Identification of protein complexes associated with myocardial infarction using a bioinformatics approach

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Abstract. Myocardial infarction (MI) is a leading cause of mortality and disability worldwide. Determination of the molecular mechanisms underlying the disease is crucial for identifying possible therapeutic targets and designing effective treatments. On the basis that MI may be caused by dysfunctional protein complexes rather than single genes, the present study aimed to use a bioinformatics approach to identifying complexes that may serve important roles in the development of MI. By investigating the proteins involved in these identified complexes, numerous proteins have been reported that are related to MI, whereas other proteins interacted with MI-related proteins, which implied that these protein complexes may indeed be related to the development of MI. The protein complexes detected in the present study may aid in our understanding of the molecular mechanisms that underlie MI pathogenesis.

Introduction

Cardiovascular disease (CVD) is a leading cause of mortality worldwide, and the rates will continue to increase in the coming decades (1). One typical CVD, myocardial infarction (MI; also known as heart attack), causes heart failure or cardiac arrest (2), and leads to millions of mortalities every year in developing countries. Epidemiological studies have shown that high blood pressure, smoking and obesity are leading factors in MI development (3,4). However, the molecular mechanisms of MI, especially its recurrence, remain unclear. Therefore, elucidation of the molecular mechanisms underlying MI is crucial for reducing the risk of recurrence.

Advances in biotechnology have allowed for the successful identification of the genes associated with biomarkers and clinical outcomes regarding high-risk MI. For example, mutations in the myocardial infarction-associated transcript have been reported to cause susceptibility to MI (5). In addition, it was demonstrated that mutations in the oxidized low-density lipoprotein receptor 1 gene may significantly increase the risk of MI (6). Although some MI-related genes have been detected, many were identified independently and functional associations among the genes have rarely been explored. Therefore, it is necessary to investigate MI from a systematic perspective, as the complex disease was reported to occur due to the dysregulation of functional gene sets (7). A previous study reported that the examination of protein complexes may provide a better understanding not only of cellular functions, but also human diseases (8). For instance, the BRAFT protein complex was reported to be involved in Fanconi anemia and Bloom Syndrome (9). The mammalian target of rapamycin complex 1 serves a crucial role in hematopoiesis, hematopoietic differentiation and leukemogenesis (10). In addition, one previous study revealed that the proteins in complexes may be responsible for diseases (11). Therefore, identification of the dysfunctional protein complexes may aid our understanding of the molecular mechanisms of MI. However, the protein complexes associated with MI have not been fully investigated.

The present study proposed a bioinformatics approach to identify protein complexes associated with MI development and recurrence (Fig. 1). Based on the gene expression profiles associated with MI, dysfunctional complexes that may be involved in MI were identified, followed by functional enrichment analysis on the protein complexes detected. Combined with previous data, the present study revealed that some proteins from the complexes were related to MI, which suggested an important role for these protein complexes in the molecular mechanism of MI.

Materials and methods

Data set. MI gene expression data set (GSE48060) was obtained from the Gene Expression Omnibus depository (12). The data set contains 52 samples, comprising 21 normal, 26 nonrecurrent and 5 recurrent samples. The normal samples had no previous history of cardiac diseases or other comorbidities, the nonrecurrent samples are the first-time patients with MI, whereas recurrence referred to those patients with any

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recurrent events within 18-months following the initial treatment. All expression values were pre-processed with Robust Multi-array Average (13). The expression value of a gene associated with multiple probes was calculated as the average expression value of all related probes. Gene expression profiles were normalized with mean 0 and standard deviation 1.

The protein complexes and protein-protein interactions were retrieved from the Human Protein Reference Database (HPRD) (14). Functional enrichment analysis of genes in each protein complex was performed by DAVID (15), which is an online tool for understanding biological functions behind a list of genes.

Identification of differentially expressed genes (DEGs). Genes that are differentially expressed between two conditions may be related to the condition and therefore may help explain how the differences occurred. In the present study, the data set was divided into three groups: Normal, Nonrecurrent and Recurrent. The differentially expressed genes between the three groups were detected by Student's t-test with a P-value cutoff of 0.01. As a result, 793 (normal vs. recurrent), 871 (normal vs. nonrecurrent) and 423 (recurrent vs. nonrecurrent) DEGs and their corresponding t-scores were obtained.

