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藉由蛋白質網絡探討脊髓肌肉萎縮症和脊髓側索硬化症的關聯性

Comparative analysis of condition-specific protein interaction networks between spinal muscular atrophy and amyotrophic lateral sclerosis

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中文摘要

脊髓型肌肉萎縮症和脊髓側索硬化症是由運動神經元退化及伴隨肌肉萎縮的致命性疾病，雖然兩者的致病突變基因不同，但兩者間有共同表現的症狀。為了探討兩疾病間可能的共同致病機制，我們分別建立了脊髓型肌肉萎縮症和脊髓側索硬化症的差異化蛋白質共表現網絡(DCPINs)。我們在此利用gene ontology將有差異的蛋白質網絡做功能上的分群，接著我們討論講疾病間模組的關係性。藉由結合靜態的蛋白質網絡以及mRNA的基因表現量的分析，我們找到了錯誤的蛋白質交互作用可能會導致細胞中鈣離子循環失控。我們發現對抗鈣離子及熱所導致的細胞壓力有關的蛋白質交互作用。此外，我們也找到和蛋白質ubiquitination與proteasome降解相關的蛋白質交互作用。同時我們進一步發現和ATP生成相關之缺失的蛋白質作用也出現在粒線體複合體I, III及V，並加以進行探討。參與RNA剪接作用的蛋白質snRNPs的一部分組成蛋白-七環Sm蛋白，也在兩個疾病中被發現有較低的相關性並可能進階導致snRNPs生成的失敗。在本篇論文中，我們認為這兩疾病的肌肉中所產生的細胞壓力，於疾病發生時可能扮演了很重要的角色。

關鍵字：脊髓型肌肉萎縮症、脊髓側索硬化症、差異化蛋白質共表現網絡、壓力、鈣離子的失調、ubiquitination、proteasome的蛋白質降解、ATP、和RNA的剪接作用

Abstract

Spinal muscular atrophy (SMA) and amyotrophic lateral sclerosis (ALS) are two devastating diseases caused by motor neuron degeneration and accompanied with muscle weakness. Though the mutated genes causing SMA and ALS are different, some of the phenotypes are the same in both diseases. To understand the possibility of common and dysregulated mechanisms between SMA and ALS, differentially co-expressed protein interaction networks (DCPINs) are constructed in SMA and ALS respectively. Gene ontology analysis is applied to help us realize the functions of these disrupted protein interactions. Both SMA and ALS related modules were further isolated and discussed. By means of integrative analysis using static protein interaction network and the microarray gene expression profiles, perturbed protein interactions involving in calcium cycling were found in this study. The possible responses against stress caused by calcium and thermogenesis were also discovered. Furthermore, we identified the protein interactions associated with protein ubiquitination and proteasomal degradation. Additionally, we found the defective protein interactions engaged in path of ATP synthesis of mitochondrial protein complex I, III and V and have further discussion. Proteins involved in RNA splicing were also found and showed the potential deformity in heptameric ring consisted of Sm proteins during formation of snRNPs. In this study, we suggest that the stress induced in the muscle of SMA and ALS might play an important role in the pathology of both diseases.

Keyword: SMA, ALS, DCPINs, module, stress, calcium dysregulation, ubiquitination,

proteasomal degradation, ATP, and RNA splicing

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Chapter 1 Introduction

1.1 Motor neuron diseases

The motor neuron diseases (MNDs) are neurological disorders that selectively affect motor neurons controlling voluntary muscle activity. Spinal muscular atrophy (SMA) and amyotrophic lateral sclerosis (ALS) are the two devastating MNDs, where SMA is one of the most severely infantile and genetic disease, and ALS is the ultimately fatal disease with a fast progression in mid-age adults [1, 2]

1.1.1 Spinal muscular atrophy

Spinal Muscular Atrophy (SMA) is an autosomal recessive disease which occurs in approximately 1 in 10000 new born babies, which is one of the most common genetic disease in infant mortality [3]. SMA is characterized by degeneration in motor neuron in the spine and by atrophy of skeletal muscle. Survival motor neuron gene 1 (*SMN1*), a SMA-determining gene, is usually homozygous deleted or mutated in most of the SMA patients [4, 5].

SMA is categorized into type I, II, III and IV, depending on the age of onset and clinical progression [4]. Type I SMA (Werdnig-Hoffmann disease) is the most severe class and diagnosed with muscle weakness and hypotonia within 6 months of birth. SMA type I patients are unable to walk and sit unaided. Type II SMA (Dubowitz Disease) is the intermediate class with an onset of weakness within 18 months of age, patients with SMA type II disease are able to sit independently and walk with assistance. Type III SMA (Kugelberg-Welander Disease) is the mild class with an onset of symptoms after 18 months of age, they can walk normally until they lost the ability later in life. The patients in type IV SMA are characterized with an onset age

older than 30-years-old as well as the mildest manifestation.

It has been reported that the copy number of *SMN2* gene, which is nearly identical to *SMN1*, modifies the severity of phenotype [6]. *SMN2* copy numbers are inversely correlated to SMA types. The major difference between *SMN1* and *SMN2* is that *SMN1* gene produces full-length transcripts; in contrast, *SMN2* gene mainly produces alternatively spliced transcripts, *SMN△7* (Figure 1) [7]. In short, full-length functional SMN protein produced by *SMN2* unable to overcome the loss of transcripts of *SMN1* leading to SMA.

Currently, there are two hypotheses for the SMN deficiency lead to SMA: 1) SMN complex consisting of SMN, Gemin2-8 and unrip is characterized to engage in ATP-dependent snRNPs assembly [8, 9]. The dysfunction of snRNPs assembly might play a major role in SMA pathology. 2) SMN proteins are important for neurite outgrowth, neuromuscular maturation and axonal transportation [10, 11]. Thus, down-regulated SMN expression may lead to selective degeneration of motor neuron with unclear mechanism.

1.1.2 Amyotrophic lateral sclerosis

The epidemiologic measures of disease frequency of Amyotrophic lateral sclerosis (ALS) is about 0.3 to 7 in 100000 each year [12]. ALS is categorized into two groups: familial inherited ALS (called fALS) and non-familial history discovered ALS (called sporadic ALS, sALS). There are about 10% of fALS and 90% of sALS cases are discovered in a survey of the literature [13]. ALS is a neurodegenerative disease and is fatal because of its fast death rate of motor neuron in the brain, brainstem and spinal cord after onset.

ALS is a multiple causing disease, mutation in RNA binding proteins such as superoxide dismutase 1 (*SOD1*), fused in sarcoma (*FUS*/ *TLS*) or TAR DNA binding protein (*TARDBP*) was found in ALS patients [14-18].

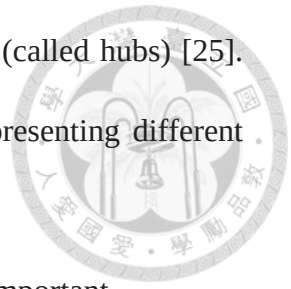
Mutated SOD1 enzyme links to toxic gain with generation of free radical and eventually leads to cell death [19, 20]. FUS and TDP-43 proteins are both involved in transcription, splicing and other processes in nuclear and cytoplasm [21]. Therefore, part of ALS may interact with protein function in splicing and leads to motor neuron degeneration.

1.1.3 Interaction between SMA and ALS

Several studies have suggested the relationship between SMA and ALS in molecular levels. SMN complex is localized in nuclear Gems and cytoplasmic compartment [22], and loss of Gems is a hallmark in SMA. Gems are also found to be losing in motor neurons of the *TDP43* knockout mouse that is the common model for studying ALS [23]. Yamazaki and his colleagues showed that aggregated FUS mutant protein could trap SMN protein and caused SMN distribution imbalanced in nuclear and cytoplasmic, which might drive motor neuron death [24]. From these studies, we learned that SMA and ALS might be related to motor neuron diseases, but the correlation between SMA and ALS is still unclear and being mapped.

1.2 Protein interaction network

Protein-protein interactions (PPIs) are one of the central roles in biological processes. PPIs can be constructed into protein interaction networks (PINs) and give us a relative macroscopic view in molecular mechanism. Protein connectivity of the PINs follows power-law distribution indicating that the most connected protein has less



abundance in comparison to small amounts of high degree protein (called hubs) [25]. PINs can be mined into smaller and meaningful modules that representing different functions [26, 27].

Topological properties of the discovered conditional PINs are important indications and can help us choose interesting targets. Higher degrees of the proteins (nodes) tend to be more important and less abundant in the PINs. Clustering coefficient represents whether the neighbors of a particular protein are closely connecting or not. Betweenness and closeness centrality show that if the interesting protein can be centers of the clusters existing in the PIN.

1.3 Microarray analysis

Microarray have been applied in lots of analyses and is a powerful technique for high-throughput exploration of gene expression profiles [28-30]. The quantification and quantitation of gene expression profiles are based on nucleotide hybridization and fluorescence detection.

Integrating microarray expression profile with PIN is able to discover biomarkers in subnetworks which has been shown to provide more accurate result than simply search for differentially expressed genes in a previous study [31].

1.4 Integrative analysis of protein interaction network

Though PINs contain all static information, not all proteins interact at the same time. Active PPIs depend on the protein expressions. To discover the complicated processes in cells, PINs can be served as backbone to construct condition-activated PINs.

To systemically discuss between SMA and ALS, we combined PINs with

microarray profiles to construct differentially co-expressed PINs (DCPINs) of SMA and ALS against normal (Figure 1). Due to the shortage of proteome data, so we used mRNA expression values to represent protein expression profiles in our study.

To further discuss whether there is any biological process involved in motor neuron degeneration or muscle atrophy, we try to mine functional modules by classifying these DCPINs with gene ontology (GO). Finally, we would like to find the common and different mechanisms leading to SMA and ALS.

Chapter 2 Materials and methods

2.1 Human protein interaction network

PINs was downloaded and integrated from 5 online databases [32-36]. Followings are the detail information of collected PPIs: MINT (2013-3-26), BIOGRID (2014-12-1, version: 3.2.119), DIP (2014-10-1), HPRD (2010-3-13, version: release 9) and IntAct (2014-11-10).

Followings are the principles for construction of human PIN backbone. First, we only retained human PPIs (taxID: 9606). Second, all protein identifiers (uniprotKB, refseq, and ensemble) were mapped to Entrez gene IDs and symbols (mapping information are collect from NCBI) and unknown/unmapped identifiers were filtered out. Third, PPIs with self interactions and duplication were removed to keep PIN backbone non-redundant.

2.2 mRNA expression profiles

The SMA and ALS mRNA expression profiles were obtained from Gene Expression Omnibus (GEO). 9 SMA samples (18 cDNA microarrays containing technical repeat of each patient with dye swap labeling), GSE8359 [37], and 9 ALS and 18 normal samples (Affymetrix chip of HG-U133A), GSE3307 [38, 39], were all muscle biopsies and used in my study.

R package ‘limma’ was applied to do background correction (RMA algorithm) and intra-array normalization (loess) for GSE8359 [40]. R package ‘affy’ was used for background correction (RMA algorithm) in GSE3307 [41]. R package ‘preprocessCore’ was used to do between-array normalization in both datasets independently [42].

The expression values of replicate probes were averaged. In order to keep

maximum information from both chips, the probes related to multiple genes were reserved and the genes were assigned with the same values for further network analysis.

2.3 Construction of differentially co-expressed PIN

2.3.1 Spearman's correlation coefficient

Before direct calculating Spearman correlation coefficient (SCC), we need to replace the expression values with rank numbers. SCC of paired genes (X and Y) that encode proteins in PIN is defined as following:

$$SCC(X,Y) = 1 - \frac{6\sum d_i^2}{n(n^2-1)} \quad ,where\ d_i = Xi - Yi$$

Where n is the number of sample of the target (9 SMA, 9 ALS or 18 normal); Xi and Yi are rank-transformed expression values of gene X and Y in different sample of target. The larger the absolute value of SCC is, the higher the correlation between the calculated gene pairs is.

2.3.2 Differentially co-expressed PIN

After calculating SCC values of SMA, ALS and normal independently, the SCC is converted to Z-score with Fisher's transformation listed as following equation. Then we want to find the differentially co-expressed PPIs (DCPPIs, P< 0.05) between diseases and normal, by means of finding the significant Z-score differences ($\text{Z-score}_{disease} - \text{Z-score}_{normal}$) between disease and normal.

$$Z - score = \sqrt{\frac{n-3}{1.06}} \times \frac{1}{2} \times ln\frac{1+SCC}{1-SCC} \quad ,where\ n = sample\ numbers$$

The significant P value derived from Z-score difference between diseases and normal were found by permutation test, which is applied to check if DCPPIs were

found by chances or not. In short, the gene expression values of gene A and B found in PPIs, were random ordered independently in disease and normal for 10000 times. Then the random Z-score and Z-score difference of disease and normal were calculated in each shuffling. P value is defined as the proportion of random Z-score differences that are bigger (or smaller) than the originally positive (or negative) Z-score difference.

Here, differentially co-expressed PIN (DCPIN) is defined as the set of DCPPIs found in the disease. SMA and ALS DCPINs are constructed individually and used for further analysis in this study.

Further more, DCPPIs with Z-score larger (smaller) than or equal to 1.96 (-1.96) were defined as positive (negative) correlation in all study groups (SMA, ALS and normal). DCPPIs with Z-score within -1.96 and 1.96 were non-correlated. To see what types of the DCPPIs were found in both DCPINs, DCPPIs were classified into 5 groups (Figure 3): gain of negative correlation (GoN), loss of positive correlation (LoP), loss of negative correlation (LoN), gain of positive correlation (GoP) and others (other_P, other_N, PP and NN).

2.4 Identification of disease-specific functional modules

To mine functional modules in DCPINs, gene ontology (GO) was used to find what biological processes are enriched and whether there is any biological process involved in muscle atrophy or motor neuron degeneration with node and edge-based hypergeometric tests.

2.4.1 Gene ontology

We used the gene annotation by Gene Ontology (GO) [43] for the functional classification of DCPINs. In GO, the genes in each term are predefined gene sets.

There are three ontology categories in GO, namely biological process, molecular function, and cellular component, but we only considered biological process GO for our analysis. The information of GO terms and its consisted genes are built by R package 'org.Hs.Eg.db' [44]. There were 18083 unique genes (in gene IDs) and 12565 unique GO terms.

2.4.2 Hypergeometric test

The normal hypergeometric distribution (node based GO enrichment) is defined as following:

$$P(X \geq k) = \sum_{k}^{min(m,n)} \frac{\binom{m}{k}\binom{N-m}{n-k}}{\binom{N}{n}}$$

X: the evaluated functional category in GO; N: genes appeared in our microarray and PPIs; m: genes we are interested with (e.g. genes found in disease DCPIN); n: numbers of gene in X. The formula calculates the over-represented probability of the evaluated functional category containing k genes in the network.

To further obtain denser functional subnetworks, we used an edge based functional enrichment as our previous study [27]. By considering whether PPIs in disease DCPIN are also enriched in the same evaluated functional categories. To achieve this analysis, we just required to change all the parameters from inputs of genes to inputs of DCPPIs for modified hypergeometric test as following:

$$P(X \geq k_e) = \sum_{k_e}^{min(m_e,n_e)} \frac{\binom{m_e}{k_e}\binom{N_e-m_e}{n_e-k_e}}{\binom{N_e}{n_e}}$$

X: the evaluated functional category in GO; N_e: all collection of GO annotated PPIs; m_e: DCPPIs found in disease DCPIN; n_e: numbers of PPIs in X. The formula

calculates the over-represented probability of the evaluated functional category containing k DCPPIs in the network.

FDR (Benjamini & Hochberg) is applied to correct P values [45]. GO functions whose FDR< 0.05 in both node and edge based methods are remained.

2.4.3 Enrichment map

To help us overall look for what functions were major enriched in our study, enrichment map was built as followings. First, we isolated common GO terms enriched in both SMA and ALS DCPINs. Second, we pooled enriched genes in each node based function. Third, we calculated the similarity between GO terms. The similarity values are manipulated as mean of Jaccard and Simpson indexes. Followings are formulas of Jaccard (J_{AB}) and Simpson (S_{AB}) indexes:

$$J_{AB} = \frac{|N(A) \cap N(B)|}{|N(A) \cup N(B)|} \quad , \quad S_{AB} = \frac{|N(A) \cap N(B)|}{\min(|N(A)|, |N(B)|)}$$

Here, A and B are two different GO terms, |N(A)| and |N(B)| which means numbers of genes in A and B independently.

2.4.4 Modules

Common GO functions with higher GO level are considered as our particular targets in both SMA and ALS. DCPPIs in some of these functions are isolated and considered as modules and being further discussion.

2.5 Network properties

Some basic network properties are calculated in this study by ‘networkx’ [46]. For protein interaction network, nodes represent proteins and edges are PPIs. Followings are topological parameters used to help us pick important targets in the PIN.

2.5.1 Degree

Degree (k) means the numbers of linkages of the node in the network. As for the PIN, proteins with high degree are called ‘hubs’.

2.5.2 Clustering coefficient

Clustering coefficient (C) of a protein means how frequently of its linking proteins interact with each other. It is defined as:

$$Ci = \frac{e_{NB_j}}{C_2^{NB_j}}$$

where e_{NBj} is the number of interactions between interacting partners of protein *i*, and NB_j is the numbers of its interacting partners. C_2^{NBj} represents the numbers of all possible interactions between its interacting partners.

2.5.3 Betweenness centrality

Betweenness centrality (BC) indicates the centrality of a protein i in the PIN, and it is defined as:

$$BC_i = \frac{SP_i}{C_2^N}$$

here, SP_i means the number of the shortest path passing through protein i, and protein N is the number of proteins in PIN.

2.5.4 Closeness centrality

Closeness centrality (CC) represents how close a protein is against all the others and it is defined as the reciprocal of the mean of the shortest path lengths (SPL_i) for protein i to all reaming proteins in PIN.

$$CC_i = \frac{1}{SPL_i}$$

Chapter 3 Results

To obtain the as complete human protein interaction networks as possible, we compiled PPIs from five databases with latest version. After merging these databases and removing the redundancies, we obtained a human PIN with 197124 interaction and 16541 proteins. Because we performed a GO enrichment analysis for further identification of functional modules, the interacting proteins with the annotated GO terms were named as GO annotated PPIs. This process resulted in 166520 GO annotated PPIs containing 12797 proteins.

The raw SMA and ALS gene expression data obtained from GEO were normalized and pre-processed (Figure 4-6). After preprocessing, a total of 2732 common genes existed in SMA, ALS and normal. Among the common genes, 2270 genes were found to form 20276 PPIs and be used for further SCC calculation..

Next, we integrated PIN and gene expression information to identify differentially co-expressed PINs (DCPIN) of SMA and ALS. The differentially co-expressed PPIs might provide the insight into the pathogenic mechanisms of these two diseases. We could compare the DCPIN to investigate the relationship between SMA and ALS.

3.1 Identification of dysregulated PPIs in SMA and ALS

To avoid the outlier effects on correlation measurement, we used Spearman correlation coefficient to measure the correlations of interacting pairs. The Z-score distributions (Fisher's z transformed SCC) of SMA, ALS and normal are shown as Figure 7.

To get the differentially co-expressed PPIs (DCPPIs), the Z-score difference between disease and normal were calculated. The histogram of Z-score difference

between SMA and ALS against normal is illustrated as Figure 8. Those PPIs passing permutation test ($P < 0.05$) are called DCPPIs and form as a DCPIN. The overall information of both DCPINs were summarized in Table 1 and Table 2.

DCPIN of SMA contains 3770 interactions and 1588 gene, and DCPIN of ALS contains 3761 interactions and 1572 genes. 1329 common genes (72.58%) are found in DCPINs of SMA and ALS, and 1313 common DCPPIs (21.12%) are found (Figure 9). The results showed that SMA and ALS might share parts of commonly dysregulated processes. Additionally, there are more loss-of-coexpression (either loss of positive correlation or loss of negative correlation) in both diseases (SMA and ALS DCPPIs: 47.21% and 44.96%), showing that losing correlation might play slightly more effect on both diseases.

To overall look at the topological structures of SMA and ALS DCPINs, the network properties of SMA and ALS DCPINs were investigated independently. Both DCPINs follow power-law distributions (Figure 10, a) and those genes with higher degree might be important for SMA and ALS. Top 1% higher degree genes are list in Table 3 & 4. Though these genes with higher degree seem to be less clustered structure (Figure 10, b), they are close to center in both DCPINs (Figure 10, c&d).

We then explored the network properties of 1313 common DCPPIs (composed with 1003 genes) between SMA and ALS. The genes with top 1% degree are list in Table 5. These genes might play important role in connections between SMA and ALS.

3.2 Recognitions of enriched modules

GO annotation were used to classify the DCPINs into modules and help us to

understand what processes do these DCPPIs get involved in each DCPIN. As our previous study, node and edge based (“dyads”) GO enrichments were used to identify the significantly GO terms (FDR< 0,05 in both methods) [27].

