736	2001	2003	
angiotensin ii	2001	7.4706	2003	2005	

Figure 6

Reference co-citation map of articles on the gene research of myocardial infarction during 2001–2015

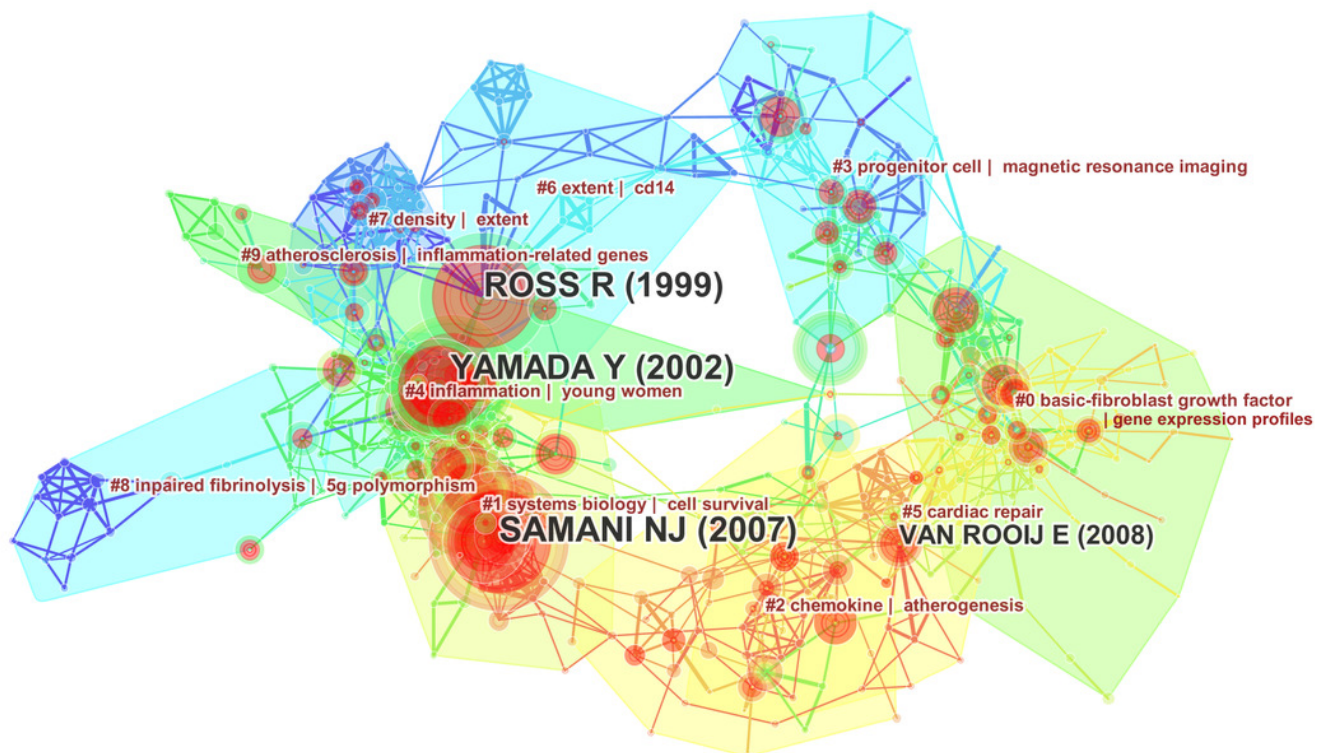
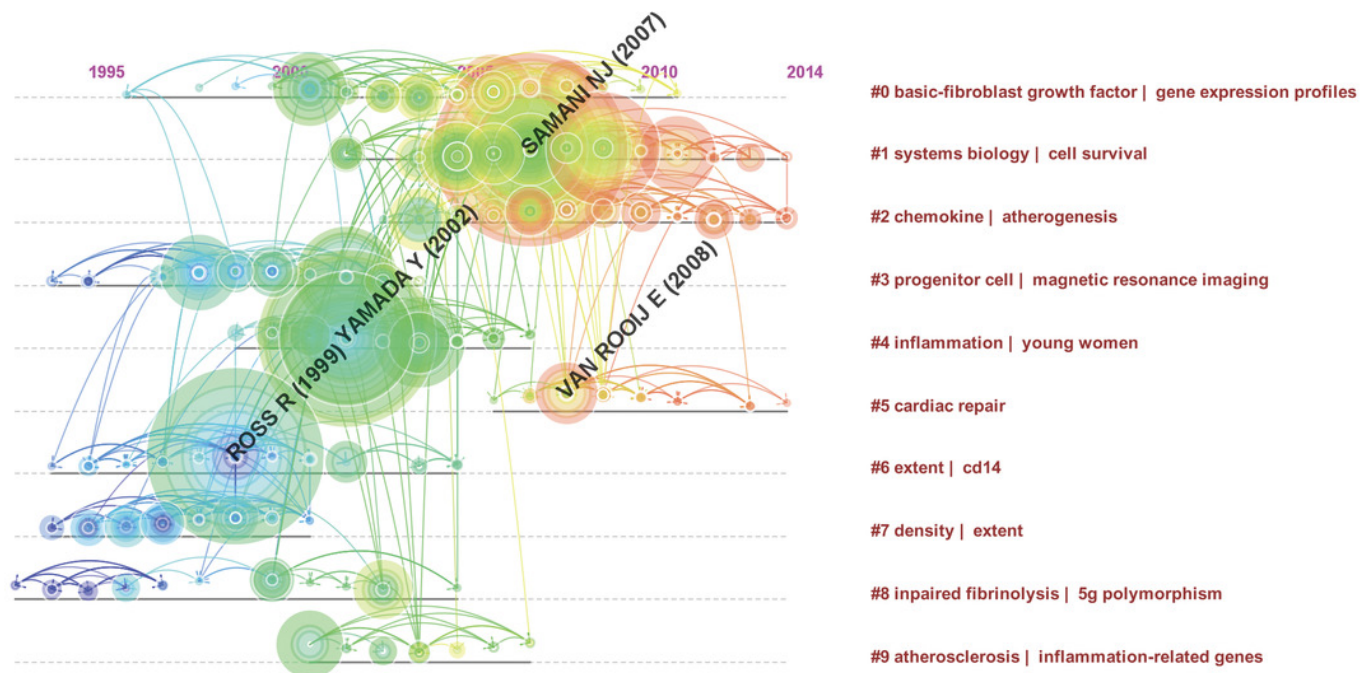