Identification of MI-related protein complexes. Protein complexes are groups of proteins that interact with each other, which are fundamental functional units of the macromolecular systems. 1,521 protein complexes were obtained from the HPRD database with detailed protein annotations. By following the work of Liu *et al* (16), a score S_c was defined for each complex to measure its relevance to the development of MI.

$$S_c = \frac{\sum_{i=1}^{N} T_i}{N}$$

where N denotes the number of genes in the complex c, and T_i represents the t-score of gene i calculated by Student's t-test using the gene expression data between two different groups.

To verify that the MI-related complexes were not detected by chance, for each complex, a gene set was randomly picked with the same number of genes as that in the complex, and for each gene set, a score was calculated with the aforementioned equation. This procedure was repeated 10,000 times and the P-value was defined as the frequency of the gene set score larger than S_c for the corresponding complex. Subsequently, the complex was identified as related to MI if P<0.01. In particular, only complexes that have at least 10 proteins were considered in the present study.

Results and Discussion

Protein complexes comprising multiple proteins are essential cellular functional units. Instead of focusing on a single gene, the present study aimed to identify the protein complexes that may serve important roles in MI. Therefore, protein complexes comprising genes that were differentially expressed among the normal, recurrent and nonrecurrent groups were regarded to serve important roles in MI. On this basis, the protein complexes that were significantly different among the three MI groups were identified and the functions of those complexes were also investigated (Fig. 1).

Table I. Protein complexes that are significantly different among the three myocardial infarction groups.

Normal_ Recurrent	Recurrent_ Nonrecurrent	Normal_ Nonrecurrent
COM_1553	COM_1553	COM_1553
COM_2750	COM_2750	COM_2750
COM_2322	COM_1422	COM_1648
COM_1422	COM_1427	
COM_1427	COM_1426	
COM_970	COM_970	
COM_2286	COM_1505	
COM_2287	COM_2286	
COM_2302	COM_2287	
COM_2296	COM_2322	
COM_2298	COM_3000	
COM_1661	COM_3014	
COM_1688	COM_2296	
COM_1685	COM_2998	
COM_33	COM_242	
COM_2796	COM_1661	
COM_2967	COM_33	
	COM_2796	
	COM_2967	

Identification of protein complexes associated with MI. Gene expression data and protein complex annotations were used to detect 17, 19 and 3 complexes as significantly different between normal vs. recurrent, recurrent vs. nonrecurrent and normal vs. nonrecurrent, respectively. Table I provides information about the protein complexes that are different among the distinct groups; protein complexes used in the present study were named and obtained from the HPRD database. A Venn diagram of the three sets of protein complexes detected for each of the three groups was created (Fig. 2A), which revealed that numerous complexes are shared among the three sets. In addition, DEGs were identified by Student's t-test with a cutoff of P<0.01. As a result, 793, 871 and 423 genes were detected to be differentially expressed in the comparison of normal vs. recurrent, normal vs. nonrecurrent and recurrent vs. nonrecurrent, respectively (Fig. 2B). It was noted that 31, 9 and 21 DEGs from the three above comparisons, respectively, belonged to protein complexes. With the functional annotations of protein complexes to which the DEGs belong, it was possible to investigate the molecular mechanisms of MI from another perspective.

The results demonstrated that some protein complexes are differentially expressed across different stages of MI; for example, COM_1553 and COM_2750. Other protein complexes, such as COM_1426 and COM_1505, are specifically differentially expressed between recurrent and nonrecurrent groups. Only three protein complexes were