GO are used to find functions in DCPINs of SMA and ALS independently with both node and edge based hypergeometric test. GO terms passed FDR< 0.05 with both node and edge based enrichments were collected as our primarily interesting targets. There were 177 and 223 terms enriched in SMA and ALS DCPINs individually.

There are 165 common GO terms in both diseases. To overall look at these biological processes, GO enrichment map was built for visualization (showed as Figure 11). The common and more specified GO functions are listed in Table 6. GO terms, such as ‘muscle system process’, ‘proteasome-mediated ubiquitin-dependent protein catabolic process’, ‘respiratory electron transport chain’ and ‘RNA spicing’, which might be related to pathogenic mechanisms of SMA and ALS were identified. DCPPIs existing in these four GO terms were isolated and become our targeting modules.

Chapter 4 Discussion

By analysis of DCPINs of SMA and ALS, GO terms of common or different DCPPIs were identified in this study. Most specified GO terms (highest levels of GO) mined from clusters in the enrichment map are our targets (Figure 11; Table 6). In our studies, we especially discussed four particular modules that might relate to the SMA and ALS functions.

4.1 'Muscle system process'

First of all, muscle system process that regulates contraction and relaxation of muscle fibers are investigated in our study due to the phenomenon of muscle twitch/ fasciculation in SMA and ALS [47-49].

There are total of 27 (34 genes) and 26 (34 genes) DCPPIs in the module of 'muscle system process' from DCPINs of SMA and ALS (Figure 12; Table 7). The network structures of this module are different in both diseases (Table 8). *ACTN2*, *TNNI1* and *TTN* (k=3) are the top three genes with highest degree in SMA group. In contrast, *TTN* (k=5), *TNNI2* (k=4), *TNNT1* and *ACTA1* (k=3) are the genes with higher degree in ALS group.

11 common DCPPIs are identified in this module, and two of them are responsible for an important role in controlling muscle movement and stress response. Recent SMA and ALS studies discover the disruption of calcium pathway in both motor neurons and skeletal muscles [50, 51]. Calcium is released from sarcoplasmic (endoplasmic) reticulum (SR/ER) to cytoplasm when action potential is transmitted from the motor neuron to the muscle, which causes muscle contraction. When calcium is finally recaptured back to SR, the muscle relaxation occurs.

Furthermore, when *SLN* (Sarcolipin) binds to *ATP2A1* (Sarcoplasmic/ endoplasmic reticulum calcium ATPase 1, SERCA1), it inhibits calcium translocation from cytoplasm to lumen of SR followed by thermogenesis [52]. Interestingly, we found the gain of positively correlated DCPPI of *ATP2A1* and *SLN* in this module that might give us the insight for calcium remaining in cytoplasm and disrupting muscle relaxation in SMA and ALS.

TTN (titin) is a crucial protein that involved in muscle movement. It is the largest spring-like protein served as an anchor for myosin, stretches as muscle excitation and relaxation [53]. A chaperone of small heat shock protein, *CRYAB* (alphaB-crystallin), is shown to retain stabilize and refold *TTN* back once stress is detected or not [54]. DCPPI of *TTN* and *CRYAB* is also found to be gain of positive correlation. This interaction might imply the response of dysregulated calcium (prolonged muscle contraction or heat generation) might occur in SMA and ALS.

4.2 'Proteasome-mediated ubiquitin-dependent protein catabolic process'

Proteasome degradation has been reported in many motor neuron diseases including SMA and ALS [55-57]. There are 92 (62 genes) and 98 (61 genes) enriched DCPPIs in the module of 'proteasome-mediated ubiquitin-dependent protein catabolic process' from DCPINs of SMA and ALS (Figure 13; Table 9). Network topologies of this module are listed in Table 10. For SMA group, *PSMD4* (k=10), *RAD23A* and *UBC* (k=8) are the top three nodes with highest degrees in this module. And, the top four high degree nodes are *UBC* (k=16), *PSMC4* (k=11), *PSMD4* and *PSMD6* (k=8) in ALS group.

RAD23A (UV excision repair protein RAD23 homolog A) was first found to get involved in nucleotide excision repair [58]. Besides DNA repair mechanism, *RAD23A* also contains both ubiquitin associated (UBA) and ubiquitin-like (UBL) domains that has been suggested to play a role in protein degradation. UBA domain of *RAD23A* has been shown to interact with poly-ubiquitinated proteins and being shuttle to transport the poly-ubiquitinated proteins to the proteasome subunit, *PSMD4* (S5a/ RPN10) that recognize the UBL domain of *RAD23A* for protein degradation [59, 60]. We found that *RAD23A* is the highest degree of 9 DCPPIs in SMA DCPINs in this module. The role of *RAD23A* and its substrates for proteasome degradation should be further explored in SMA.

35 common DCPPIs found in this module, most of which are derived from high-throughput experiments and containing protein complex interactions. We only discuss the common DCPPIs with proves of direct interaction here.

The process of ubiquitin-dependent and proteasome-mediated degradation requires poly-ubiquitin to be added onto specified lysine sites of a protein and then the proteolysis can be performed in 26S proteasome (Figure 14). Three enzymes are involved in the ubiquitination: E1 (ubiquitin-activating enzyme), E2 (ubiquitin-conjugating enzyme) and E3 (ubiquitin ligase).

STUB1 (CHIP, a E3 ligase), gained positive correlation with *UBE2D3* (a E2 enzyme) might indicate the increases of ubiquitination for the substrates (proteins) of *STUB1* and *UBE2D3* in both diseases. However, STUB1 decreased interact with *PSMD4*, the polyubiquitin receptor sites for recognition of proteolysis, in SMA and ALS. We come up with two possible hypotheses for this phenomenon. First, this

might imply that the substrates of *STUB1* are monoubiquitinated or incomplete polyubiquitinated proteins that are unable to be recognized by proteasome for degradation. Second, these polyubiquitinated proteins would aggregate in the cells.

In previous study, when *CLU* and *HSPA5* (GRP78) interacted together, it tends to bind to an unfolded protein which partially prevent cell apoptosis caused by ER stress in hepatocellular carcinoma cells [61]. We found that *CLU* and *HSPA5* gain positive correlation in ALS, which indicates the activation of ER stress caused by calcium cycle disruption or protein aggregation.

Similarly, in our study, *HSP90B1* is lost of positive correlation with *UBC*, a poly-uqbiquitin precursor in both SMA and ALS. This shows that *HSP90B1* could not be degraded easily and might be responsible for dysregulated calcium homeostasis, heat stress or trap the accumulated proteins in SMA and ALS.

4.3 'respiratory electron transport chain'

Decreasing of activities in mitochondrial complexes has been found in both SMA and ALS in the previous studies [62-64].

There are 23 (28 genes) and 27 (28 genes) enriched DCPPIs in the module of 'respiratory electron transport chain' from DCPINs of SMA and ALS (Figure 15 and Table 11). Detail network structures are listed in Table 12. *NDUFA2* (k=7), *ATP5B* (k=4) and *CYCS* (k=3) are the genes with higher degree in SMA. *ATP5B*, *ATP5F1*, *ATP5C1*, *UQCRQ*, and *SDHA* (k=4) are the highest degree genes in ALS.

The DCPPIs found here are mainly in the subunits of complexes that involved in respiratory electron transport chain (oxidative phosphorylation) and located at the mitochondrial inner membrane. The roles of these complexes (I, II, III, IV, V) are

summarized and illustrated in Figure 16.

For SMA group, the DCPPIs (*NDUFA2 – NDUFA8*; *NDUFA2 - NDUFB11*; *NDUFA9 – NDUFV1*; *NDUFS1 - NDUFS2*; *NDUFS6 – NDUFS8*) identified here are dysregulated in the complex I, and lost of positive correlation comparing to normal. These might cause decreasing amount of proton gradients and reductive form of UQ, and eventually reduce the rate of ATP synthesis.

For ALS group, there are 3 DCPPIs gaining of positive expression between SDHA (a member of complex II) and *NDUFS6*, *NDUFS8*, *NDUFV2* (subunits of complex I) in ALS group. A previous study showed that supercomplex formation between complex I and III, and IV but not complex II as we found in this module [65]. These three DCPPIs were discovered by high-throughput data of soluble complex and identified as co-fraction [66]. Therefore, these PPIs might not really exist. In contrast, there are 4 DCPPIs composed in complex V (*ATP5A1 – ATP5C1*; *ATP5A1 – ATP5F1*; *ATP5B – ATTP5C1*; *ATP5B – ATP5F1*) which might cause defects in ATP synthesis.

There are 8 common DCPPIs, and 6 DCPPIs are lost of positive correlation among them. They are major dysregulated in complex I (*NDUFA2 – NDUFA9*; *NDUFA2 – NDUFA13; NDUFA2 – NDUFB7*), and complex III (*CYC1 – CYCS*; *CYC1 – UQCR10*). Moreover, we found that *CYC1* and *CYCS* lost positive correlation or from positive to negative correlation in ALS and SMA. *CYC1* captures electron from UQH2 and passes it to *CYCS* in complex III. Lost of positive correlation of *CYC1* and *CYCS* might prevent the reduction of oxygen to water and reduce proton gradient.

The components for decreasing of ATP synthesis in mitochondrial complex are

different in SMA and ALS. Complexes I might major involve in SMA group and Complex V might major involve in ALS group. Complex III might involve in both SMA and ALS.

4.4 RNA splicing

As our expectation, we identify modules related to 'RNA splicing' because one role of SMN protein is to help snRNPs assemble for splicing [67, 68].

There are 109 (85 genes) and 102 (76 genes) DCPPIs in module of 'RNA splicing' derived from DCPINs of SMA and ALS (Figure 17 and Table 13). 39 common DCPPIs are found among them.

The network properties of this module are listed in Table 14. *HNRNPK* (k=9), *SFPQ* and *SRRM1* (k=7) are the genes with higher degree in this module for SMA group. In contrast, *SMN2*, *HNRNPU* (k=10), and *YBX1* (k=9) are the higher degree nodes in ALS.

Small nuclear ribonucleic proteins (snRNPs) are consisted of snRNAs, heptameric Sm proteins (Sm B/B', D1, D2, D3, E, F and G) and other associated proteins to form spliceosome (U1, U2, U4, U5, U6) that are involved in pre-mRNA splicing. SMN complex (SMN and Gemin 2-8) is helped to co-operated with other related protein complexes. A review paper showed detail process of spliceosome formation and the splicing processes [68].

Disrupted formation of snRNPs' biogenesis has been studied in SMA patients [69]. *SNRPD1* (Sm D1), *SNRPD2* (Sm D2), *SNRPE* (Sm E), *SNRPF* (Sm F) and *SNRPG* (Sm G) are members of heptameric Sm proteins, which are parts of mature snRNP (U1, U2, U4, U5). *LSM3*, *LSM5*, *LSM7* and *LSM8* are members of heptameric

Sm proteins consisted in U6. We find that these 5 DCPPIs (*SNRPD1 - SNRPE*; *SNRPD2 - SNRPF*; *SNRPE – SNRPG; LSM3 – LSM7*; *LSM5 –LSM8*) are either lost of positive correlation or gain of negative correlation in both diseases, which might imply the defects in formation of snRNPs.

Recent studies showed that some alternative splicing mRNAs is due to SMN deficiency that might play an important role in SMA and ALS pathology. So, it is important to screen more deeply with RNA-seq to include effects of alternative splicing.

Results found in this thesis are summarized in Figure 18.

Chapter 5 Conclusion

By analyzing disease specified DCPINs, we found the common and dysregulated PPIs which might shed light on the connection between common phenotypes in SMA and ALS. The gain of interaction between *SLN* and *ATP2A1* showed the possible mechanism leading to irregulation of calcium cycle in both SMA and ALS. The stress responses might further prove the importance in temporal regulation of calcium in SR and cytoplasm. Besides, deregulations in protein ubiquitination and proteasomal degradation were also found in SMA and ALS, and the chance leading to further protein aggregation should be concerned.

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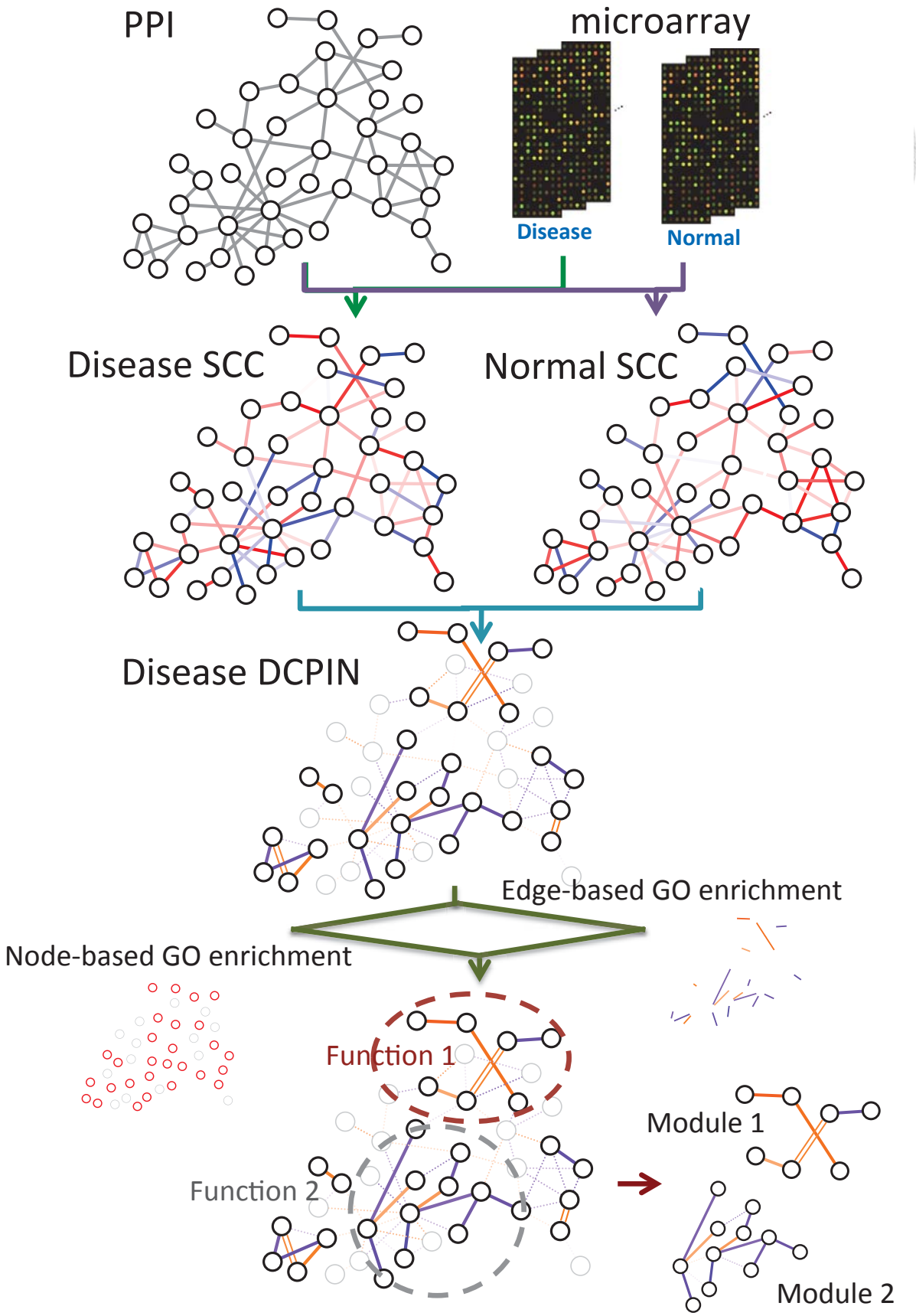

Figure 1. Experimental design. To construct disease specified differentially co-expressed PIN (PIN), we integrate PIN and microarray by manipulating the SCC and SCC differences in SMA and ALS individually. To further mine functional modules, GO were used to classify the functions of theses dysregulated PPIs.

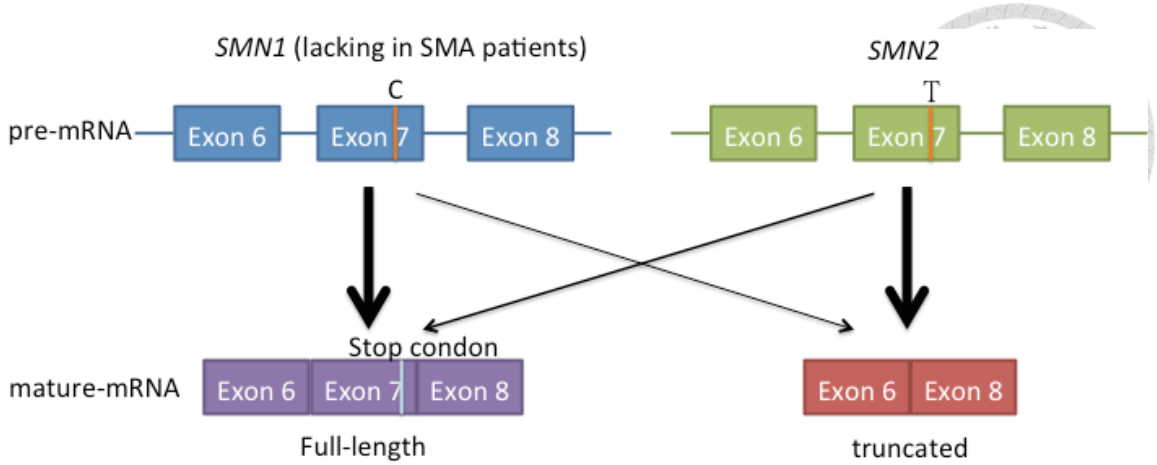

Figure 2. Comparison between *SMN1* and *SMN2*. The alternative splicing mechanism of transcripts made from *SMN1* and *SMN2* is major due to a single nucleotide difference in exon7. *SMN1* can produce near 100% of mature full-length SMN mRNA. However, *SMN2* produces high percentage of truncated SMN transcript lacking exon7 (SMNΔ7). Only small amounts of full-length SMN mRNA are produced by *SMN2* in SMA patients.

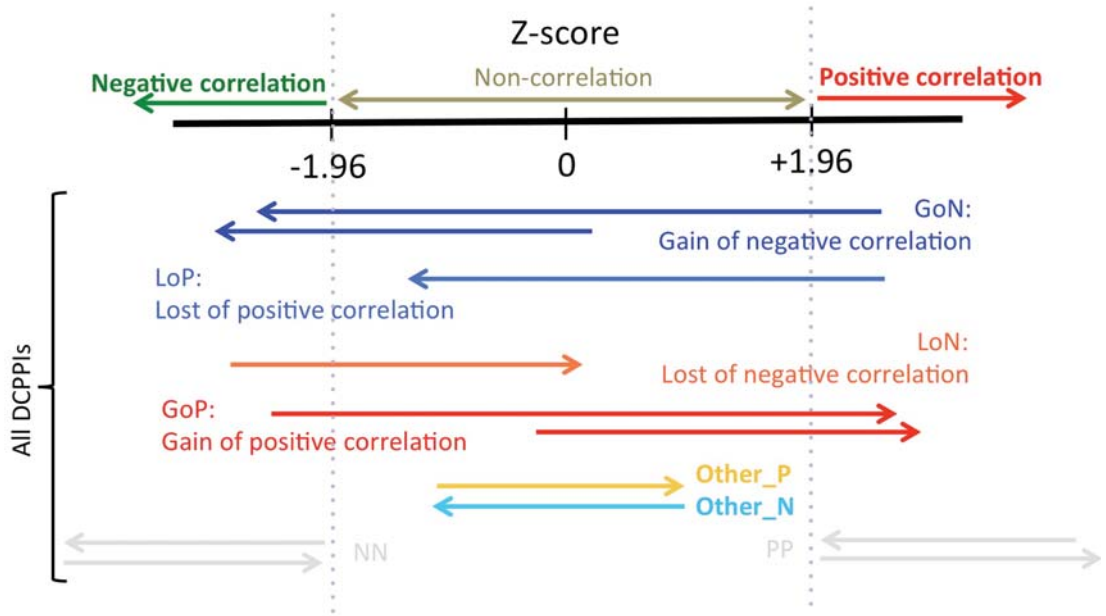

Figure 3. Illustration of DCPPIs groups classification. DCPPIs with Z-score larger (smaller) than or equal to 1.96 (-1.96) were defined as positive (negative) correlation in all study groups (SMA, ALS and normal). DCPPIs with Z-score within -1.96 and 1.96 were non-correlated. DCPPIs were classified into: gain of negative correlation (GoN), loss of positive correlation (LoP), loss of negative correlation (LoN), gain of positive correlation (GoP) and others (other_P, other_N, PP and NN). *Arrow direction: from disease (arrow head) to normal

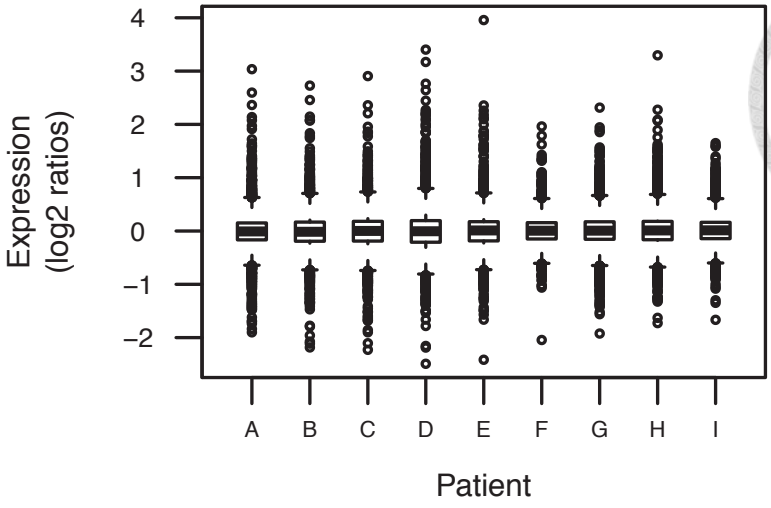

Figure 4. Expression values of SMA. After normalization, common gene expression values are averaged. Then relative expression values were log2 transformed. (ratio: SMA intensity/ control intensity)

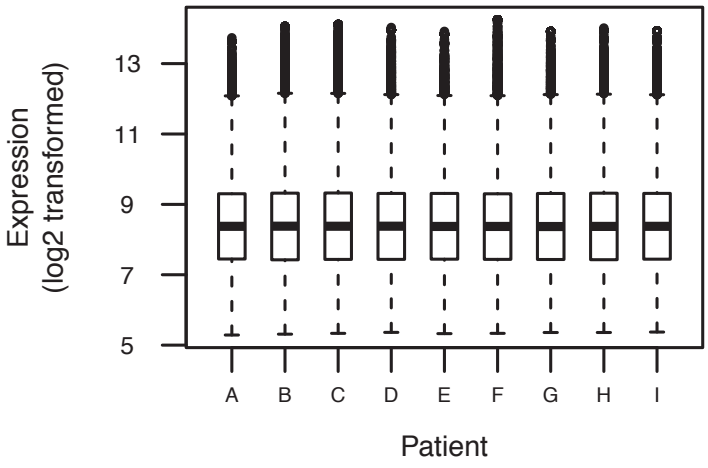

Figure 5. Expression intensity of ALS . After normalization, common gene expression values are averaged. The expression values are $\log_2$ transformed.