Figure 7

Reference co-citation time-view map of articles on the gene research of myocardial infarction during 2001–2015

Ranking of countries and institutions that published articles on the gene research of myocardial infarction indexed in the Web of Science during 2001–2015

1 **Table 1 Ranking of countries and institutions that published articles on the gene research of**
2 **myocardial infarction indexed in the Web of Science during 2001–2015**

Rank	Country	Counts(%)	Institution	Counts(%)
1	USA	509(27.469)	HARVARD UNIV	88(4.749)
2	CHINA	297(16.028)	KAROLINSKA INST	37(1.997)
3	JAPAN	205(11.063)	UNIV WASHINGTON	35(1.889)
4	GERMANY	180(9.714)	UNIV TORONTO	35(1.889)
5	ITALY	128(6.908)	LEIDEN UNIV	29(1.565)
6	ENGLAND	102(5.505)	HUAZHONG UNIV SCI TECHNOL	28(1.511)
7	NETHERLAND	97(5.235)	KAROLINSKA UNIV HOSP	27(1.457)
8	CANADA	97(5.235)	OSAKA UNIV	25(1.349)
9	SWEDEN	81(4.371)	TECH UNIV MUNICH	24(1.295)
10	FRANCE	62(3.346)	DUKE UNIV	23(1.241)