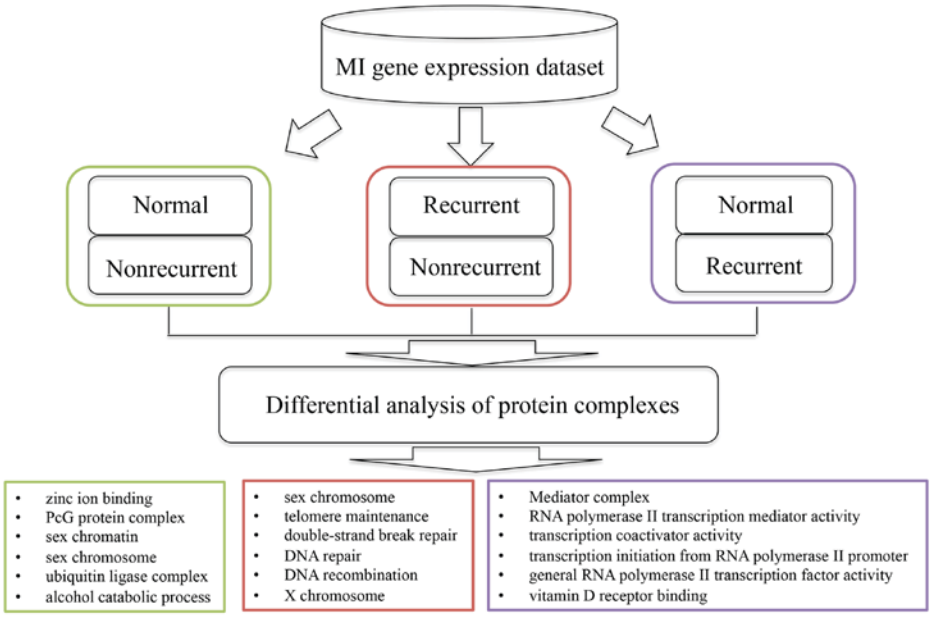

Figure 1. Flowchart for detecting protein complexes related to MI. MI, myocardial infarction; PcG, polycomb group.

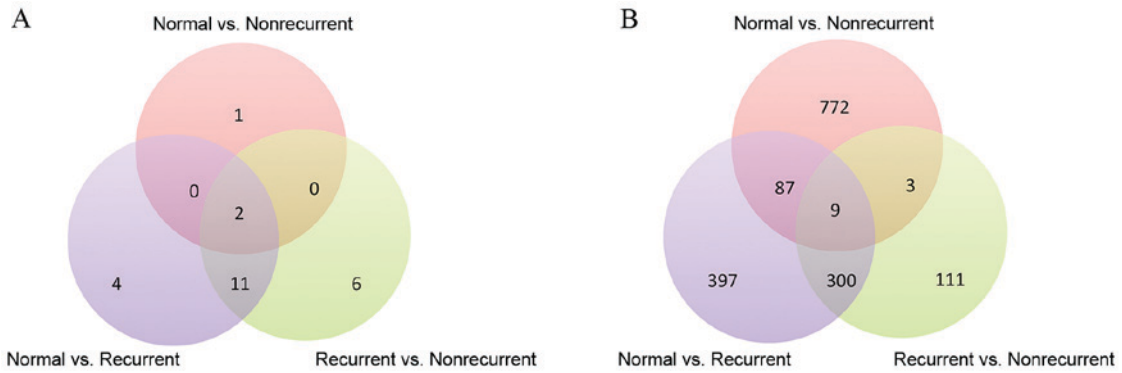

Figure 2. Comparison of three groups. (A) Venn diagram of detected protein complexes between Normal vs. Recurrent, Normal vs. Nonrecurrent and Recurrent vs. Nonrecurrent. (B) Venn diagram of differentially expressed genes among the three groups.

detected to be significantly different between normal and nonrecurrent groups, two of which were also detected in the comparisons of other groups. The small number of protein complexes detected between normal and nonrecurrent groups may be explained as no significant differences between these two groups from the perspectives of molecules. This suggested that MI patients in the absence of recurrence may restore to full health at greater rates compared with MI patients with recurrence. The functions of those proteins involved in the three complexes and their enriched biological processes and pathways were also examined (Table II). The biological function annotations were identified from the Gene Ontology database and the pathway information is from the Kyoto Encyclopedia of Genes and Genomes database; functional enrichment analysis was performed with DAVID for each complex to determine the biological processes associated with these protein complexes. For protein complex COM_1648, which was differentially expressed only between normal and nonrecurrent groups, several over-represented biological processes have been detected to be associated with MI. For example, it was reported that oxidized lipids and proteins, as well as decreased antioxidant levels catalyzed by iron and copper, may be detected in human atherosclerotic lesions (17). One previous study proposed that zinc may displace iron and copper from oxidation-vulnerable sites to limit the atherosclerotic damage (18). Another study suggested that the polycomb-group complex serves a central role in the regulation of heart development and functions (19). With an increased understanding of ubiquitin ligases in cardiac disease, a number of studies have emphasized the role of ubiquitin ligases in heart disease. For instance, it was reported that specific ubiquitin ligases may serve a role in the processes of cardiac hypertrophy and atrophy (20), and the potential therapeutic target roles of ubiquitin ligases in MI have also been demonstrated (21). In addition, it has been reported that microRNA (miRNA) miR-99a and let-7c promoted cardiomyogenesis by upregulating their target genes, whereas SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member identified in COM_1648 in the present study is a target gene of let-7c (22). These findings suggested that the complexes detected by the present study may be associated with MI.