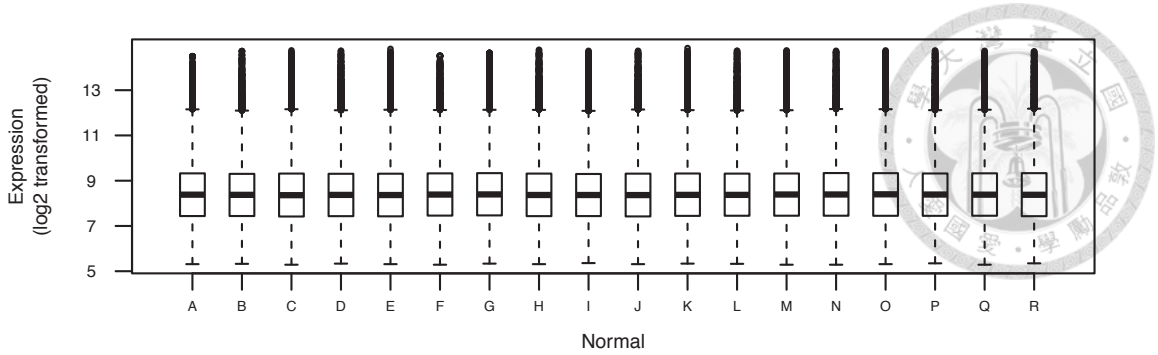

Figure 6. Expression intensity of normal. After normalization, common gene expression values are averaged. The expression values are $\log_2$ transformed.

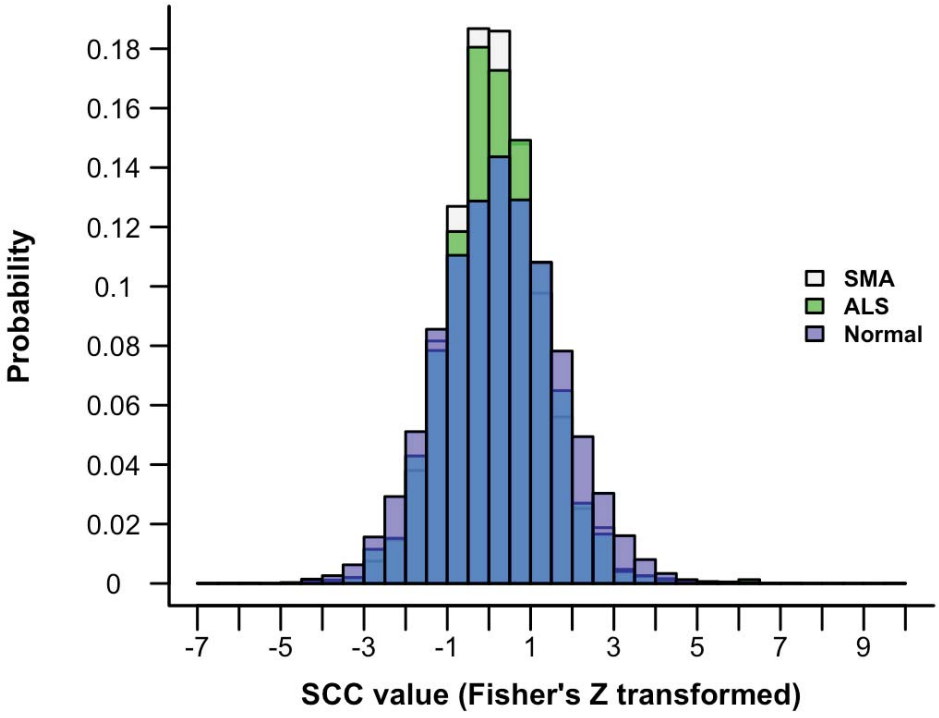

Figure 7. Fisher's z transformed SCC histogram of SMA, ALS and normal. The histogram showed that most of the PPIs are centered at SCC equal to 0, which means most PPIs are not correlated. Besides, There are more co-expressed PPIs (either positive or negative correlated) in normal comparing with SMA and ALS.

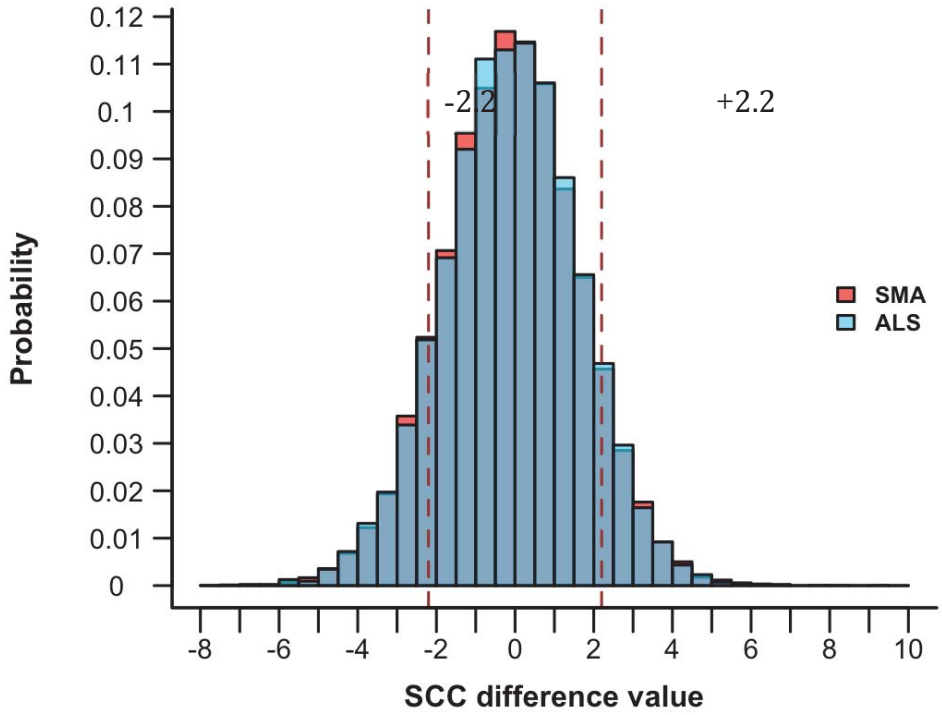

Figure 8. Distributions of the Fisher's z transformed SCC differences in SMA and ALS. Those PPIs with P< 0.05 were collected as DCPPIs and formed as SMA ad ALS DCPINs (The SCC difference (with z-transformed) cut-off : ~ ±2.2).

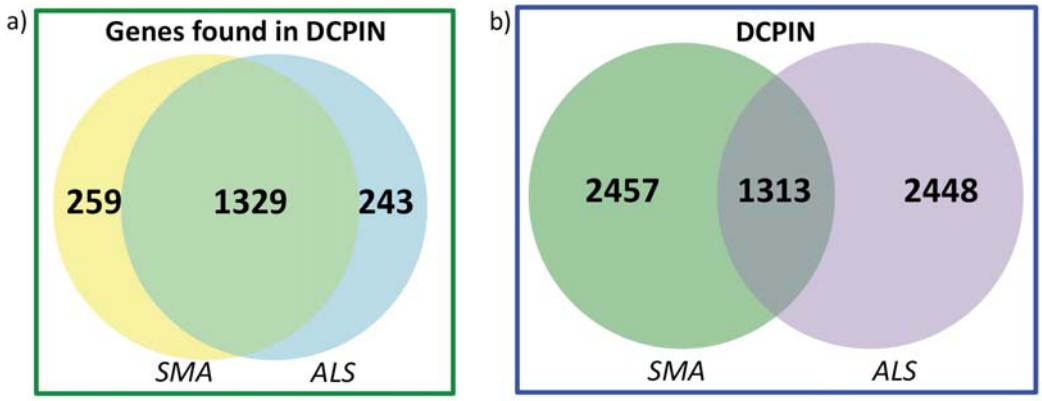

Figure 9. Overviews of genes and DCPPIs derived from DCPINs of SMA and ALS. a) We found 1329 common genes between DCPINs of SMA and ALS; b) 1313 common DCPPIs in DCPINs of SMA and ALS were found. 3770 (containing 1588 genes) and 3761 (consisted with 1572 genes) DCPPIs were found in SMA and ALS, respectively.

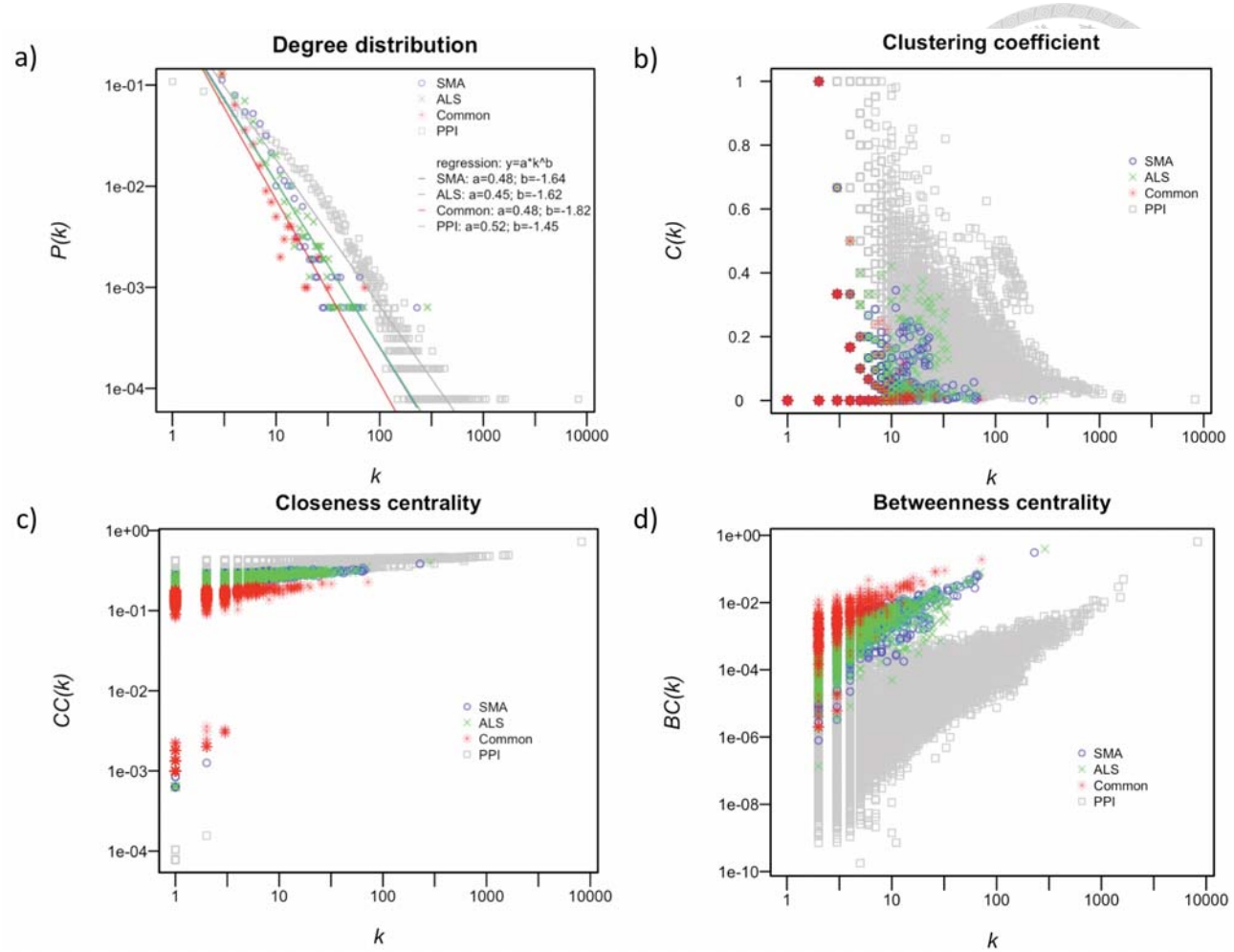

Figure 10. Network properties of integrated PPIs, and DCPINs of SMA, ALS and common. a) Degree, the degree distributions followed power-law property (only small amounts of nodes are found with higher degrees, vice versa); b) Clustering coefficient, genes with higher degree were found with lower clustering coefficient which showed all DCPINs were not highly clustered networks; c & d) betweenness and closseness centralities, nodes with higher degrees seem to be connectors and centers in all DCPINs.

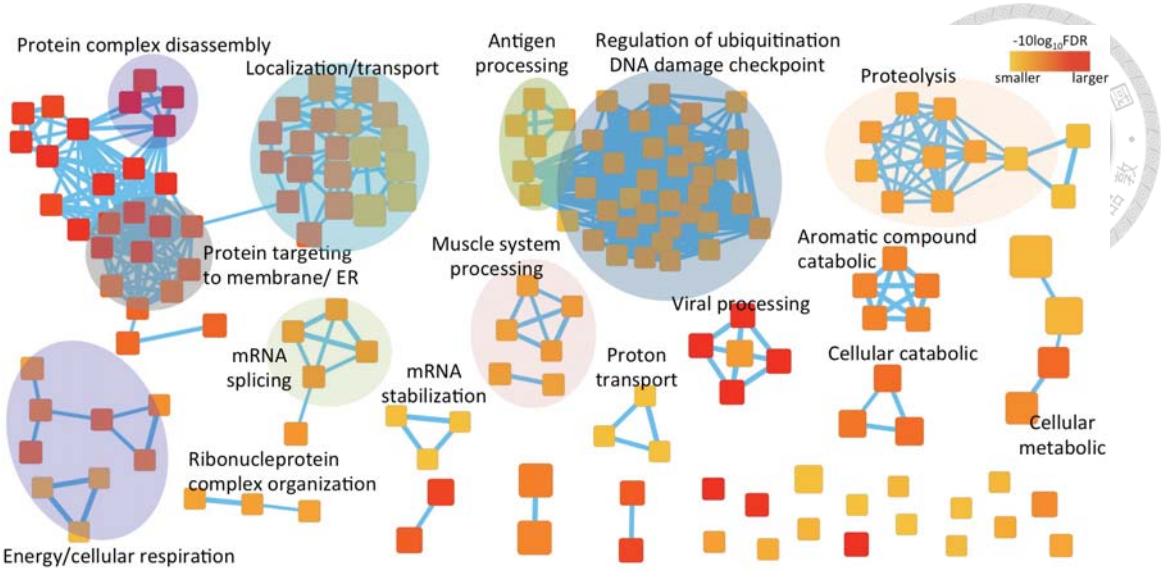

Figure 11. Clusters found in Enrichment map of common GO terms derived from DCPINs of SMA and ALS are shown with different background colors. We isolate common GO functions in both DCPINs with genes of node-based enrichment. To combine these DCPINs in one plot, we pooled genes in both diseases together in each GO term. Then we calculated the similarity between terms with average values of Jaccard and Simpson indexes. The edges here represent the similarity between GO terms. The color bar showed here is represented of $-10\times log_{10}\sqrt{FDR_{SMA}\times FDR_{ALS}}$. Edge cutoff: similarity$\geqq$0.8.

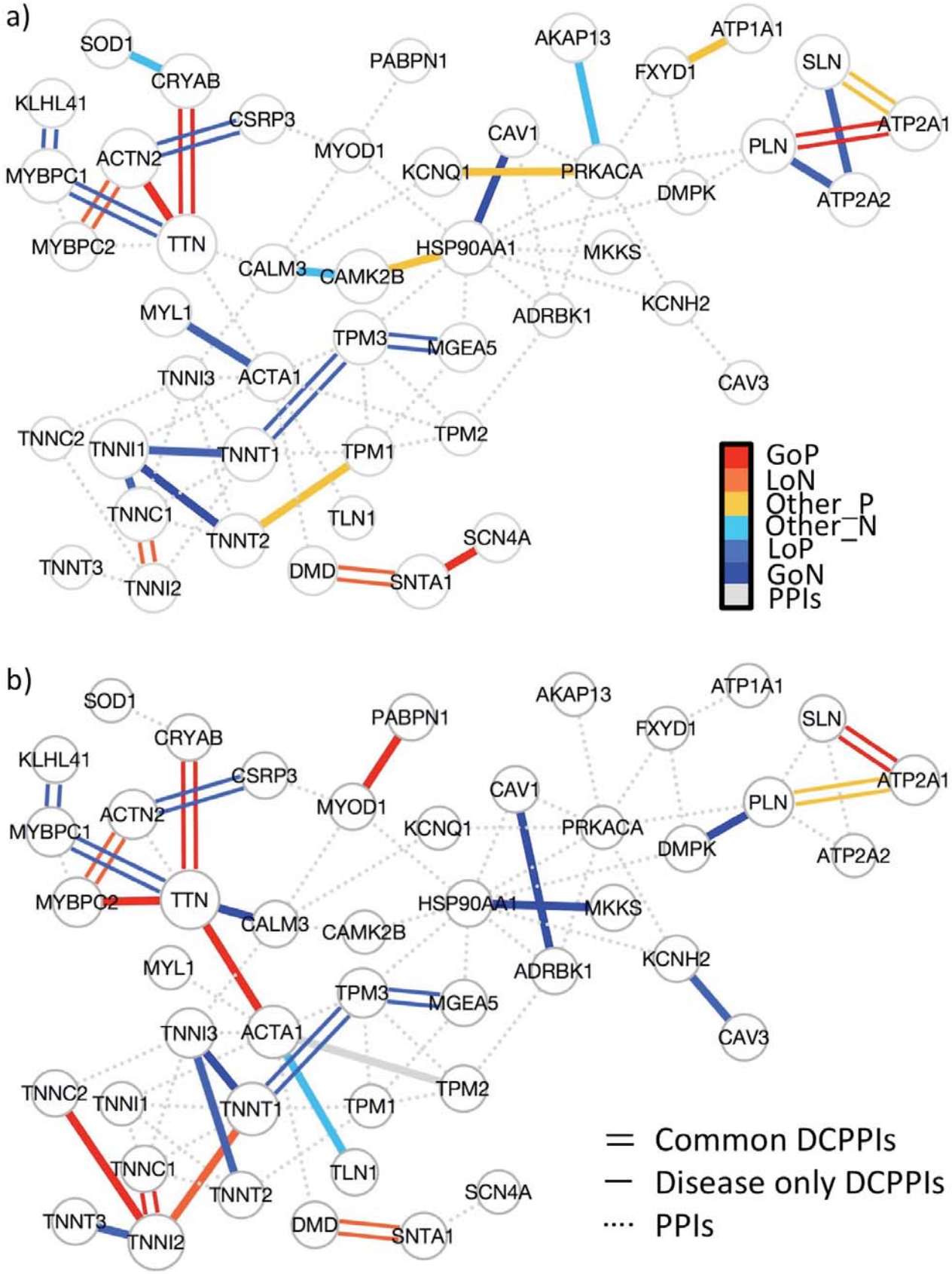

Figure 12. Module of 'muscle system process'. a) and b) plots for module of 'muscle system process' in SMA and ALS, respectively.

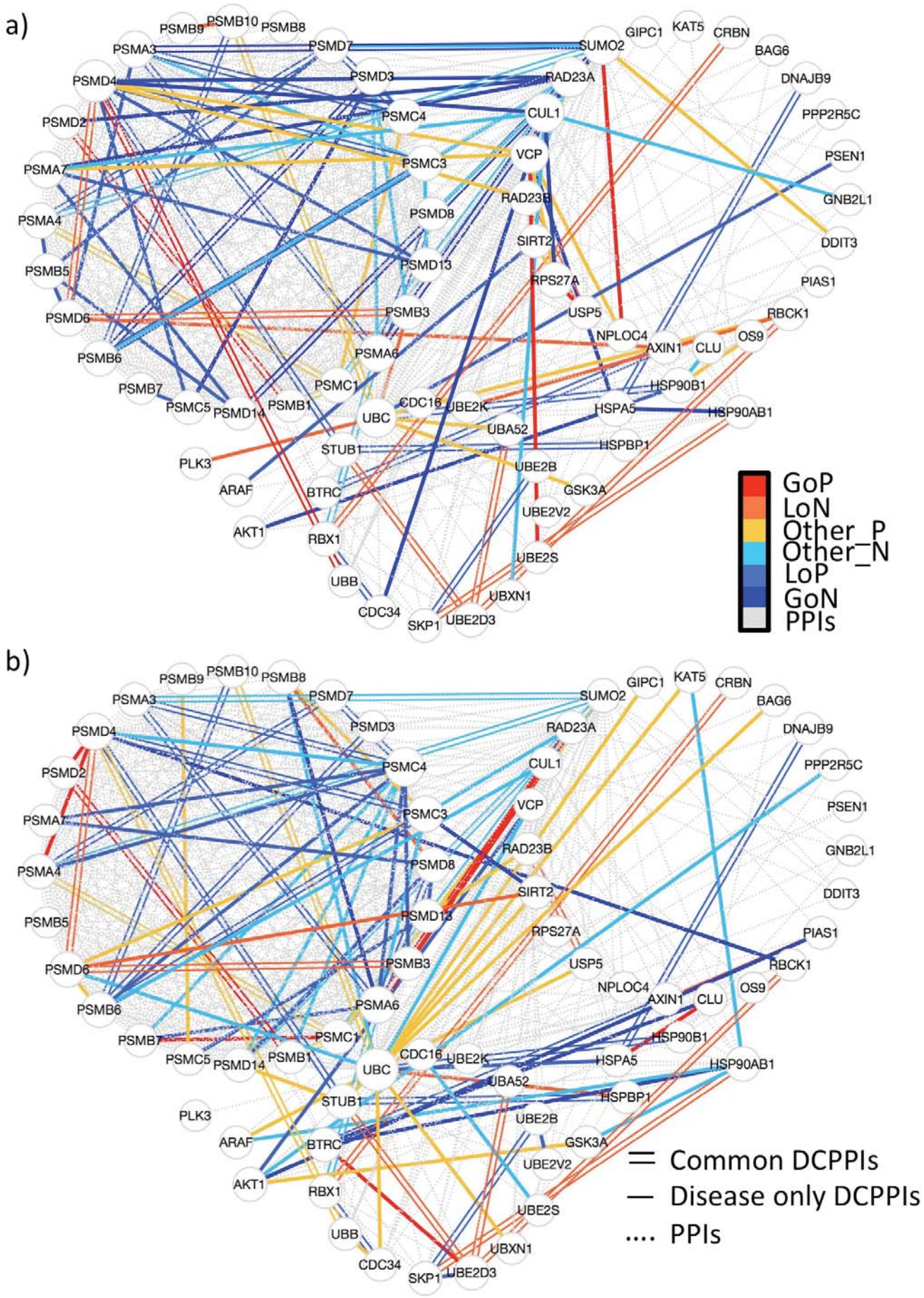

Figure 13. Module of 'proteasome-mediated ubiquitin-dependent protein catabolic process'. a) and b) plots for module of 'proteasome-mediated ubiquitin-dependent protein catabolic process' in SMA and ALS, respectively.

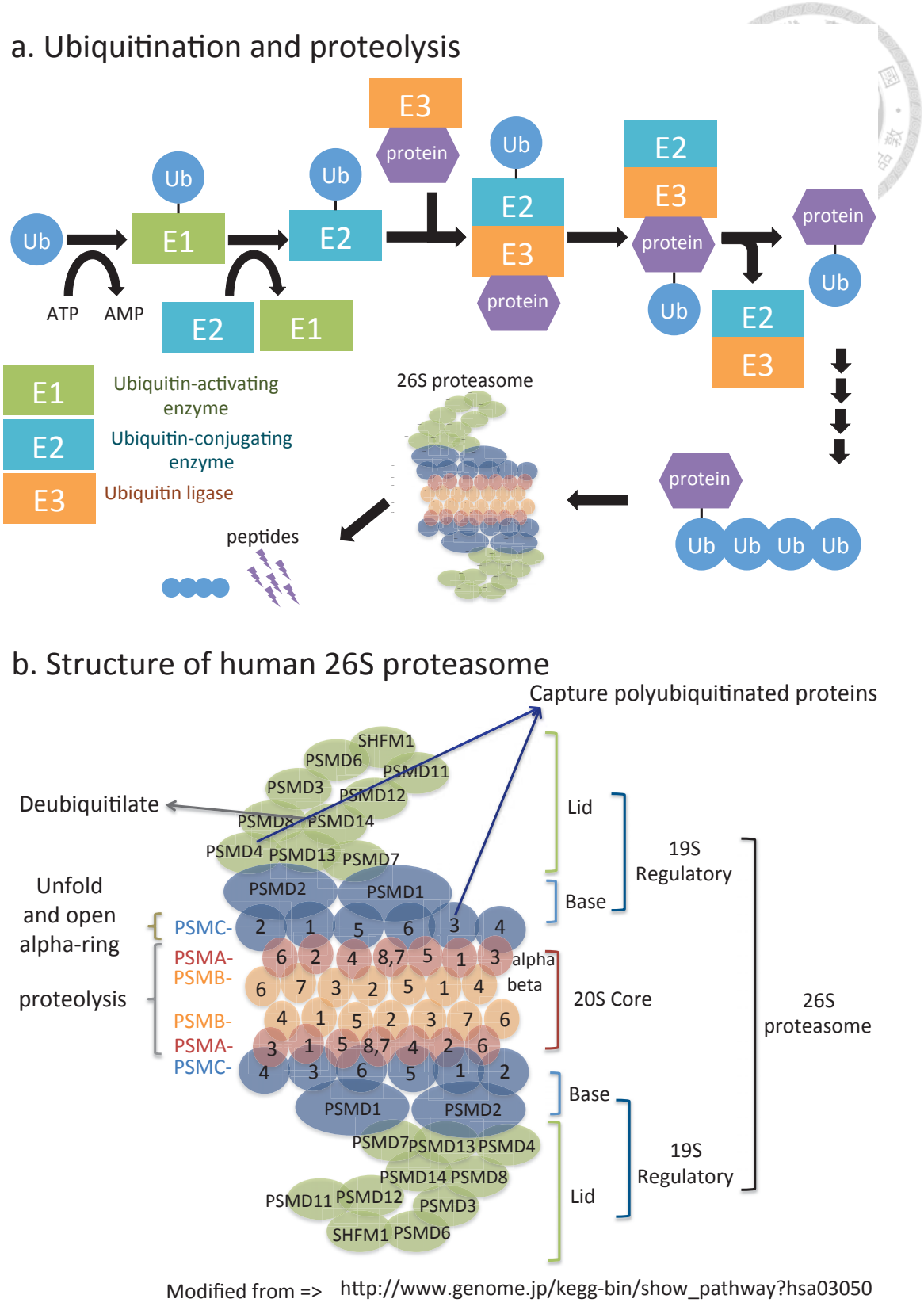

Figure 14. The illustrations showed the procedure of ubiquitination and proteolysis, and structure of 26S proteasome. a) Ubiquitination process; b) The plot showed the structure and components of 26S proteasome.

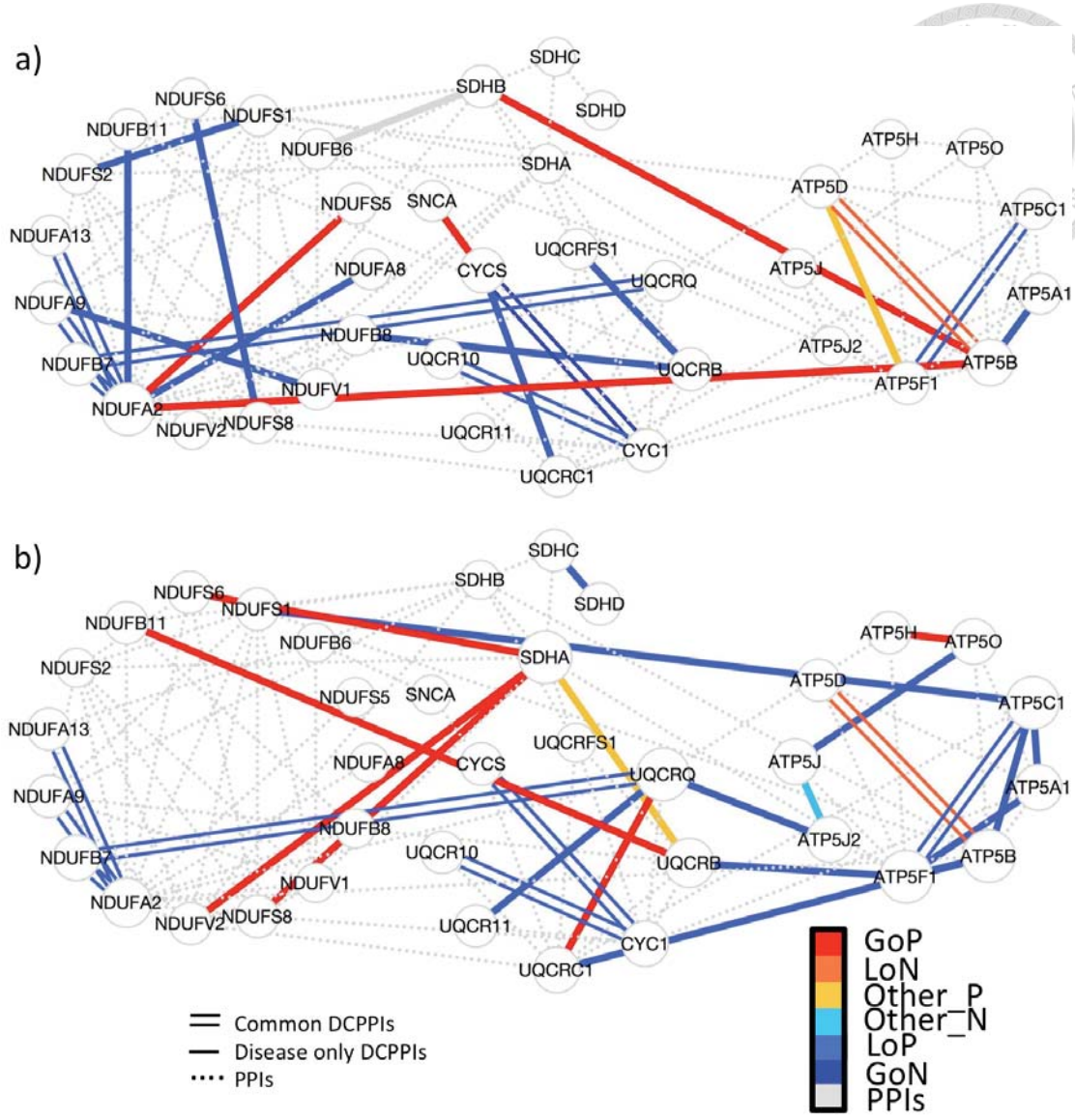

Figure 15. Module of 'respiratory electron transport chain'. a) and b) plots for module of 'respiratory electron transport chain' in SMA and ALS, respectively.

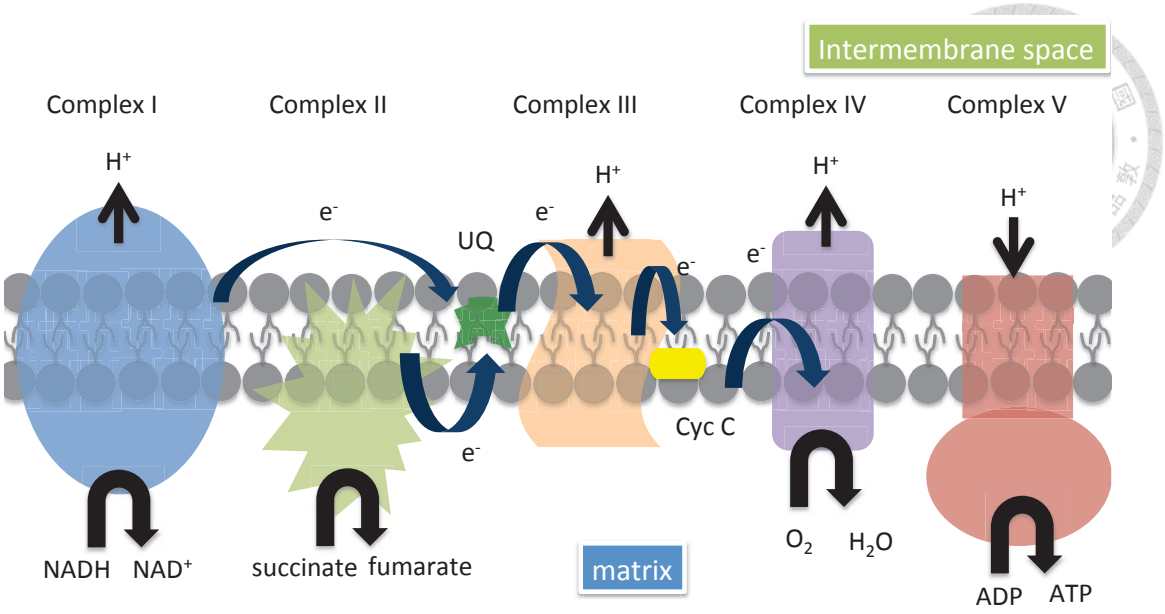

Figure 16. Protein complexes involved in respiratory electron transport chain. The figure illustrates the processes of ATP synthesis by proton gradient, which was made with the complex I, II, III and IV. Complex I (NADH dehydrogenase) oxidizes NADHs, transfers electron to ubiquinone (UQ) and translocates the protons to intermembrane space of the mitochondrion to make proton gradient. Complex II (succinate dehydrogenase) turns succinate into fumarate (involved in TCA cycle) and passes electron to UQ (reduce to UQH2). Complex III (cytochrome C reductase) makes proton gradient and transfer electrons from UQH2 to cytochrome C (oxidize to UQ). The function of complex IV (cytochrome C oxidase) is to transfer protons to intermembrane space and capture the electron from complex III and oxidize the reduce oxygen to water. Finally, complex V (ATP synthase) is to make usages of the proton gradient making upon to turn ADPs to ATPs.

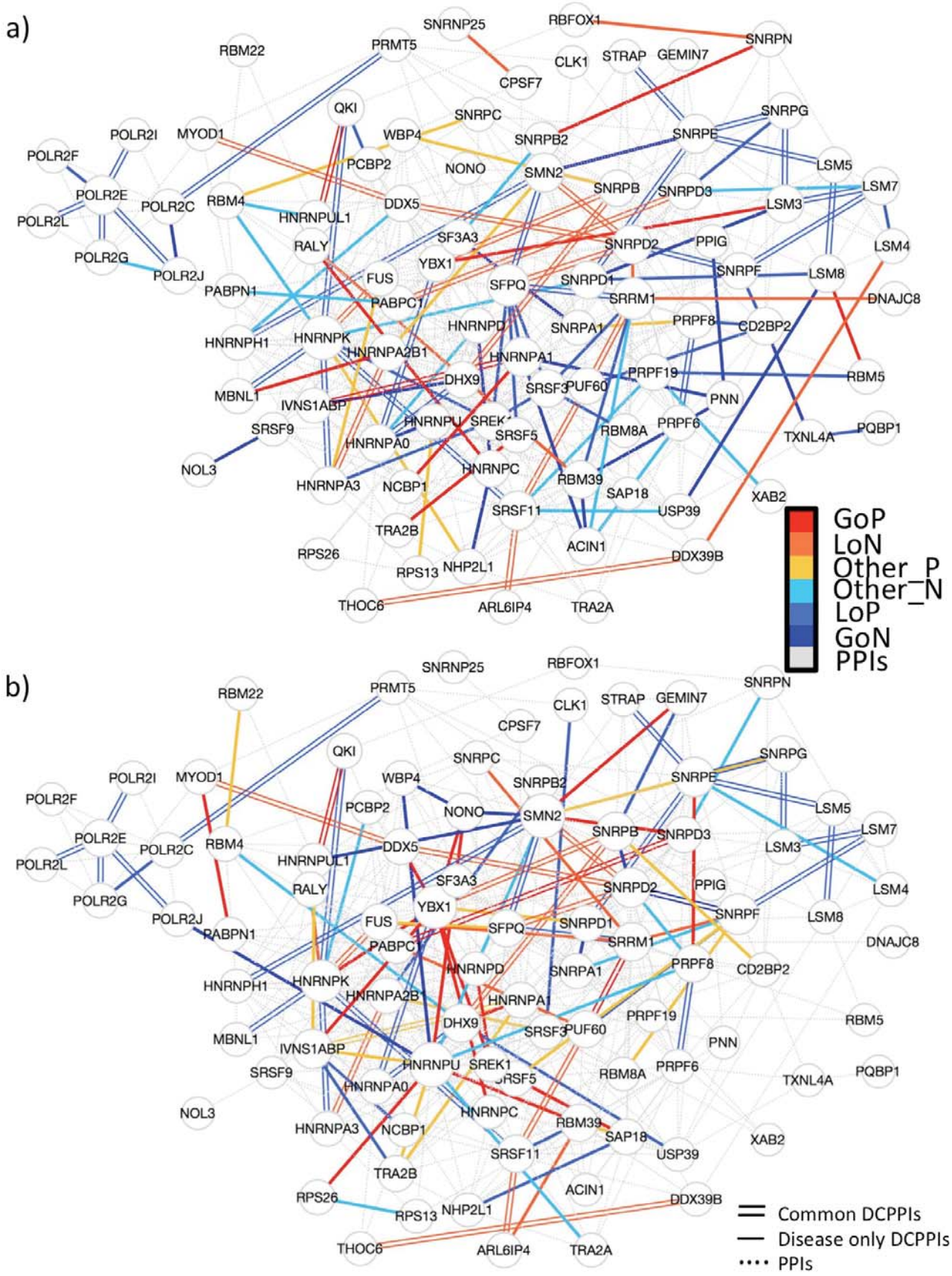

Figure 17. Module of 'RNA splicing'. a) and b) plots for module of 'RNA splicing' in SMA and ALS, respectively.