Table II. GO function and KEGG pathway enrichment analysis of genes from protein complexes that differ between Normal and Nonrecurrent groups.

Category	Term	P-value
GOTERM_MF_FAT	GO:0008270~zinc ion binding	3.45×10^{-03}
GOTERM_CC_FAT	GO:0031519~PcG protein complex	4.69×10^{-03}
GOTERM_CC_FAT	GO:0001739~sex chromatin	6.56×10^{-03}
GOTERM_CC_FAT	GO:0000803~sex chromosome	7.02×10^{-03}
GOTERM_CC_FAT	GO:0000151~ubiquitin ligase complex	4.15×10^{-02}
GOTERM_CC_FAT	GO:0005829~cytosol	1.10×10^{-12}
GOTERM_BP_FAT	GO:0006096~glycolysis	2.14×10^{-07}
GOTERM_BP_FAT	GO:0046164~alcohol catabolic process	3.33×10^{-06}
GOTERM_BP_FAT	GO:0051789~response to protein stimulus	3.58×10^{-03}
KEGG_PATHWAY	hsa04530:Tight junction	8.35×10^{-03}

GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; MF, molecular function; CC, cellular component; BP, biological process; PcG, polycomb group.

Table III. GO function and KEGG pathway enrichment analysis of protein complexes that differ between Recurrent and Nonrecurrent groups.

Category	Term	P-value
KEGG_PATHWAY	hsa05322:Systemic lupus erythematosus	1.58×10^{-05}
GOTERM_CC_FAT	GO:0001739~sex chromatin	7.31×10^{-05}
GOTERM_CC_FAT	GO:0000803~sex chromosome	8.43×10^{-05}
GOTERM_BP_FAT	GO:0000723~telomere maintenance	3.18×10^{-04}
GOTERM_BP_FAT	GO:0032200~telomere organization	3.41×10^{-04}
GOTERM_BP_FAT	GO:0006302~double-strand break repair	1.56×10^{-03}
GOTERM_BP_FAT	GO:0006281~DNA repair	2.24×10^{-03}
GOTERM_BP_FAT	GO:0006310~DNA recombination	4.40×10^{-03}
GOTERM_CC_FAT	GO:0000805~X chromosome	4.69×10^{-03}
GOTERM_BP_FAT	GO:0033554~cellular response to stress	1.52×10^{-02}
GOTERM_CC_FAT	GO:0005853~eukaryotic translation elongation factor 1 complex	3.91×10^{-03}
GOTERM_BP_FAT	GO:0008380~RNA splicing	1.43×10^{-02}
GOTERM_CC_FAT	GO:0005829~cytosol	1.47×10^{-02}
GOTERM_MF_FAT	GO:0003723~RNA binding	1.51×10^{-02}

GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; CC, cellular component; BP, biological process; MF, molecular function.

Identification of protein complexes associated with MI recurrence. By investigating the protein complexes that were detected between recurrent and nonrecurrent groups, the enriched biological processes and pathways were identified (Table III), some of which were strongly implicated in MI, such as systemic lupus erythematosus. In addition, it has been reported that patients with systemic lupus erythematosus have an increased risk of CVD (23,24). It has been reported that the incidence rates of coronary heart disease exhibit differences according to sex, whereas the potential role of the sex chromosomes has been unexplored to date. Recent studies have shown that the sex chromosomes serve critical roles in the difference in myocardial injury between the sexes (25,26). In the present study, the over-represented cellular components of the protein complexes were significantly enriched in sex chromatin, sex chromosomes and X chromosomes, which suggested an association between these complexes and MI. As shown in Table III, the protein complexes are also enriched in DNA repair and telomere dysfunction. It was demonstrated that the DNA repair genes, such as nei-like DNA glycosylase 3, were also associated with increased risk of MI (27,28). Furthermore, telomere dysfunction has also emerged as an important factor in the molecular mechanism of heart failure and the telomere-associated proteins were reported to be involved in cardiovascular pathobiology (29,30). These findings confirm that the proteins we detected here are indeed related to MI.