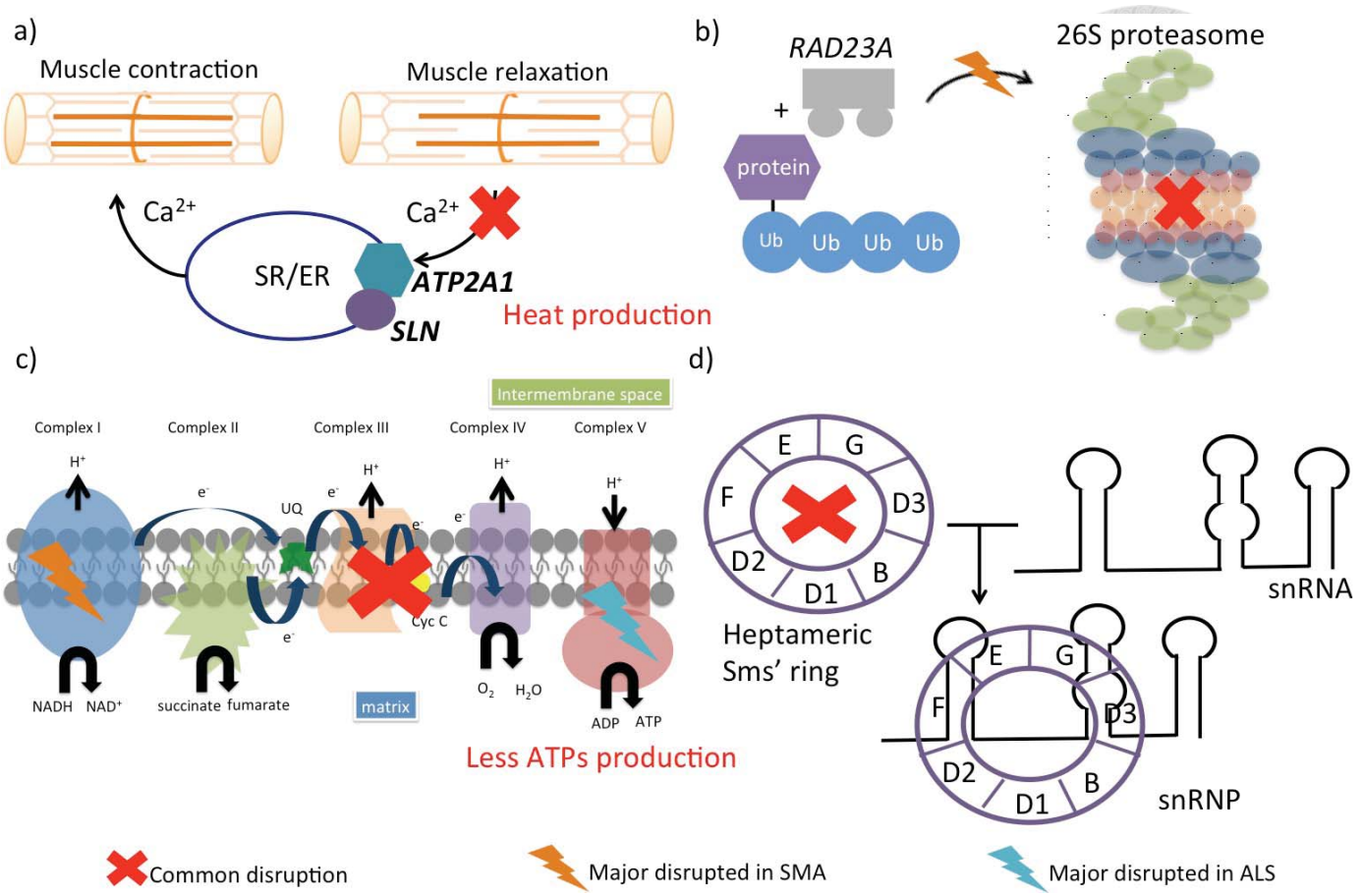

Figure 18. The diagram summarized the overall results found in this study. a) Interaction of *ATP2A1* and *SLN* inhibited calcium recapturing back to SR and caused stress and thermogenesis. b) PPIs were disrupted in protein ubiquitination and proteasomal degradation, such as lost of co-expression between *RAD23A* and *PSMD4*. c) Disrupted PPIs in mitochondrial complex I, III and V were found in SMA and ALS. The lost of interaction between *CYCS* and *CYC1* caused disruption of oxygen being reduced into water. d) snRNPs biogenesis might be interrupted.

Table 1. Overall information of SMA and ALS DCPINs

Groups/ Disease	SMA (3770)	ALS (3761)
GoN	366	364
LoP	1102	1077
LoN	678	614
GoP	450	487
Other_P	555	596
Other_N	612	600
PP	7	23
NN	0	0

Most DCPPIs are loss of co-expression (either loss of positive/negative correlation) in SMA and ALS DCPINs. GoN: gain of negative correlation (disease: negative correlation; normal: positive or non-correlation); LoP: loss of positive correlation (disease: non-correlation; normal: positive correlation); LoN: loss of negative correlation (disease: non-correlation; normal: negative correlation); GoP: gain of positive correlation (disease: positive correlation; normal: negative or non-correlation); Other_P: DCPPIs with positive Z-score difference; Other_N: DCPPIs with negative Z-score difference; PP: DCPPIs with positive correlation in both disease and normal; NN: DCPPIs with negative correlation in both disease and normal (illustrated as Figure 3); Positive correlation: Z-score≥ 1.96; Negative correlation: Z-score ≤ -1.96

Table 2. Information of 1313 common DCPPIs found in SMA and ALS DCPINs

Groups/ Disease	SMA	ALS	Same trend*
GoN	61	51	5
LoP	586	574	163
LoN	390	384	80
GoP	62	63	11
Other_P	119	124	18
Other_N	91	102	20
PP	4	15	0
NN	0	0	0

Same trend: common DCPPIs within the same classified group

Table 3. Network properties of top 1% degree's genes of SMA DCPIN

Gene	Degree	Clustering coefficient	Betweenness centrality	Closeness centrality
UBC	229	0.002	0.308	0.385
FN1	67	0.009	0.062	0.323
ELAVL1	64	0.001	0.059	0.309
NEDD8	64	0.013	0.068	0.342
CUL1	62	0.057	0.027	0.315
SUMO2	61	0.007	0.045	0.314
UBL4A	56	0.023	0.037	0.321
KIAA0101	55	0.006	0.048	0.319
EEF1A1	51	0.037	0.035	0.328
MAP1LC3B	45	0.013	0.029	0.314
GABARAP	42	0.012	0.016	0.295
VCP	42	0.009	0.032	0.312
HLA-B	39	0.008	0.029	0.302
RPS9	39	0.049	0.016	0.318
HDAC5	35	0.003	0.022	0.309
HSP90AA1	34	0.004	0.027	0.310
RPA3	34	0.016	0.023	0.310

Genes with high degree (Hubs) are tempt to be centers in SMA DCPIN.

Table 4. Network properties of top 1% degree's genes of ALS DCPIN

Gene	Degree	Clustering coefficient	Betweenness centrality	Closeness centrality
UBC	289	0.002	0.393	0.402
FN1	70	0.023	0.081	0.351
GRB2	61	0.011	0.052	0.324
UBL4A	56	0.038	0.041	0.325
HDAC5	55	0.006	0.040	0.323
NEDD8	54	0.005	0.046	0.313
ELAVL1	51	0.004	0.040	0.298
KIAA0101	46	0.007	0.031	0.306
HSP90AB1	40	0.026	0.029	0.319
HSP90AA1	39	0.023	0.025	0.307
HLA-B	38	0.013	0.028	0.298
RPS3	35	0.129	0.010	0.311
RPL18	34	0.160	0.009	0.313
RPS23	33	0.278	0.004	0.298
GABARAP	32	0.020	0.015	0.301
RPS21	32	0.192	0.004	0.300
YBX1	32	0.014	0.011	0.298

Genes with high degree (Hubs) are tempt to be centers in ALS DCPIN.

Table 5. Network properties of top 1% degree's genes of common DCPPIs between DCPINs of SMA and ALS

Gene	Degree	Clustering coefficient	Betweenness centrality	Closeness centrality
UBC	72	0.002	0.190	0.229
FN1	32	0.006	0.090	0.217
NEDD8	26	0.006	0.085	0.214
UBL4A	26	0.018	0.079	0.227
HLA-B	20	0.011	0.033	0.195
RPS9	19	0.029	0.044	0.208
EEF1A1	16	0.008	0.056	0.210
ELAVL1	16	0.008	0.037	0.182
GABARAP	16	0.000	0.024	0.195
CDC37	15	0.057	0.037	0.206
ILF3	15	0.019	0.028	0.209
YWHAB	15	0.010	0.024	0.195

Degree of the genes found in common DCPPIs of SMA and ALS DCPINs were usually much smaller than the degree found in SMA or ALS individually.

Table 6. Detail information for common and more specified terms classified by node- and edge-based GO functions

GO term	Level	Node-based GO enrichment result						Edge-based GO enrichment result					
		Gene 1	Gene 2	Intersect.	Union	FDR 1	FDR 2	DCPPI 1	DCPPI 2	Intersect.	Union	FDR 1	FDR 2
actin-myosin filament sliding	6	21	26	20	27	79.129	131.978	10	12	4	18	50.505	73.665
antigen processing and presentation of exogenous peptide antigen via MHC class I, TAP-dependent	6	36	38	36	38	112.594	130.503	44	54	22	76	50.505	96.776
DNA damage response, signal transduction by p53 class mediator resulting in cell cycle arrest	8	30	30	30	30	87.333	88.781	36	42	16	62	23.642	46.371
hydrogen ion transmembrane transport	6	18	22	17	23	20.455	41.301	8	11	3	16	27.236	57.371
mRNA stabilization	5	12	11	11	12	30.332	24.104	7	7	4	10	26.375	28.902
muscle system process	3	77	85	69	93	73.753	108.005	27	26	11	42	35.619	33.829
nuclear-transcribed mRNA catabolic process, nonsense-mediated decay	7	87	86	86	87	485.775	478.110	258	394	94	558	1084.655	2381.801
nucleobase-containing compound catabolic process	5	221	227	209	239	190.918	219.389	332	470	123	679	689.636	1564.822
proteasome-mediated ubiquitin-dependent protein catabolic process	7	78	77	77	78	125.630	123.226	92	98	35	155	55.282	74.732
protein complex disassembly	5	98	98	95	101	373.319	376.832	253	391	92	552	1127.463	2497.697
protein transport	6	265	256	238	283	144.513	125.612	383	505	138	750	565.501	1199.043
respiratory electron transport chain	5	49	45	39	55	164.245	133.678	23	27	8	42	71.738	103.415
ribonucleoprotein complex assembly	5	51	45	45	51	124.825	89.568	21	31	12	40	16.708	63.508
RNA splicing	6	101	100	94	107	152.009	149.896	109	102	39	172	51.217	38.190
SRP-dependent cotranslational protein targeting to membrane	7	78	76	76	78	439.192	417.246	246	385	89	542	1129.053	2538.740

GO term	Level	Node-based GO enrichment result						Edge-based GO enrichment result					
		Gene 1	Gene 2	Intersect.	Union	FDR 1	FDR 2	DCPPI 1	DCPPI 2	Intersect.	Union	FDR 1	FDR 2
translational elongation	5	81	80	80	81	476.313	467.823	269	398	95	572	1242.356	2548.472
translational initiation	6	101	100	98	103	513.522	506.024	269	418	97	590	1092.846	2495.291
translational termination	6	78	77	77	78	522.809	510.260	250	389	91	548	1168.912	2594.257

* 1: SMA DCPIN; 2: ALS DCPIN; FDR presented in this table is $-10*\log_{10}$(Hypergeometric test with Benjamini & Hochberg correction). Modules discussed in this study are in Bold.

Table 7. DCPPIs of the module: 'muscle system process'

Gene 1	Gene 2	SMA	ALS	Normal	Z-score difference		P value		Correlation			Groups		Disease
		Z-score	Z-score	Z-score	SMA	ALS	SMA	ALS	SMA	ALS	Normal	SMA	ALS	
CRYAB	SOD1	-1.845	-0.269	1.181	-3.025	-1.449	0.014	0.139	Non	Non	Non	Other_Neg	Non_DCPPIs	SMA
KCNQ1	PRKACA	0.961	0.650	-1.401	2.362	2.051	0.047	0.064	Non	Non	Non	Other_Pos	Non_DCPPIs	SMA
ATP1A1	FXYD1	1.777	-0.482	-1.696	3.473	1.214	0.008	0.185	Non	Non	Non	Other_Pos	Non_DCPPIs	SMA
ATP2A2	PLN	-0.915	1.845	2.581	-3.496	-0.736	0.007	0.292	Non	Non	P	LoP	Non_DCPPIs	SMA
ATP2A2	SLN	-0.693	1.307	2.077	-2.770	-0.770	0.025	0.290	Non	Non	P	LoP	Non_DCPPIs	SMA
PRKACA	AKAP13	-1.845	0.441	1.463	-3.308	-1.022	0.010	0.224	Non	Non	Non	Other_Neg	Non_DCPPIs	SMA
ACTA1	MYL1	-0.040	1.415	2.425	-2.465	-1.010	0.035	0.237	Non	Non	P	LoP	Non_DCPPIs	SMA
SCN4A	SNTA1	4.006	-0.229	-1.799	5.804	1.570	0.000	0.122	P	Non	Non	GoP	Non_DCPPIs	SMA
TNNC1	TNNI1	0.566	1.415	3.491	-2.925	-2.075	0.018	0.067	Non	Non	P	LoP	Non_DCPPIs	SMA
TNNI1	TNNT1	0.360	1.471	3.102	-2.742	-1.630	0.028	0.120	Non	Non	P	LoP	Non_DCPPIs	SMA
TNNI1	TNNT2	-2.408	0.869	1.039	-3.447	-0.169	0.006	0.453	N	Non	Non	GoN	Non_DCPPIs	SMA
TNNT2	TPM1	0.524	-0.079	-1.789	2.313	1.710	0.046	0.113	Non	Non	Non	Other_Pos	Non_DCPPIs	SMA
CALM3	CAMK2B	-1.471	-0.825	1.252	-2.723	-2.076	0.025	0.065	Non	Non	Non	Other_Neg	Non_DCPPIs	SMA
CAMK2B	HSP90AA1	1.471	-0.693	-1.208	2.680	0.515	0.026	0.359	Non	Non	Non	Other_Pos	Non_DCPPIs	SMA
CAV1	HSP90AA1	-2.408	1.153	1.628	-4.036	-0.475	0.003	0.362	N	Non	Non	GoN	Non_DCPPIs	SMA
ACTN2	TTN	3.309	0.825	0.528	2.781	0.297	0.022	0.413	P	Non	Non	GoP	Non_DCPPIs	SMA
CRYAB	TTN	1.987	6.297	-1.443	3.430	7.740	0.007	0.000	P	P	Non	GoP	GoP	Common
DMD	SNTA1	1.307	-0.726	-3.441	4.748	2.716	0.001	0.026	Non	Non	N	LoN	LoN	Common
MYBPC1	KLHL41	0.524	0.079	3.571	-3.047	-3.491	0.013	0.007	Non	Non	P	LoP	LoP	Common
MYBPC1	TTN	0.566	1.415	4.568	-4.003	-3.153	0.003	0.012	Non	Non	P	LoP	LoP	Common
ATP2A1	PLN	2.063	0.780	-1.513	3.576	2.293	0.006	0.045	P	Non	Non	GoP	Other_Pos	Common

Gene 1	Gene 2	SMA	ALS	Normal	Z-score difference		P value		Correlation			Groups		Disease
		Z-score	Z-score	Z-score	SMA	ALS	SMA	ALS	SMA	ALS	Normal	SMA	ALS	
ATP2A1	SLN	1.415	6.297	-1.813	3.228	8.110	0.009	0.000	Non	P	Non	Other_Pos	GoP	Common
TNNC1	TNNI2	1.104	6.297	-3.062	4.166	9.359	0.003	0.000	Non	P	N	LoN	GoP	Common
TNNT1	TPM3	-0.400	1.104	3.832	-4.233	-2.728	0.002	0.025	Non	Non	P	LoP	LoP	Common
TPM3	MGEA5	-0.608	0.159	2.463	-3.070	-2.304	0.016	0.047	Non	Non	P	LoP	LoP	Common
ACTN2	MYBPC2	0.040	0.825	-3.094	3.134	3.919	0.013	0.004	Non	Non	N	LoN	LoN	Common
ACTN2	CSRP3	0.961	-0.119	3.458	-2.497	-3.577	0.032	0.006	Non	Non	P	LoP	LoP	Common
ADRBK1	CAV1	-0.319	-2.408	-0.019	-0.300	-2.389	0.410	0.042	Non	N	Non	Non_DCPPIs	GoN	ALS
DMPK	PLN	1.104	-1.987	1.694	-0.590	-3.681	0.337	0.005	Non	N	Non	Non_DCPPIs	GoN	ALS
HSP90AA1	MKKS	-0.482	-2.614	1.348	-1.830	-3.961	0.094	0.003	Non	N	Non	Non_DCPPIs	GoN	ALS
MYBPC2	TTN	-0.040	6.297	0.302	-0.341	5.995	0.404	0.000	Non	P	Non	Non_DCPPIs	GoP	ALS
MYOD1	PABPN1	0.869	2.728	-1.234	2.104	3.963	0.062	0.003	Non	P	Non	Non_DCPPIs	GoP	ALS
ACTA1	TLN1	0.360	-1.360	1.605	-1.245	-2.965	0.175	0.018	Non	Non	Non	Non_DCPPIs	Other_Neg	ALS
ACTA1	TPM2	1.415	4.358	2.147	-0.732	2.211	0.291	0.050	Non	P	P	Non_DCPPIs	PP	ALS
ACTA1	TTN	0.650	6.297	0.386	0.264	5.911	0.415	0.000	Non	P	Non	Non_DCPPIs	GoP	ALS
TNNC2	TNNI2	0.825	6.297	1.518	-0.693	4.779	0.297	0.001	Non	P	Non	Non_DCPPIs	GoP	ALS
TNNI2	TNNT1	-1.056	1.777	-2.354	1.299	4.132	0.169	0.001	Non	Non	N	Non_DCPPIs	LoN	ALS
TNNI2	TNNT3	2.227	-1.471	3.856	-1.629	-5.327	0.117	0.000	P	Non	P	Non_DCPPIs	LoP	ALS
TNNI3	TNNT1	0.279	-2.728	-0.142	0.421	-2.586	0.367	0.029	Non	N	Non	Non_DCPPIs	GoN	ALS
TNNI3	TNNT2	0.441	-0.441	1.997	-1.556	-2.438	0.126	0.037	Non	Non	P	Non_DCPPIs	LoP	ALS
CALM3	TTN	0.608	-2.063	0.989	-0.381	-3.052	0.392	0.016	Non	N	Non	Non_DCPPIs	GoN	ALS
CAV3	KCNH2	1.915	-1.588	2.326	-0.412	-3.915	0.387	0.003	Non	Non	P	Non_DCPPIs	LoP	ALS

* Common: both SMA & ALS; P: positive correlation; N: negative correlation; Non: non-correlation

Table 8. Network properties of 'muscle system process' for genes derived from DCPINs of SMA and ALS

Gene Symbol	Gene ID	Description	Degree		Clustering coefficient	
			SMA	ALS	SMA	ALS
ACTA1	58	actin, alpha 1, skeletal muscle	1	3	0	0
ACTN2	88	actinin, alpha 2	3	2	0	0
ADRBK1	156	adrenergic, beta, receptor kinase 1	0	1	0	0
AKAP13	11214	A kinase (PRKA) anchor protein 13	1	0	0	0
ATP1A1	476	ATPase, Na+/K+ transporting, alpha 1 polypeptide	1	0	0	0
ATP2A1	487	ATPase, Ca++ transporting, cardiac muscle, fast twitch 1	2	2	0	0
ATP2A2	488	ATPase, Ca++ transporting, cardiac muscle, slow twitch 2	2	0	0	0
CALM3	808	calmodulin 3 (phosphorylase kinase, delta)	1	1	0	0
CAMK2B	816	calcium/calmodulin-dependent protein kinase II beta	2	0	0	0
CAV1	857	caveolin 1, caveolae protein, 22kDa	1	1	0	0
CAV3	859	caveolin 3	0	1	0	0
CRYAB	1410	crystallin, alpha B	2	1	0	0
CSRP3	8048	cysteine and glycine-rich protein 3 (cardiac LIM protein)	1	1	0	0
DMD	1756	dystrophin	1	1	0	0
DMPK	1760	dystrophia myotonica-protein kinase	0	1	0	0
FXYD1	5348	FXYD domain containing ion transport regulator 1	1	0	0	0
HSP90AA1	3320	heat shock protein 90kDa alpha (cytosolic), class A member 1	2	1	0	0
KCNH2	3757	potassium voltage-gated channel, subfamily H (eag-related), member 2	0	1	0	0
KCNQ1	3784	potassium voltage-gated channel, KQT-like subfamily, member 1	1	0	0	0
KLHL41	10324	kelch-like family member 41	1	1	0	0
MGEA5	10724	meningioma expressed antigen 5 (hyaluronidase)	1	1	0	0

Gene Symbol	Gene ID	Description	Degree		Clustering coefficient	
			SMA	ALS	SMA	ALS
MKKS	8195	McKusick-Kaufman syndrome	0	1	0	0
MYBPC1	4604	myosin binding protein C, slow type	2	2	0	0
MYBPC2	4606	myosin binding protein C, fast type	1	2	0	0
MYL1	4632	myosin, light chain 1, alkali; skeletal, fast	1	0	0	0
MYOD1	4654	myogenic differentiation 1	0	1	0	0
PABPN1	8106	poly(A) binding protein, nuclear 1	0	1	0	0
PLN	5350	phospholamban	2	2	0	0
PRKACA	5566	protein kinase, cAMP-dependent, catalytic, alpha	2	0	0	0
SCN4A	6329	sodium channel, voltage-gated, type IV, alpha subunit	1	0	0	0
SLN	6588	sarcolipin	2	1	0	0
SNTA1	6640	syntrophin, alpha 1	2	1	0	0
SOD1	6647	superoxide dismutase 1, soluble	1	0	0	0
TLN1	7094	talin 1	0	1	0	0
TNNC1	7134	troponin C type 1 (slow)	2	1	0	0
TNNC2	7125	troponin C type 2 (fast)	0	1	0	0
TNNI1	7135	troponin I type 1 (skeletal, slow)	3	0	0	0
TNNI2	7136	troponin I type 2 (skeletal, fast)	1	4	0	0
TNNI3	7137	troponin I type 3 (cardiac)	0	2	0	0
TNNT1	7138	troponin T type 1 (skeletal, slow)	2	3	0	0
TNNT2	7139	troponin T type 2 (cardiac)	2	1	0	0
TNNT3	7140	troponin T type 3 (skeletal, fast)	0	1	0	0
TPM1	7168	tropomyosin 1 (alpha)	1	0	0	0

Gene Symbol	Gene ID	Description	Degree		Clustering coefficient	
			SMA	ALS	SMA	ALS
TPM2	7169	tropomyosin 2 (beta)	0	1	0	0
TPM3	7170	tropomyosin 3	2	2	0	0
TTN	7273	titin	3	5	0	0

Table 9. DCPPIs in the module: 'proteasome-mediated ubiquitin-dependent protein catabolic process'

Gene 1	Gene 2	SMA	ALS	Normal	Z-score difference		P value		Correlation condition			Groups		Disease
		Z-score	Z-score	Z-score	SMA	ALS	SMA	ALS	SMA	ALS	Normal	SMA	ALS	
CLU	HSP90B1	-1.588	0.961	0.808	-2.396	0.153	0.039	0.456	Non	Non	Non	Other_Neg	Non_DCPPIs	SMA
PLK3	UBC	0.040	-0.608	-2.474	2.514	1.867	0.035	0.088	Non	Non	N	LoN	Non_DCPPIs	SMA
DDIT3	SUMO2	1.649	-0.825	-0.816	2.465	-0.008	0.037	0.490	Non	Non	Non	Other_Pos	Non_DCPPIs	SMA
AKT1	HSPA5	-4.358	1.777	1.448	-5.806	0.330	0.000	0.405	N	Non	Non	GoN	Non_DCPPIs	SMA
GSK3A	UBC	1.104	0.736	-1.269	2.373	2.005	0.043	0.073	Non	Non	Non	Other_Pos	Non_DCPPIs	SMA
UBE2K	RBCK1	0.239	-3.503	-3.268	3.507	-0.235	0.006	0.419	Non	N	N	LoN	Non_DCPPIs	SMA
HSPA5	HSP90AB1	-2.315	2.063	0.220	-2.534	1.844	0.033	0.090	N	P	Non	GoN	Non_DCPPIs	SMA
HSPA5	HSP90B1	-0.441	0.319	2.077	-2.518	-1.758	0.035	0.098	Non	Non	P	LoP	Non_DCPPIs	SMA
HSPA5	VCP	-2.614	-0.693	1.547	-4.161	-2.240	0.002	0.053	N	Non	Non	GoN	Non_DCPPIs	SMA
ARAF	SIRT2	-0.482	2.728	3.059	-3.541	-0.331	0.004	0.401	Non	P	P	LoP	Non_DCPPIs	SMA
PSEN1	UBC	-0.608	0.780	1.987	-2.595	-1.207	0.032	0.190	Non	Non	P	LoP	Non_DCPPIs	SMA
PSMA3	PSMC3	-1.777	1.008	0.703	-2.480	0.305	0.039	0.420	Non	Non	Non	Other_Neg	Non_DCPPIs	SMA
PSMA3	PSMD6	-0.360	1.712	2.383	-2.742	-0.671	0.024	0.308	Non	Non	P	LoP	Non_DCPPIs	SMA
PSMA4	PSMB5	-1.845	1.845	2.454	-4.299	-0.610	0.002	0.331	Non	Non	P	LoP	Non_DCPPIs	SMA
PSMA6	PSMD3	-1.307	-0.482	1.392	-2.699	-1.874	0.026	0.082	Non	Non	Non	Other_Neg	Non_DCPPIs	SMA
PSMA7	PSMD14	1.203	1.987	4.125	-2.922	-2.138	0.018	0.061	Non	P	P	LoP	Non_DCPPIs	SMA
PSMA7	PSMD13	-0.079	2.728	2.557	-2.636	0.171	0.031	0.439	Non	P	P	LoP	Non_DCPPIs	SMA
PSMA7	RAD23A	-3.309	0.482	1.269	-4.578	-0.787	0.000	0.275	N	Non	Non	GoN	Non_DCPPIs	SMA
PSMA7	VCP	0.961	-0.159	-1.410	2.371	1.251	0.043	0.176	Non	Non	Non	Other_Pos	Non_DCPPIs	SMA
PSMA7	CUL1	-0.869	1.415	1.927	-2.796	-0.511	0.023	0.351	Non	Non	Non	Other_Neg	Non_DCPPIs	SMA
PSMB3	PSMD3	-1.588	0.869	0.759	-2.347	0.110	0.044	0.474	Non	Non	Non	Other_Neg	Non_DCPPIs	SMA

Gene 1	Gene 2	SMA	ALS	Normal	Z-score difference		P value		Correlation condition			Groups		Disease
		Z-score	Z-score	Z-score	SMA	ALS	SMA	ALS	SMA	ALS	Normal	SMA	ALS	
PSMB3	UBC	0.524	0.000	-2.038	2.562	2.038	0.033	0.067	Non	Non	N	LoN	Non_DCPPIs	SMA
PSMB5	PSMD14	0.319	1.777	2.608	-2.289	-0.831	0.044	0.267	Non	Non	P	LoP	Non_DCPPIs	SMA
PSMB5	PSMD7	-0.119	0.780	2.581	-2.700	-1.801	0.027	0.094	Non	Non	P	LoP	Non_DCPPIs	SMA
PSMB5	PSMD6	-0.566	1.307	2.374	-2.940	-1.067	0.016	0.218	Non	Non	P	LoP	Non_DCPPIs	SMA
PSMB6	RAD23A	-1.255	0.736	1.628	-2.883	-0.892	0.019	0.249	Non	Non	Non	Other_Neg	Non_DCPPIs	SMA
PSMB7	PSMC5	-0.119	1.529	2.195	-2.314	-0.667	0.049	0.317	Non	Non	P	LoP	Non_DCPPIs	SMA
PSMB9	PSMB10	1.649	-0.360	-2.383	4.032	2.023	0.002	0.067	Non	Non	N	LoN	Non_DCPPIs	SMA
PSMC1	PSMC4	0.961	-1.360	-1.609	2.570	0.249	0.031	0.417	Non	Non	Non	Other_Pos	Non_DCPPIs	SMA
PSMC3	PSMD13	-0.780	0.441	1.847	-2.628	-1.406	0.027	0.148	Non	Non	Non	Other_Neg	Non_DCPPIs	SMA
PSMC4	PSMD3	-1.845	1.307	1.828	-3.673	-0.521	0.004	0.348	Non	Non	Non	Other_Neg	Non_DCPPIs	SMA
PSMC5	PSMD3	-3.139	0.279	-0.074	-3.066	0.353	0.014	0.397	N	Non	Non	GoN	Non_DCPPIs	SMA
PSMC5	PSMD4	0.869	1.987	3.753	-2.883	-1.765	0.018	0.102	Non	P	P	LoP	Non_DCPPIs	SMA
PSMD2	RAD23A	-2.614	0.040	1.877	-4.491	-1.837	0.001	0.093	N	Non	Non	GoN	Non_DCPPIs	SMA
PSMD4	PSMD13	-0.040	0.961	3.223	-3.262	-2.261	0.008	0.051	Non	Non	P	LoP	Non_DCPPIs	SMA
PSMD4	RAD23A	-2.408	-0.360	0.647	-3.055	-1.006	0.017	0.228	N	Non	Non	GoN	Non_DCPPIs	SMA
PSMD4	RAD23B	0.915	0.239	-1.887	2.802	2.126	0.021	0.063	Non	Non	Non	Other_Pos	Non_DCPPIs	SMA
PSMD4	VCP	1.203	-0.400	-1.818	3.022	1.418	0.018	0.153	Non	Non	Non	Other_Pos	Non_DCPPIs	SMA
PSMD4	CUL1	-2.063	0.736	1.582	-3.645	-0.845	0.005	0.267	N	Non	Non	GoN	Non_DCPPIs	SMA
PSMD7	SUMO2	-0.693	0.825	1.835	-2.528	-1.011	0.033	0.220	Non	Non	Non	Other_Neg	Non_DCPPIs	SMA
PSMD8	RAD23A	-1.529	1.044	0.776	-2.304	0.268	0.047	0.420	Non	Non	Non	Other_Neg	Non_DCPPIs	SMA
RAD23A	RAD23B	-1.008	0.159	1.582	-2.590	-1.423	0.031	0.150	Non	Non	Non	Other_Neg	Non_DCPPIs	SMA
RPS27A	SIRT2	1.471	0.390	-1.185	2.656	1.575	0.029	0.124	Non	Non	Non	Other_Pos	Non_DCPPIs	SMA

Gene 1	Gene 2	SMA	ALS	Normal	Z-score difference		P value		Correlation condition			Groups		Disease
		Z-score	Z-score	Z-score	SMA	ALS	SMA	ALS	SMA	ALS	Normal	SMA	ALS	
RPS27A	CUL1	-2.507	-0.229	0.323	-2.830	-0.552	0.022	0.339	N	Non	Non	GoN	Non_DCPPIs	SMA
RPS27A	USP5	3.139	-0.390	0.315	2.824	-0.705	0.019	0.300	P	Non	Non	GoP	Non_DCPPIs	SMA
RPS27A	VCP	0.693	-0.149	-1.887	2.580	1.738	0.030	0.100	Non	Non	Non	Other_Pos	Non_DCPPIs	SMA
SUMO2	NPLOC4	2.614	-1.712	-0.751	3.365	-0.961	0.008	0.236	P	Non	Non	GoP	Non_DCPPIs	SMA
SUMO2	CUL1	-1.987	-0.915	0.711	-2.698	-1.626	0.028	0.114	N	Non	Non	GoN	Non_DCPPIs	SMA
HSP90B1	OS9	1.529	-1.153	-1.304	2.833	0.151	0.024	0.455	Non	Non	Non	Other_Pos	Non_DCPPIs	SMA
UBA52	UBC	0.736	-1.360	-1.809	2.545	0.448	0.034	0.367	Non	Non	Non	Other_Pos	Non_DCPPIs	SMA
UBC	RBCK1	0.825	-0.524	-1.647	2.471	1.123	0.040	0.206	Non	Non	Non	Other_Pos	Non_DCPPIs	SMA
VCP	UBE2S	2.614	-0.915	-2.360	4.974	1.445	0.001	0.138	P	Non	N	GoP	Non_DCPPIs	SMA
VCP	NPLOC4	1.777	0.159	-1.751	3.528	1.910	0.006	0.081	Non	Non	Non	Other_Pos	Non_DCPPIs	SMA
AXIN1	PSMD6	0.441	-1.104	-2.510	2.951	1.406	0.017	0.155	Non	Non	N	LoN	Non_DCPPIs	SMA
CUL1	GNB2L1	-1.104	-0.239	1.838	-2.942	-2.076	0.019	0.067	Non	Non	Non	Other_Neg	Non_DCPPIs	SMA
CUL1	UBXN1	-1.203	-0.524	1.427	-2.631	-1.951	0.032	0.076	Non	Non	Non	Other_Neg	Non_DCPPIs	SMA
CDC34	CUL1	-2.507	-0.079	0.989	-3.496	-1.068	0.007	0.218	N	Non	Non	GoN	Non_DCPPIs	SMA
STUB1	HSPBP1	-1.307	0.736	3.208	-4.514	-2.471	0.001	0.037	Non	Non	P	LoP	LoP	Common
HSPA5	DNAJB9	-0.869	-1.529	1.974	-2.844	-3.503	0.021	0.007	Non	Non	P	LoP	LoP	Common
HSP90AB1	SKP1	0.650	0.825	-2.510	3.160	3.334	0.014	0.010	Non	Non	N	LoN	LoN	Common
PSMA3	PSMA6	0.199	0.199	3.048	-2.849	-2.849	0.019	0.020	Non	Non	P	LoP	LoP	Common
PSMA3	PSMC4	0.079	-0.119	2.394	-2.315	-2.513	0.047	0.034	Non	Non	P	LoP	LoP	Common
PSMA3	SUMO2	-2.728	-1.203	1.427	-4.156	-2.631	0.003	0.031	N	Non	Non	GoN	Other_Neg	Common
PSMA4	PSMC1	1.008	1.529	-1.937	2.945	3.465	0.017	0.007	Non	Non	Non	Other_Pos	Other_Pos	Common
PSMA4	PSMD7	0.000	0.119	3.003	-3.003	-2.884	0.016	0.019	Non	Non	P	LoP	LoP	Common

Gene 1	Gene 2	SMA	ALS	Normal	Z-score difference		P value		Correlation condition			Groups		Disease
		Z-score	Z-score	Z-score	SMA	ALS	SMA	ALS	SMA	ALS	Normal	SMA	ALS	
PSMA4	SUMO2	-1.415	-0.400	1.897	-3.312	-2.297	0.009	0.046	Non	Non	Non	Other_Neg	Other_Neg	Common
PSMA6	PSMD8	0.650	0.329	3.253	-2.603	-2.923	0.028	0.018	Non	Non	P	LoP	LoP	Common
PSMA6	RAD23A	-2.315	3.309	0.159	-2.474	3.150	0.036	0.014	N	P	Non	GoN	GoP	Common
PSMA6	RBX1	-0.780	-0.360	1.947	-2.727	-2.306	0.023	0.046	Non	Non	Non	Other_Neg	Other_Neg	Common
PSMB1	PSMC1	1.845	0.693	-1.780	3.624	2.473	0.005	0.038	Non	Non	Non	Other_Pos	Other_Pos	Common
PSMB1	PSMD2	2.852	2.227	-1.226	4.078	3.452	0.002	0.006	P	P	Non	GoP	GoP	Common
PSMB3	PSMD6	0.524	0.961	-2.132	2.655	3.093	0.029	0.014	Non	Non	N	LoN	LoN	Common
PSMB6	PSMB10	0.239	-0.482	2.938	-2.699	-3.420	0.028	0.007	Non	Non	P	LoP	LoP	Common
PSMB6	PSMC3	0.279	0.239	2.741	-2.462	-2.503	0.036	0.035	Non	Non	P	LoP	LoP	Common
PSMB6	PSMD3	-2.989	-0.736	1.987	-4.976	-2.723	0.000	0.026	N	Non	P	GoN	LoP	Common
PSMB10	UBC	1.153	0.961	-1.472	2.625	2.433	0.032	0.040	Non	Non	Non	Other_Pos	Other_Pos	Common
PSMC1	RAD23A	-1.104	-1.203	1.675	-2.779	-2.878	0.023	0.020	Non	Non	Non	Other_Neg	Other_Neg	Common
PSMC3	PSMD4	1.203	0.693	3.558	-2.354	-2.865	0.044	0.021	Non	Non	P	LoP	LoP	Common
PSMC4	PSMD7	0.119	-1.104	2.448	-2.329	-3.552	0.042	0.006	Non	Non	P	LoP	LoP	Common
PSMD4	STUB1	-0.319	-0.524	2.897	-3.217	-3.421	0.012	0.007	Non	Non	P	LoP	LoP	Common
PSMD4	UBB	2.614	0.736	-1.894	4.508	2.631	0.001	0.028	P	Non	Non	GoP	Other_Pos	Common
PSMD4	PSMD6	0.239	1.255	-2.121	2.360	3.376	0.043	0.008	Non	Non	N	LoN	LoN	Common
RAD23B	USP5	0.159	1.104	-2.533	2.692	3.637	0.027	0.005	Non	Non	N	LoN	LoN	Common
SKP1	UBE2B	-1.008	-0.780	2.924	-3.932	-3.704	0.003	0.005	Non	Non	P	LoP	LoP	Common
SUMO2	PSMD14	-2.227	-1.415	1.041	-3.268	-2.456	0.010	0.038	N	Non	Non	GoN	Other_Neg	Common
HSP90B1	UBC	-1.056	-0.736	2.326	-3.382	-3.063	0.007	0.015	Non	Non	P	LoP	LoP	Common
UBA52	UBE2D3	-0.693	-0.239	-3.532	2.839	3.294	0.022	0.008	Non	Non	N	LoN	LoN	Common

Gene 1	Gene 2	SMA	ALS	Normal	Z-score difference		P value		Correlation condition			Groups		Disease
		Z-score	Z-score	Z-score	SMA	ALS	SMA	ALS	SMA	ALS	Normal	SMA	ALS	
UBE2D3	STUB1	1.056	0.915	-2.405	3.461	3.320	0.008	0.007	Non	Non	N	LoN	LoN	Common
UBE2D3	RBCK1	-0.780	-1.845	-4.479	3.698	2.634	0.004	0.032	Non	Non	N	LoN	LoN	Common
AXIN1	BTRC	0.079	0.566	2.911	-2.831	-2.345	0.019	0.044	Non	Non	P	LoP	LoP	Common
CDC34	RBX1	-0.279	-0.961	2.028	-2.307	-2.989	0.046	0.016	Non	Non	P	LoP	LoP	Common
RBX1	CRBN	1.056	0.319	-2.028	3.083	2.347	0.015	0.045	Non	Non	N	LoN	LoN	Common
PSMD14	STUB1	-0.279	0.961	-1.394	1.115	2.355	0.208	0.044	Non	Non	Non	Non_DCPPIs	Other_Pos	ALS
CLU	HSPA5	1.307	2.315	-0.774	2.080	3.088	0.065	0.014	Non	P	Non	Non_DCPPIs	GoP	ALS
CLU	BTRC	-1.415	-3.730	-0.759	-0.656	-2.971	0.316	0.016	Non	N	Non	Non_DCPPIs	GoN	ALS
AKT1	GSK3A	0.524	0.869	-1.647	2.170	2.516	0.053	0.034	Non	Non	Non	Non_DCPPIs	Other_Pos	ALS
AKT1	PPP2R5C	0.079	-1.415	1.226	-1.146	-2.641	0.200	0.033	Non	Non	Non	Non_DCPPIs	Other_Neg	ALS
AKT1	VCP	2.852	0.079	2.498	0.355	-2.418	0.398	0.041	P	Non	P	Non_DCPPIs	LoP	ALS
AKT1	PIAS1	0.566	-2.227	1.665	-1.100	-3.892	0.212	0.003	Non	N	Non	Non_DCPPIs	GoN	ALS
GSK3A	HSP90AB1	0.279	-0.869	1.401	-1.122	-2.270	0.200	0.046	Non	Non	Non	Non_DCPPIs	Other_Neg	ALS
HSPA5	UBC	1.649	0.040	2.982	-1.333	-2.942	0.161	0.020	Non	Non	P	Non_DCPPIs	LoP	ALS
HSP90AB1	KAT5	0.400	-1.529	1.947	-1.546	-3.475	0.130	0.006	Non	Non	Non	Non_DCPPIs	Other_Neg	ALS
HSP90AB1	BTRC	0.239	-2.063	0.237	0.002	-2.301	0.505	0.044	Non	N	Non	Non_DCPPIs	GoN	ALS
ARAF	HSP90AB1	0.566	-1.915	1.917	-1.351	-3.831	0.165	0.003	Non	Non	Non	Non_DCPPIs	Other_Neg	ALS
ARAF	UBC	-0.040	0.441	-1.877	1.837	2.318	0.090	0.045	Non	Non	Non	Non_DCPPIs	Other_Pos	ALS
PSMA4	PSMC4	2.063	-1.056	3.524	-1.461	-4.580	0.149	0.001	P	Non	P	Non_DCPPIs	LoP	ALS
PSMA4	PSMD4	0.400	2.989	-0.323	0.723	3.312	0.288	0.007	Non	P	Non	Non_DCPPIs	GoP	ALS
PSMA6	PSMB7	1.307	-0.566	2.217	-0.910	-2.782	0.245	0.023	Non	Non	P	Non_DCPPIs	LoP	ALS
PSMA6	PSMB8	0.608	-2.408	-0.089	0.697	-2.319	0.295	0.041	Non	N	Non	Non_DCPPIs	GoN	ALS