Protein complexes were also detected between normal and recurrent groups, and their enriched functions are listed

Table IV. GO function and KEGG pathway enrichment analysis of protein complexes that differ between Normal and Recurrent groups.

Category	Term	P-value
GOTERM_CC_FAT	GO:0016592~Mediator complex	$7.25x10^{-29}$
GOTERM_MF_FAT	GO:0016455~RNA polymerase II transcription mediator activity	$2.47x10^{-22}$
GOTERM_MF_FAT	GO:0003713~transcription coactivator activity	$3.78x10^{-21}$
GOTERM_BP_FAT	GO:0006367~transcription initiation from RNA polymerase II promoter	$5.07x10^{-21}$
GOTERM_MF_FAT	GO:0016251~general RNA polymerase II transcription factor activity	$6.14x10^{-20}$
GOTERM_MF_FAT	GO:0042809~vitamin D receptor binding	$3.39x10^{-17}$
GOTERM_MF_FAT	GO:0046966~thyroid hormone receptor binding	$4.64x10^{-16}$
GOTERM_MF_FAT	GO:0003702~RNA polymerase II transcription factor activity	$1.24x10^{-15}$
GOTERM_BP_FAT	GO:0030521~androgen receptor signaling pathway	$1.72x10^{-15}$
GOTERM_BP_FAT	GO:0006366~transcription from RNA polymerase II promoter	$1.85x10^{-15}$
GOTERM_MF_FAT	GO:0051427~hormone receptor binding	$8.56x10^{-13}$
GOTERM_BP_FAT	GO:0006461~ transcription regulator activity	$6.95x10^{-11}$

GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; CC, cellular component; MF, molecular function; BP, biological process.

Table V. GO Functional enrichment analysis of overlapped protein complexes between normal vs. recurrent and nonrecurrent vs. recurrent.

Category	Term	P-value
GOTERM_BP_FAT	GO:0008380~RNA splicing	$5.90x10^{-29}$
GOTERM_CC_FAT	GO:0030529~ribonucleoprotein complex	$3.66x10^{-22}$
GOTERM_MF_FAT	GO:0003723~RNA binding	$2.80x10^{-08}$
GOTERM_CC_FAT	GO:0005686~snRNP U2	$8.48x10^{-06}$
GOTERM_CC_FAT	GO:0005829~cytosol	$1.40x10^{-09}$
GOTERM_BP_FAT	GO:0032268~regulation of cellular protein metabolic process	$3.75x10^{-02}$
GOTERM_CC_FAT	GO:0005730~nucleolus	$1.71x10^{-03}$
GOTERM_BP_FAT	GO:0006281~DNA repair	$4.85x10^{-02}$
GOTERM_BP_FAT	GO:0042254~ribosome biogenesis	$2.26x10^{-11}$
GOTERM_CC_FAT	GO:0015934~large ribosomal subunit	$4.79x10^{-11}$
GOTERM_CC_FAT	GO:0022625~cytosolic large ribosomal subunit	$1.01x10^{-10}$
GOTERM_BP_FAT	GO:0042273~ribosomal large subunit biogenesis	$1.35x10^{-04}$
GOTERM_CC_FAT	GO:0044452~nucleolar part	$1.35x10^{-03}$
GOTERM_MF_FAT	GO:0003684~damaged DNA binding	$2.38x10^{-03}$
GOTERM_CC_FAT	GO:0015935~small ribosomal subunit	$7.20x10^{-03}$
GOTERM_BP_FAT	GO:0006974~response to DNA damage stimulus	$4.48x10^{-02}$
GOTERM_BP_FAT	GO:0007049~cell cycle	$6.93x10^{-24}$
GOTERM_MF_FAT	GO:0016887~ATPase activity	$5.67x10^{-06}$

GO, Gene Ontology; BP, biological process; CC, cellular component; MF, molecular function; snRNP, small nuclear ribonucleoprotein.

in Table IV, in which only the processes related to heart disease, particularly MI, are listed for clarification. These data indicated that the protein complexes were mainly enriched in RNA polymerase II-associated activities. A recent study have revealed that many of the CVD-associated mutant genes were involved in transcription regulation, whereas RNA polymerase II serves a key role in catalyzing the transcription of DNA to mRNA, small nuclear RNA and miRNA (31). It has also been determined that vitamin D receptor was able to reduce oxidative stress and inhibit apoptosis in the MI injury, which suggested that the receptor may be an attractive target for the treatment of heart disease (32). These results may help us further understand the roles of protein complexes in heart disease and gain more insights into MI.

The overlapped protein complexes identified in both normal vs. recurrent and nonrecurrent vs. recurrent

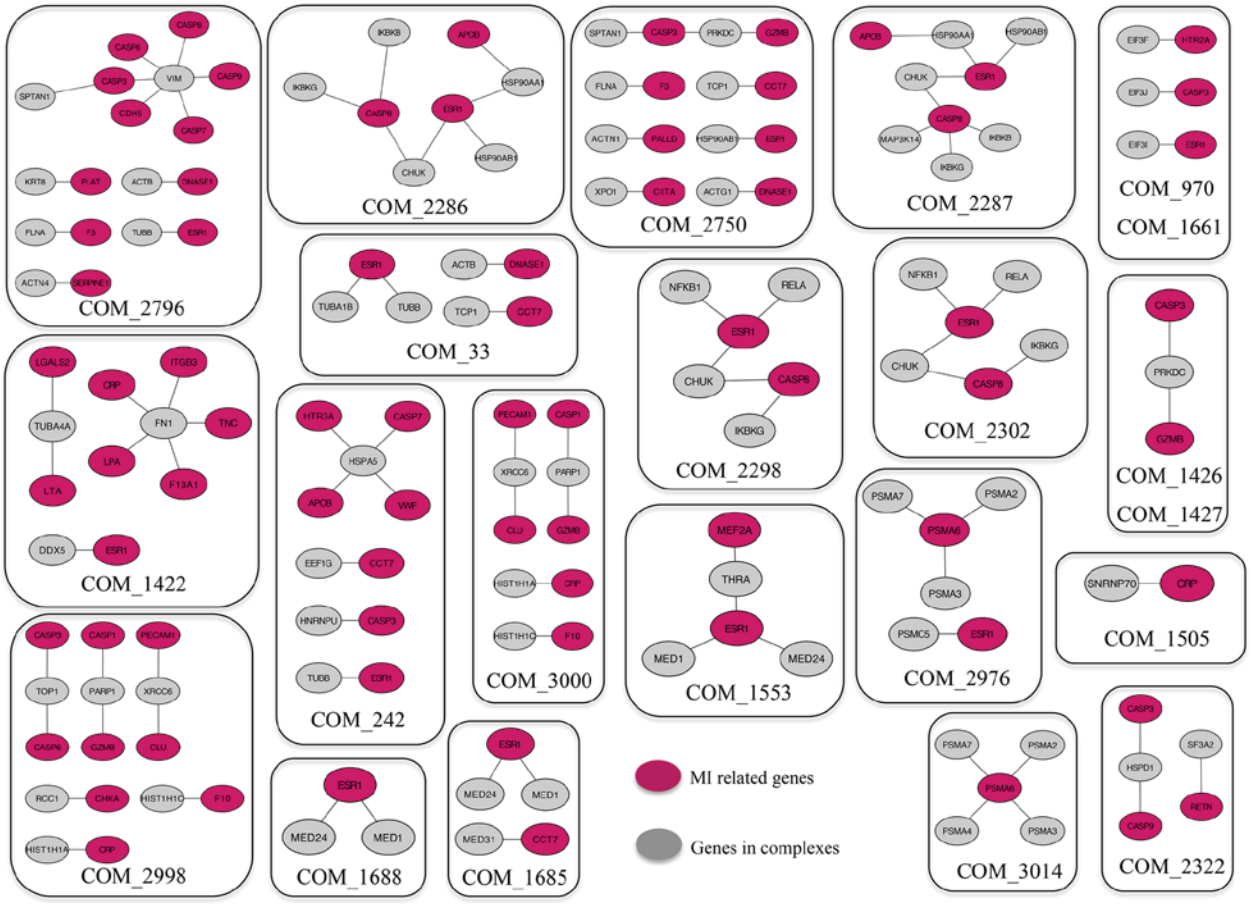

Figure 3. Interactions between MI-related genes and proteins which form the complexes detected. Red nodes represent MI-related genes; grey nodes represent genes from complexes. MI, myocardial infarction.