Gene 1	Gene 2	SMA	ALS	Normal	Z-score difference		P value		Correlation condition			Groups		Disease
		Z-score	Z-score	Z-score	SMA	ALS	SMA	ALS	SMA	ALS	Normal	SMA	ALS	
PSMA6	PSMC3	1.104	-1.777	1.157	-0.053	-2.934	0.487	0.017	Non	Non	Non	Non_DCPPIs	Other_Neg	ALS
PSMA6	PSMC4	1.153	-1.415	2.965	-1.812	-4.380	0.088	0.001	Non	Non	P	Non_DCPPIs	LoP	ALS
PSMA7	PSMC4	1.529	-1.529	2.007	-0.478	-3.536	0.361	0.006	Non	Non	P	Non_DCPPIs	LoP	ALS
PSMA7	PSMD8	0.961	-0.010	3.062	-2.101	-3.072	0.061	0.012	Non	Non	P	Non_DCPPIs	LoP	ALS
PSMB1	PSMC4	1.255	-0.869	1.694	-0.439	-2.563	0.372	0.030	Non	Non	Non	Non_DCPPIs	Other_Neg	ALS
PSMB3	PSMC4	2.408	-0.400	2.217	0.191	-2.617	0.444	0.029	P	Non	P	Non_DCPPIs	LoP	ALS
PSMB3	CUL1	0.524	1.987	-0.615	1.139	2.602	0.199	0.031	Non	P	Non	Non_DCPPIs	GoP	ALS
PSMB6	PSMC4	2.408	-1.255	3.020	-0.612	-4.275	0.318	0.002	P	Non	P	Non_DCPPIs	LoP	ALS
PSMB6	CUL1	0.736	-1.153	1.809	-1.072	-2.962	0.210	0.017	Non	Non	Non	Non_DCPPIs	Other_Neg	ALS
PSMB6	PSMD6	-1.056	1.777	-1.463	0.408	3.240	0.377	0.011	Non	Non	Non	Non_DCPPIs	Other_Pos	ALS
PSMB7	PSMC1	-0.441	2.989	-0.370	-0.071	3.359	0.480	0.009	Non	P	Non	Non_DCPPIs	GoP	ALS
PSMB7	PSMC4	0.482	-0.524	1.741	-1.259	-2.265	0.176	0.048	Non	Non	Non	Non_DCPPIs	Other_Neg	ALS
PSMB8	PSMC3	-0.524	1.588	-1.312	0.789	2.901	0.285	0.021	Non	Non	Non	Non_DCPPIs	Other_Pos	ALS
PSMB8	PSMD8	-1.307	0.904	-1.977	0.670	2.880	0.313	0.019	Non	Non	N	Non_DCPPIs	LoN	ALS
PSMB8	UBC	0.566	-1.255	1.527	-0.961	-2.781	0.237	0.023	Non	Non	Non	Non_DCPPIs	Other_Neg	ALS
PSMB9	PSMC5	-0.650	1.588	-1.191	0.541	2.779	0.340	0.023	Non	Non	Non	Non_DCPPIs	Other_Pos	ALS
PSMC1	SUMO2	-0.400	1.104	-1.278	0.877	2.381	0.253	0.040	Non	Non	Non	Non_DCPPIs	Other_Pos	ALS
PSMC3	SIRT2	0.566	-2.507	1.792	-1.226	-4.299	0.187	0.001	Non	N	Non	Non_DCPPIs	GoN	ALS
PSMC3	RAD23A	-1.153	-1.712	0.832	-1.986	-2.545	0.072	0.033	Non	Non	Non	Non_DCPPIs	Other_Neg	ALS
PSMC3	PSMD6	-0.119	0.650	-1.799	1.680	2.449	0.112	0.037	Non	Non	Non	Non_DCPPIs	Other_Pos	ALS
PSMC4	PSMD14	0.441	-0.693	1.705	-1.264	-2.399	0.172	0.040	Non	Non	Non	Non_DCPPIs	Other_Neg	ALS
PSMC4	PSMD4	1.588	-1.777	0.528	1.061	-2.305	0.215	0.044	Non	Non	Non	Non_DCPPIs	Other_Neg	ALS

Gene 1	Gene 2	SMA	ALS	Normal	Z-score difference		P value		Correlation condition			Groups		Disease
		Z-score	Z-score	Z-score	SMA	ALS	SMA	ALS	SMA	ALS	Normal	SMA	ALS	
PSMC5	PSMD13	0.319	-0.400	2.315	-1.996	-2.716	0.074	0.024	Non	Non	P	Non_DCPPIs	LoP	ALS
PSMD2	PSMD4	2.728	3.139	0.679	2.049	2.460	0.065	0.034	P	P	Non	Non_DCPPIs	GoP	ALS
PSMD4	RBCK1	-0.524	-2.408	1.365	-1.889	-3.773	0.085	0.004	Non	N	Non	Non_DCPPIs	GoN	ALS
PSMD8	PSMD14	0.736	-0.309	2.460	-1.724	-2.769	0.099	0.023	Non	Non	P	Non_DCPPIs	LoP	ALS
PSMD8	PSMD13	-0.079	-0.576	2.174	-2.253	-2.750	0.054	0.024	Non	Non	P	Non_DCPPIs	LoP	ALS
PSMD13	RAD23B	-0.159	1.415	-1.312	1.154	2.728	0.189	0.022	Non	Non	Non	Non_DCPPIs	Other_Pos	ALS
SKP1	UBE2D3	0.079	-0.961	2.174	-2.095	-3.135	0.064	0.012	Non	Non	P	Non_DCPPIs	LoP	ALS
UBC	STUB1	-0.825	1.153	-1.665	0.841	2.819	0.268	0.023	Non	Non	Non	Non_DCPPIs	Other_Pos	ALS
UBC	KAT5	-1.777	1.649	-0.623	-1.154	2.272	0.192	0.047	Non	Non	Non	Non_DCPPIs	Other_Pos	ALS
UBC	GIPC1	0.199	0.961	-1.957	2.155	2.918	0.060	0.017	Non	Non	Non	Non_DCPPIs	Other_Pos	ALS
UBC	SIRT2	-1.008	0.915	-1.598	0.590	2.513	0.335	0.032	Non	Non	Non	Non_DCPPIs	Other_Pos	ALS
UBC	HSPBP1	-0.825	0.119	-2.239	1.414	2.358	0.141	0.045	Non	Non	N	Non_DCPPIs	LoN	ALS
UBC	UBXN1	0.915	1.415	-1.269	2.184	2.684	0.058	0.027	Non	Non	Non	Non_DCPPIs	Other_Pos	ALS
UBC	VCP	-0.650	-1.588	0.981	-1.631	-2.569	0.115	0.033	Non	Non	Non	Non_DCPPIs	Other_Neg	ALS
UBC	BAG6	0.079	1.777	-1.022	1.101	2.799	0.209	0.021	Non	Non	Non	Non_DCPPIs	Other_Pos	ALS
UBC	USP5	0.360	0.360	-1.917	2.276	2.276	0.052	0.050	Non	Non	Non	Non_DCPPIs	Other_Pos	ALS
UBC	PSMD6	1.104	-1.712	0.947	0.157	-2.659	0.447	0.028	Non	Non	Non	Non_DCPPIs	Other_Neg	ALS
UBE2B	UBE2V2	1.008	0.040	2.440	-1.432	-2.400	0.142	0.039	Non	Non	P	Non_DCPPIs	LoP	ALS
UBE2D3	BTRC	-1.415	2.143	-0.719	-0.696	2.862	0.301	0.019	Non	P	Non	Non_DCPPIs	GoP	ALS
AXIN1	PIAS1	-0.608	0.400	-2.405	1.798	2.806	0.092	0.025	Non	Non	N	Non_DCPPIs	LoN	ALS
CDC16	UBE2S	0.360	-1.360	1.089	-0.730	-2.450	0.298	0.037	Non	Non	Non	Non_DCPPIs	Other_Neg	ALS
PSMD6	SIRT2	-1.255	-0.780	-3.211	1.957	2.431	0.074	0.039	Non	Non	N	Non_DCPPIs	LoN	ALS

Gene 1	Gene 2	SMA	ALS	Normal	Z-score difference		P value		Correlation condition			Groups		Disease
		Z-score	Z-score	Z-score	SMA	ALS	SMA	ALS	SMA	ALS	Normal	SMA	ALS	
CDC34	UBB	0.199	1.255	-1.117	1.315	2.371	0.168	0.045	Non	Non	Non	Non_DCPPIs	Other_Pos	ALS
CDC34	UBC	-0.199	1.008	-1.445	1.247	2.453	0.179	0.035	Non	Non	Non	Non_DCPPIs	Other_Pos	ALS

* Common: both SMA & ALS

Table 10. Network properties of 'proteasome-mediated ubiquitin-dependent protein catabolic process' for genes derived from DCPINs of SMA and ALS

Gene Symbol	Gene ID	Description	Degree		Clustering coefficient	
			SMA	ALS	SMA	ALS
AKT1	207	v-akt murine thymoma viral oncogene homolog 1	1	4	0.000	0.000
ARAF	369	A-Raf proto-oncogene, serine/threonine kinase	1	2	0.000	0.000
AXIN1	8312	axin 1	2	2	0.000	0.000
BAG6	7917	BCL2-associated athanogene 6	0	1	0.000	0.000
BTRC	8945	beta-transducin repeat containing E3 ubiquitin protein ligase	1	4	0.000	0.000
CDC16	8881	cell division cycle 16	0	1	0.000	0.000
CDC34	997	cell division cycle 34	2	3	0.000	0.000
CLU	1191	clusterin	1	2	0.000	0.000
CRBN	51185	cereblon	1	1	0.000	0.000
CUL1	8454	cullin 1	7	2	0.000	0.000
DDIT3	1649	DNA-damage-inducible transcript 3	1	0	0.000	0.000
DNAJB9	4189	DnaJ (Hsp40) homolog, subfamily B, member 9	1	1	0.000	0.000
GIPC1	10755	GIPC PDZ domain containing family, member 1	0	1	0.000	0.000
GNB2L1	10399	guanine nucleotide binding protein (G protein), beta polypeptide 2-like 1	1	0	0.000	0.000
GSK3A	2931	glycogen synthase kinase 3 alpha	1	2	0.000	0.000
HSP90AB1	3326	heat shock protein 90kDa alpha (cytosolic), class B member 1	2	5	0.000	0.000
HSP90B1	7184	heat shock protein 90kDa beta (Grp94), member 1	4	1	0.000	0.000
HSPA5	3309	heat shock 70kDa protein 5 (glucose-regulated protein, 78kDa)	5	3	0.000	0.000
HSPBP1	23640	HSPA (heat shock 70kDa) binding protein, cytoplasmic cochaperone 1	1	2	0.000	1.000
KAT5	10524	K(lysine) acetyltransferase 5	0	2	0.000	0.000

Gene Symbol	Gene ID	Description	Degree		Clustering coefficient	
			SMA	ALS	SMA	ALS
NPLOC4	55666	nuclear protein localization 4 homolog (S. cerevisiae)	2	0	0.000	0.000
OS9	10956	osteosarcoma amplified 9, endoplasmic reticulum lectin	1	0	0.000	0.000
PIAS1	8554	protein inhibitor of activated STAT, 1	0	2	0.000	0.000
PLK3	1263	polo-like kinase 3	1	0	0.000	0.000
PPP2R5C	5527	protein phosphatase 2, regulatory subunit B', gamma	0	1	0.000	0.000
PSEN1	5663	presenilin 1	1	0	0.000	0.000
PSMA3	5684	proteasome (prosome, macropain) subunit, alpha type, 3	5	3	0.000	0.333
PSMA4	5685	proteasome (prosome, macropain) subunit, alpha type, 4	4	5	0.333	0.300
PSMA6	5687	proteasome (prosome, macropain) subunit, alpha type, 6	5	8	0.100	0.179
PSMA7	5688	proteasome (prosome, macropain) subunit, alpha type, 7	5	2	0.000	0.000
PSMB1	5689	proteasome (prosome, macropain) subunit, beta type, 1	2	3	0.000	0.000
PSMB10	5699	proteasome (prosome, macropain) subunit, beta type, 10	3	2	0.000	0.000
PSMB3	5691	proteasome (prosome, macropain) subunit, beta type, 3	3	3	0.000	0.000
PSMB5	5693	proteasome (prosome, macropain) subunit, beta type, 5	4	0	0.167	0.000
PSMB6	5694	proteasome (prosome, macropain) subunit, beta type, 6	4	6	0.000	0.067
PSMB7	5695	proteasome (prosome, macropain) subunit, beta type, 7	1	3	0.000	0.333
PSMB8	5696	proteasome (prosome, macropain) subunit, beta type, 8	0	4	0.000	0.333
PSMB9	5698	proteasome (prosome, macropain) subunit, beta type, 9	1	1	0.000	0.000
PSMC1	5700	proteasome (prosome, macropain) 26S subunit, ATPase, 1	4	5	0.000	0.100
PSMC3	5702	proteasome (prosome, macropain) 26S subunit, ATPase, 3	4	7	0.167	0.238
PSMC4	5704	proteasome (prosome, macropain) 26S subunit, ATPase, 4	4	11	0.000	0.073
PSMC5	5705	proteasome (prosome, macropain) 26S subunit, ATPase, 5	3	2	0.000	0.000

Gene Symbol	Gene ID	Description	Degree		Clustering coefficient	
			SMA	ALS	SMA	ALS
PSMD13	5719	proteasome (prosome, macropain) 26S subunit, non-ATPase, 13	3	3	0.333	0.000
PSMD14	10213	proteasome (prosome, macropain) 26S subunit, non-ATPase, 14	3	4	0.000	0.000
PSMD2	5708	proteasome (prosome, macropain) 26S subunit, non-ATPase, 2	2	2	0.000	0.000
PSMD3	5709	proteasome (prosome, macropain) 26S subunit, non-ATPase, 3	5	1	0.000	0.000
PSMD4	5710	proteasome (prosome, macropain) 26S subunit, non-ATPase, 4	10	8	0.044	0.071
PSMD6	9861	proteasome (prosome, macropain) 26S subunit, non-ATPase, 6	5	6	0.000	0.267
PSMD7	5713	proteasome (prosome, macropain) 26S subunit, non-ATPase, 7	4	2	0.333	1.000
PSMD8	5714	proteasome (prosome, macropain) 26S subunit, non-ATPase, 8	2	5	1.000	0.100
RAD23A	5886	RAD23 homolog A (S. cerevisiae)	8	3	0.071	0.333
RAD23B	5887	RAD23 homolog B (S. cerevisiae)	3	2	0.333	0.000
RBCK1	10616	RanBP-type and C3HC4-type zinc finger containing 1	3	2	0.000	0.000
RBX1	9978	ring-box 1, E3 ubiquitin protein ligase	3	3	0.000	0.000
RPS27A	6233	ribosomal protein S27a	4	0	0.000	0.000
SIRT2	22933	sirtuin 2	2	3	0.000	0.667
SKP1	6500	S-phase kinase-associated protein 1	2	3	0.000	0.000
STUB1	10273	STIP1 homology and U-box containing protein 1, E3 ubiquitin protein ligase	3	5	0.000	0.100
SUMO2	6613	small ubiquitin-like modifier 2	7	4	0.048	0.167
UBA52	7311	ubiquitin A-52 residue ribosomal protein fusion product 1	2	1	0.000	0.000
UBB	7314	ubiquitin B	1	2	0.000	0.000
UBC	7316	ubiquitin C	8	16	0.000	0.017
UBE2B	7320	ubiquitin-conjugating enzyme E2B	1	2	0.000	0.000
UBE2D3	7323	ubiquitin-conjugating enzyme E2D 3	3	5	0.000	0.000

Gene Symbol	Gene ID	Description	Degree		Clustering coefficient	
			SMA	ALS	SMA	ALS
UBE2K	3093	ubiquitin-conjugating enzyme E2K	1	0	0.000	0.000
UBE2S	27338	ubiquitin-conjugating enzyme E2S	1	1	0.000	0.000
UBE2V2	7336	ubiquitin-conjugating enzyme E2 variant 2	0	1	0.000	0.000
UBXN1	51035	UBX domain protein 1	1	1	0.000	0.000
USP5	8078	ubiquitin specific peptidase 5 (isopeptidase T)	2	2	0.000	0.000
VCP	7415	valosin containing protein	6	2	0.000	0.000

Table 11. DCPPIs in the module: 'respiratory electron transport chain'

Gene 1	Gene 2	SMA	ALS	Normal	Z-score difference		P value		Correlation condition			Groups		Disease
		Z-score	Z-score	Z-score	SMA	ALS	SMA	ALS	SMA	ALS	Normal	SMA	ALS	
NDUFA2	NDUFA8	0.279	1.415	2.554	-2.275	-1.139	0.050	0.204	Non	Non	P	LoP	Non_DCPPIs	SMA
NDUFA2	NDUFS5	4.358	0.441	1.330	3.028	-0.889	0.013	0.253	P	Non	Non	GoP	Non_DCPPIs	SMA
NDUFA2	NDUFB11	-1.008	0.693	2.030	-3.038	-1.337	0.015	0.164	Non	Non	P	LoP	Non_DCPPIs	SMA
NDUFA9	NDUFV1	0.608	2.248	3.429	-2.821	-1.181	0.021	0.195	Non	P	P	LoP	Non_DCPPIs	SMA
NDUFB6	SDHB	5.685	2.063	3.268	2.417	-1.204	0.040	0.192	P	P	P	PP	Non_DCPPIs	SMA
NDUFB8	UQCRB	0.000	1.987	2.463	-2.463	-0.475	0.035	0.362	Non	P	P	LoP	Non_DCPPIs	SMA
NDUFS1	NDUFS2	-0.199	1.529	3.627	-3.826	-2.098	0.004	0.064	Non	Non	P	LoP	Non_DCPPIs	SMA
NDUFS6	NDUFS8	-0.608	2.063	3.134	-3.742	-1.071	0.004	0.211	Non	P	P	LoP	Non_DCPPIs	SMA
ATP5A1	ATP5B	0.608	1.008	3.116	-2.508	-2.108	0.037	0.061	Non	Non	P	LoP	Non_DCPPIs	SMA
ATP5B	NDUFA2	2.315	-0.441	-0.212	2.527	-0.229	0.033	0.434	P	Non	Non	GoP	Non_DCPPIs	SMA
ATP5B	SDHB	2.408	0.000	0.006	2.402	-0.006	0.044	0.495	P	Non	Non	GoP	Non_DCPPIs	SMA
ATP5D	ATP5F1	0.693	0.199	-1.770	2.463	1.969	0.037	0.074	Non	Non	Non	Other_Pos	Non_DCPPIs	SMA
SNCA	CYCS	2.143	-0.199	-0.190	2.333	-0.008	0.043	0.496	P	Non	Non	GoP	Non_DCPPIs	SMA
UQCRB	UQCRFS1	0.915	1.649	3.545	-2.630	-1.896	0.030	0.086	Non	Non	P	LoP	Non_DCPPIs	SMA
UQCRC1	CYCS	-1.915	1.712	2.015	-3.930	-0.303	0.004	0.404	Non	Non	P	LoP	Non_DCPPIs	SMA
CYC1	CYCS	-2.315	0.109	2.691	-5.006	-2.582	0.000	0.030	N	Non	P	GoN	LoP	Common
CYC1	UQCR10	-0.400	0.576	2.924	-3.324	-2.348	0.010	0.042	Non	Non	P	LoP	LoP	Common
NDUFA2	NDUFA9	-0.079	1.845	4.339	-4.418	-2.494	0.001	0.033	Non	Non	P	LoP	LoP	Common
NDUFA2	NDUFB7	0.825	1.008	3.627	-2.802	-2.619	0.020	0.026	Non	Non	P	LoP	LoP	Common
NDUFA2	NDUFA13	0.780	0.441	4.491	-3.711	-4.050	0.005	0.002	Non	Non	P	LoP	LoP	Common
NDUFB7	UQCRQ	-0.482	0.608	2.951	-3.434	-2.344	0.006	0.045	Non	Non	P	LoP	LoP	Common