comparison were investigated further, as these complexes were considered to be important in the recurrence of MI. Examination of the enriched functions of these protein complexes revealed that some of them were related to MI or heart disease (Table V). For example, aberrant RNA splicing has been reported in heart diseases (33,34); DNA damage and repair in atherosclerosis, which may lead to MI, have also been reported, which suggested a novel mechanism of MI (33). The release of DNA resulting from damaged binding has also been reported to be associated with MI (35), and DNA-binding dyes, such as Hoechst, have been used to bind exposed DNA and target injured myocardium (34,36). Furthermore, previous studies have reported that cardiomyocyte cell cycle activation may restore and enhance functions in injured hearts after MI (37,38).

Results from these functional enrichment analyses indicated that the protein complexes detected by the present study may serve important roles in promoting the development and recurrence of MI. Although a number of enriched pathways were identified, only a partial list of the known pathways related to MI are presented in this study for clarification, where those novel pathways may provide new insights into the molecular mechanism underlying MI.

Identification of MI-associated genes. In addition to the functional enrichment analyses of the protein complexes aforementioned, the genes encoding proteins from each complex were investigated to determine if they are related to MI. Previous studies have revealed that several genes were identified in the complexes that have been previously reported to be relevant to cardiac disease. For example, it was reported that the genes in the mediator of RNA polymerase II transcription (MED) complex, such as MED1, MED12, MED13, MED14, MED23 and MED30, serve important roles in CVD initiation and progression (39). In addition, mutations in MED13 have been reported to be linked to CVDs and mutations in MED30 were suggested to be important in CVD progression (31).

The present study identified 114 MI-associated genes ranked by their relevant score from the GeneCards database (40). Examination of these genes in the protein complexes identified by the present study revealed that numerous genes have been previously reported related to MI. For example, mutations in proteasome subunit α6, a proteasome that regulates the inflammation processes, have been demonstrated to be a risk factor of MI (41,42). In addition, the chaperonin-containing TCP1 subunit 7 (CCT7) gene may severely impair soluble guanylyl cyclase activity (43). A recent study determined the relationship between impaired soluble guanylyl cyclase-dependent nitric oxide signaling and MI risk, and suggested that CCT7 may be a new therapeutic target for MI (44).

The verification of the above genes in the protein complexes related to MI as described above implied that the

protein complexes detected may be related to MI disease. In addition, the complexes that were identified as significantly different among the three groups, but in which no MI-related genes were found, were also examined to determine whether the proteins from these complexes interacted with known MI-related genes. Among the 24 complexes identified, proteins from 22 complexes exhibited interactions with MI-related genes (Fig. 3), which indicated that these proteins may also be related to MI and the corresponding complexes may be important in MI development. For example, caspases have been implicated in the molecular mechanism of MI (45,46); heat shock protein family D, member, conserved helix-loop-helix ubiquitous kinase and eukaryotic translation initiation factor 3 subunit J have been reported to interact with caspases, such as caspase (CASP)3, CASP8 and CASP9, which suggested that these genes may also be related to MI (43). In summary, several proteins from the complexes identified by the present study were validated to be related to MI, implying that the corresponding complexes may be related to the development of MI.

In conclusion, MI is the leading cause of mortality worldwide. Elucidation of the molecular mechanisms underlying MI may aid in better prevention of development of the disease and in designing more effective treatments. Protein complexes composed of multiple proteins are functional units of complex biological systems, the dysfunction of which often leads to diseases. In the present study, a bioinformatics approach was used to identify the protein complexes associated with MI. Functional enrichment analysis demonstrated that the protein complexes detected may serve important roles in MI. Investigations of the proteins in the detected complexes implied that some of the proteins have already been reported as related to MI, whereas other proteins interacted with known MI genes, which indicated that the protein complexes detected are indeed important in MI. The protein complexes detected here may improve our understanding of the molecular mechanisms underlying MI, and may be used as biomarkers in the future.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. The public dataset GSE48060 can be obtain from Gene Expression Omnibus (GEO) database.

Authors' contributions

NJ, FY, YQ, CL and HL analyzed and interpreted the patient data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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