Gene 1	Gene 2	SMA	ALS	Normal	Z-score difference		P value		Correlation condition			Groups		Disease
		Z-score	Z-score	Z-score	SMA	ALS	SMA	ALS	SMA	ALS	Normal	SMA	ALS	
ATP5B	ATP5D	0.869	1.203	-2.651	3.520	3.854	0.006	0.003	Non	Non	N	LoN	LoN	Common
ATP5C1	ATP5F1	1.203	-0.319	3.698	-2.495	-4.017	0.032	0.002	Non	Non	P	LoP	LoP	Common
UQCR11	UQCRQ	2.507	0.780	4.568	-2.061	-3.788	0.069	0.003	P	Non	P	Non_DCPPIs	LoP	ALS
NDUFS6	SDHA	1.588	2.989	0.496	1.092	2.493	0.214	0.036	Non	P	Non	Non_DCPPIs	GoP	ALS
NDUFS8	SDHA	-0.650	2.227	-0.113	-0.538	2.339	0.354	0.042	Non	P	Non	Non_DCPPIs	GoP	ALS
NDUFV2	SDHA	0.159	2.227	-0.520	0.678	2.746	0.308	0.022	Non	P	Non	Non_DCPPIs	GoP	ALS
ATP5A1	ATP5C1	2.728	0.736	3.871	-1.142	-3.134	0.199	0.012	P	Non	P	Non_DCPPIs	LoP	ALS
ATP5A1	ATP5F1	2.227	0.279	3.871	-1.644	-3.592	0.110	0.004	P	Non	P	Non_DCPPIs	LoP	ALS
ATP5B	ATP5C1	1.104	-0.079	2.874	-1.770	-2.953	0.101	0.019	Non	Non	P	Non_DCPPIs	LoP	ALS
ATP5B	ATP5F1	1.649	-0.360	2.921	-1.272	-3.280	0.177	0.012	Non	Non	P	Non_DCPPIs	LoP	ALS
ATP5B	UQCRC1	0.915	0.608	3.013	-2.098	-2.406	0.060	0.043	Non	Non	P	Non_DCPPIs	LoP	ALS
ATP5C1	NDUFS1	1.987	0.736	3.771	-1.784	-3.035	0.094	0.017	P	Non	P	Non_DCPPIs	LoP	ALS
ATP5F1	UQCRB	0.360	0.239	2.521	-2.162	-2.283	0.056	0.050	Non	Non	P	Non_DCPPIs	LoP	ALS
ATP5J	ATP5O	1.712	0.869	3.193	-1.481	-2.323	0.140	0.045	Non	Non	P	Non_DCPPIs	LoP	ALS
ATP5J	ATP5J2	0.825	-0.693	1.914	-1.090	-2.607	0.203	0.026	Non	Non	Non	Non_DCPPIs	Other_Neg	ALS
ATP5O	ATP5H	0.961	4.006	1.398	-0.437	2.607	0.381	0.031	Non	P	Non	Non_DCPPIs	GoP	ALS
SDHA	UQCRB	0.040	1.649	-0.671	0.711	2.320	0.302	0.047	Non	Non	Non	Non_DCPPIs	Other_Pos	ALS
SDHC	SDHD	4.358	0.319	3.377	0.981	-3.058	0.235	0.015	P	Non	P	Non_DCPPIs	LoP	ALS
UQCRB	NDUFB11	-1.360	2.614	0.177	-1.537	2.437	0.126	0.038	Non	P	Non	Non_DCPPIs	GoP	ALS
UQCRC1	UQCRQ	0.524	2.063	-0.647	1.171	2.710	0.193	0.026	Non	P	Non	Non_DCPPIs	GoP	ALS
ATP5J2	UQCRQ	1.649	1.008	3.474	-1.825	-2.466	0.089	0.036	Non	Non	P	Non_DCPPIs	LoP	ALS

* Common: both SMA & ALS

Table 12. Network properties of 'respiratory electron transport chain' for genes derived from DCPINs of SMA and ALS

Gene Symbol	Gene ID	Description	Degree		Clustering coefficient	
			SMA	ALS	SMA	ALS
ATP5A1	498	ATP synthase, H+ transporting, mitochondrial F1 complex, alpha subunit 1, cardiac muscle	1	2	0.000	1.000
ATP5B	506	ATP synthase, H+ transporting, mitochondrial F1 complex, beta polypeptide	4	4	0.000	0.167
ATP5C1	509	ATP synthase, H+ transporting, mitochondrial F1 complex, gamma polypeptide 1	1	4	0.000	0.333
ATP5D	513	ATP synthase, H+ transporting, mitochondrial F1 complex, delta subunit	2	1	0.000	0.000
ATP5F1	515	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit B1	2	4	0.000	0.333
ATP5H	10476	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit d	0	1	0.000	0.000
ATP5J	522	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit F6	0	2	0.000	0.000
ATP5J2	9551	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit F2	0	2	0.000	0.000
ATP5O	539	ATP synthase, H+ transporting, mitochondrial F1 complex, O subunit	0	2	0.000	0.000
CYC1	1537	cytochrome c-1	2	2	0.000	0.000
CYCS	54205	cytochrome c, somatic	3	1	0.000	0.000
NDUFA13	51079	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 13	1	1	0.000	0.000
NDUFA2	4695	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 2, 8kDa	7	3	0.000	0.000
NDUFA8	4702	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 8, 19kDa	1	0	0.000	0.000
NDUFA9	4704	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 9, 39kDa	2	1	0.000	0.000
NDUFB11	54539	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 11, 17.3kDa	1	1	0.000	0.000
NDUFB6	4712	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 6, 17kDa	1	0	0.000	0.000
NDUFB7	4713	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 7, 18kDa	2	2	0.000	0.000
NDUFB8	4714	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 8, 19kDa	1	0	0.000	0.000
NDUFS1	4719	NADH dehydrogenase (ubiquinone) Fe-S protein 1, 75kDa (NADH-coenzyme Q reductase)	1	1	0.000	0.000
NDUFS2	4720	NADH dehydrogenase (ubiquinone) Fe-S protein 2, 49kDa (NADH-coenzyme Q reductase)	1	0	0.000	0.000

Gene Symbol	Gene ID	Description	Degree		Clustering coefficient	
			SMA	ALS	SMA	ALS
NDUFS5	4725	NADH dehydrogenase (ubiquinone) Fe-S protein 5, 15kDa (NADH-coenzyme Q reductase)	1	0	0.000	0.000
NDUFS6	4726	NADH dehydrogenase (ubiquinone) Fe-S protein 6, 13kDa (NADH-coenzyme Q reductase)	1	1	0.000	0.000
NDUFS8	4728	NADH dehydrogenase (ubiquinone) Fe-S protein 8, 23kDa (NADH-coenzyme Q reductase)	1	1	0.000	0.000
NDUFV1	4723	NADH dehydrogenase (ubiquinone) flavoprotein 1, 51kDa	1	0	0.000	0.000
NDUFV2	4729	NADH dehydrogenase (ubiquinone) flavoprotein 2, 24kDa	0	1	0.000	0.000
SDHA	6389	succinate dehydrogenase complex, subunit A, flavoprotein (Fp)	0	4	0.000	0.000
SDHB	6390	succinate dehydrogenase complex, subunit B, iron sulfur (Ip)	2	0	0.000	0.000
SDHC	6391	succinate dehydrogenase complex, subunit C, integral membrane protein, 15kDa	0	1	0.000	0.000
SDHD	6392	succinate dehydrogenase complex, subunit D, integral membrane protein	0	1	0.000	0.000
SNCA	6622	synuclein, alpha (non A4 component of amyloid precursor)	1	0	0.000	0.000
UQCR10	29796	ubiquinol-cytochrome c reductase, complex III subunit X	1	1	0.000	0.000
UQCR11	10975	ubiquinol-cytochrome c reductase, complex III subunit XI	0	1	0.000	0.000
UQCRB	7381	ubiquinol-cytochrome c reductase binding protein	2	3	0.000	0.000
UQCRC1	7384	ubiquinol-cytochrome c reductase core protein I	1	2	0.000	0.000
UQCRFS1	7386	ubiquinol-cytochrome c reductase, Rieske iron-sulfur polypeptide 1	1	0	0.000	0.000
UQCRQ	27089	ubiquinol-cytochrome c reductase, complex III subunit VII, 9.5kDa	1	4	0.000	0.000

Table 13. DCPPIs in the module: 'RNA splicing'

Gene 1	Gene 2	SMA	ALS	Normal	Z-score difference		P value		Correlation condition			Groups		Disease
		Z-score	Z-score	Z-score	SMA	ALS	SMA	ALS	SMA	ALS	Normal	SMA	ALS	
PQBP1	TXNL4A	-1.777	1.008	2.338	-4.115	-1.330	0.002	0.166	Non	Non	P	LoP	Non_DCPPIs	SMA
RBM5	PRPF19	-1.588	0.524	2.302	-3.890	-1.778	0.004	0.098	Non	Non	P	LoP	Non_DCPPIs	SMA
RBM5	LSM8	2.728	-0.566	-0.873	3.602	0.308	0.005	0.409	P	Non	Non	GoP	Non_DCPPIs	SMA
SRRM1	DNAJC8	-0.441	-1.203	-2.924	2.483	1.721	0.039	0.103	Non	Non	N	LoN	Non_DCPPIs	SMA
SRRM1	ACIN1	-1.203	2.315	1.656	-2.859	0.659	0.018	0.315	Non	P	Non	Other_Neg	Non_DCPPIs	SMA
CD2BP2	PRPF8	-1.008	1.649	2.521	-3.529	-0.872	0.005	0.261	Non	Non	P	LoP	Non_DCPPIs	SMA
CD2BP2	TXNL4A	-1.987	0.000	1.637	-3.625	-1.637	0.005	0.114	N	Non	Non	GoN	Non_DCPPIs	SMA
CD2BP2	PUF60	-1.712	1.529	2.754	-4.466	-1.225	0.001	0.182	Non	Non	P	LoP	Non_DCPPIs	SMA
USP39	LSM8	-2.315	2.227	0.276	-2.591	1.951	0.030	0.079	N	P	Non	GoN	Non_DCPPIs	SMA
SREK1	HNRNPA3	0.159	2.614	4.152	-3.993	-1.538	0.003	0.129	Non	P	P	LoP	Non_DCPPIs	SMA
DDX5	HNRNPH1	-0.566	1.360	1.828	-2.394	-0.468	0.043	0.367	Non	Non	Non	Other_Neg	Non_DCPPIs	SMA
DHX9	IVNS1ABP	-2.408	1.203	0.512	-2.920	0.692	0.018	0.296	N	Non	Non	GoN	Non_DCPPIs	SMA
ACIN1	PRPF6	-0.961	-0.239	1.454	-2.415	-1.693	0.041	0.106	Non	Non	Non	Other_Neg	Non_DCPPIs	SMA
FUS	HNRNPA3	0.566	0.279	-1.703	2.269	1.982	0.045	0.069	Non	Non	Non	Other_Pos	Non_DCPPIs	SMA
LSM4	LSM7	0.159	0.319	2.581	-2.422	-2.262	0.039	0.052	Non	Non	P	LoP	Non_DCPPIs	SMA
PRPF19	XAB2	-0.961	2.143	1.705	-2.667	0.438	0.026	0.383	Non	P	Non	Other_Neg	Non_DCPPIs	SMA
HNRNPA1	ACIN1	-1.987	-0.319	0.362	-2.350	-0.681	0.048	0.305	N	Non	Non	GoN	Non_DCPPIs	SMA
HNRNPA1	NCBP1	2.227	0.360	-1.191	3.418	1.551	0.007	0.122	P	Non	Non	GoP	Non_DCPPIs	SMA
HNRNPA1	PNN	-2.614	0.079	1.508	-4.122	-1.429	0.002	0.145	N	Non	Non	GoN	Non_DCPPIs	SMA
HNRNPA1	SFPQ	-1.360	1.845	2.729	-4.089	-0.884	0.002	0.256	Non	Non	P	LoP	Non_DCPPIs	SMA
HNRNPA2B1	MBNL1	3.309	0.159	-1.418	4.727	1.577	0.000	0.122	P	Non	Non	GoP	Non_DCPPIs	SMA

Gene 1	Gene 2	SMA	ALS	Normal	Z-score difference		P value		Correlation condition			Groups		Disease
		Z-score	Z-score	Z-score	SMA	ALS	SMA	ALS	SMA	ALS	Normal	SMA	ALS	
HNRNPA2B1	SMN2	1.360	-0.650	-1.140	2.500	0.490	0.036	0.360	Non	Non	Non	Other_Pos	Non_DCPPIs	SMA
HNRNPC	RALY	2.507	-1.845	-0.103	2.610	-1.742	0.028	0.105	P	Non	Non	GoP	Non_DCPPIs	SMA
HNRNPC	HNRNPD	-1.987	1.360	0.300	-2.287	1.061	0.045	0.219	N	Non	Non	GoN	Non_DCPPIs	SMA
HNRNPC	NHP2L1	-2.728	-0.279	0.964	-3.692	-1.243	0.004	0.180	N	Non	Non	GoN	Non_DCPPIs	SMA
HNRNPD	HNRNPA0	-0.961	-0.040	1.809	-2.770	-1.848	0.022	0.087	Non	Non	Non	Other_Neg	Non_DCPPIs	SMA
HNRNPK	SREK1	-0.319	1.845	3.034	-3.353	-1.190	0.009	0.192	Non	Non	P	LoP	Non_DCPPIs	SMA
HNRNPK	NHP2L1	1.415	-0.608	-1.427	2.843	0.820	0.019	0.268	Non	Non	Non	Other_Pos	Non_DCPPIs	SMA
HNRNPK	RBM4	-1.649	1.056	0.849	-2.498	0.207	0.037	0.440	Non	Non	Non	Other_Neg	Non_DCPPIs	SMA
HNRNPK	SNRPD1	-1.777	0.441	0.800	-2.577	-0.359	0.029	0.389	Non	Non	Non	Other_Neg	Non_DCPPIs	SMA
HNRNPU	HNRNPA0	-2.227	0.482	2.121	-4.348	-1.639	0.001	0.112	N	Non	P	GoN	Non_DCPPIs	SMA
HNRNPU	RPS13	1.203	-0.400	-1.245	2.448	0.845	0.040	0.267	Non	Non	Non	Other_Pos	Non_DCPPIs	SMA
YBX1	LSM3	2.408	-1.104	0.072	2.336	-1.176	0.047	0.195	P	Non	Non	GoP	Non_DCPPIs	SMA
PCBP2	QKI	-1.203	1.777	2.195	-3.399	-0.418	0.008	0.377	Non	Non	P	LoP	Non_DCPPIs	SMA
PNN	PPIG	-2.614	2.989	0.784	-3.397	2.205	0.008	0.054	N	P	Non	GoN	Non_DCPPIs	SMA
PNN	RBM39	-2.063	1.987	1.217	-3.280	0.770	0.009	0.284	N	P	Non	GoN	Non_DCPPIs	SMA
POLR2C	POLR2J	-3.503	0.279	-0.027	-3.475	0.306	0.006	0.414	N	Non	Non	GoN	Non_DCPPIs	SMA
POLR2E	POLR2F	0.079	0.608	2.858	-2.778	-2.250	0.025	0.053	Non	Non	P	LoP	Non_DCPPIs	SMA
POLR2G	POLR2J	-1.529	-0.693	0.735	-2.264	-1.428	0.049	0.143	Non	Non	Non	Other_Neg	Non_DCPPIs	SMA
RBM4	HNRNPUL1	-1.915	1.529	0.735	-2.650	0.794	0.027	0.271	Non	Non	Non	Other_Neg	Non_DCPPIs	SMA
RBM4	SNRPC	1.777	0.119	-1.252	3.029	1.371	0.015	0.155	Non	Non	Non	Other_Pos	Non_DCPPIs	SMA
SFPQ	SREK1	0.079	1.153	2.521	-2.442	-1.368	0.043	0.154	Non	Non	P	LoP	Non_DCPPIs	SMA
SFPQ	SRSF3	-1.104	1.712	2.792	-3.896	-1.080	0.002	0.214	Non	Non	P	LoP	Non_DCPPIs	SMA

Gene 1	Gene 2	SMA	ALS	Normal	Z-score difference		P value		Correlation condition			Groups		Disease
		Z-score	Z-score	Z-score	SMA	ALS	SMA	ALS	SMA	ALS	Normal	SMA	ALS	
SFPQ	SRSF5	-1.008	0.199	2.271	-3.279	-2.073	0.011	0.067	Non	Non	P	LoP	Non_DCPPIs	SMA
SRSF3	SRRM1	0.360	1.255	2.741	-2.382	-1.487	0.044	0.134	Non	Non	P	LoP	Non_DCPPIs	SMA
SRSF3	SREK1	-1.255	3.309	3.253	-4.507	0.056	0.001	0.483	Non	P	P	LoP	Non_DCPPIs	SMA
SRSF3	RBM8A	-0.319	2.063	2.349	-2.668	-0.285	0.028	0.414	Non	P	P	LoP	Non_DCPPIs	SMA
SRSF5	TRA2B	2.315	0.400	-1.072	3.387	1.473	0.009	0.141	P	Non	Non	GoP	Non_DCPPIs	SMA
SMN2	SNRPE	-2.227	0.279	0.906	-3.133	-0.627	0.013	0.317	N	Non	Non	GoN	Non_DCPPIs	SMA
SNRPA1	PRPF8	0.915	-0.319	-1.907	2.822	1.588	0.021	0.123	Non	Non	Non	Other_Pos	Non_DCPPIs	SMA
SNRPA1	SF3A3	-1.987	0.608	1.741	-3.729	-1.133	0.005	0.204	N	Non	Non	GoN	Non_DCPPIs	SMA
SNRPB	WBP4	1.471	0.079	-0.956	2.427	1.035	0.037	0.226	Non	Non	Non	Other_Pos	Non_DCPPIs	SMA
SNRPB2	SF3A3	-1.471	0.566	1.582	-3.053	-1.016	0.014	0.228	Non	Non	Non	Other_Neg	Non_DCPPIs	SMA
SNRPB2	SNRPN	2.507	-0.400	-0.425	2.932	0.025	0.020	0.499	P	Non	Non	GoP	Non_DCPPIs	SMA
SNRPD1	LSM3	-1.987	-0.239	1.376	-3.364	-1.615	0.009	0.116	N	Non	Non	GoN	Non_DCPPIs	SMA
SNRPD1	LSM8	-0.869	1.153	2.818	-3.688	-1.665	0.005	0.108	Non	Non	P	LoP	Non_DCPPIs	SMA
SNRPD2	SRRM1	-0.319	-1.845	-3.905	3.586	2.060	0.005	0.065	Non	Non	N	LoN	Non_DCPPIs	SMA
SNRPD3	LSM7	-0.869	0.780	1.821	-2.690	-1.040	0.028	0.222	Non	Non	Non	Other_Neg	Non_DCPPIs	SMA
SNRPD3	SNRPG	-0.319	1.255	2.907	-3.227	-1.653	0.011	0.111	Non	Non	P	LoP	Non_DCPPIs	SMA
SNRPF	CD2BP2	-1.415	-0.079	2.153	-3.568	-2.232	0.006	0.053	Non	Non	P	LoP	Non_DCPPIs	SMA
SNRPN	RBFOX1	1.845	-0.199	-2.090	3.934	1.891	0.003	0.082	Non	Non	N	LoN	Non_DCPPIs	SMA
DDX39B	LSM4	1.008	-0.040	-2.185	3.193	2.145	0.011	0.058	Non	Non	N	LoN	Non_DCPPIs	SMA
SNRNP25	CPSF7	0.869	-2.507	-2.874	3.744	0.367	0.003	0.386	Non	N	N	LoN	Non_DCPPIs	SMA
PABPN1	PABPC1	-1.008	0.441	1.427	-2.435	-0.986	0.041	0.237	Non	Non	Non	Other_Neg	Non_DCPPIs	SMA
SRSF9	NOL3	-1.987	0.780	1.410	-3.397	-0.629	0.008	0.322	N	Non	Non	GoN	Non_DCPPIs	SMA

Gene 1	Gene 2	SMA	ALS	Normal	Z-score difference		P value		Correlation condition			Groups		Disease
		Z-score	Z-score	Z-score	SMA	ALS	SMA	ALS	SMA	ALS	Normal	SMA	ALS	
SRSF11	USP39	-1.649	0.079	0.824	-2.473	-0.745	0.039	0.287	Non	Non	Non	Other_Neg	Non_DCPPIs	SMA
SRSF11	PRPF19	-1.471	1.008	1.159	-2.630	-0.151	0.028	0.458	Non	Non	Non	Other_Neg	Non_DCPPIs	SMA
RBM39	SRRM1	0.780	0.961	3.149	-2.368	-2.187	0.042	0.060	Non	Non	P	LoP	Non_DCPPIs	SMA
RBM39	RALY	0.239	-2.728	-2.285	2.524	-0.443	0.031	0.380	Non	N	N	LoN	Non_DCPPIs	SMA
RBM39	ACIN1	-2.989	-0.199	-0.066	-2.923	-0.133	0.019	0.461	N	Non	Non	GoN	Non_DCPPIs	SMA
SRRM1	PUF60	0.239	2.408	-2.440	2.678	4.848	0.024	0.001	Non	P	N	LoN	GoP	Common
PRPF8	PRPF6	-0.915	-0.915	1.997	-2.912	-2.912	0.017	0.021	Non	Non	P	LoP	LoP	Common
DDX5	MYOD1	0.915	1.056	-2.521	3.436	3.577	0.010	0.006	Non	Non	N	LoN	LoN	Common
DDX5	SNRPD2	1.008	-0.040	-2.729	3.737	2.689	0.004	0.024	Non	Non	N	LoN	LoN	Common
DHX9	HNRNPA0	-1.471	-0.524	2.121	-3.592	-2.645	0.007	0.026	Non	Non	P	LoP	LoP	Common
DHX9	SNRPB	-0.482	-0.441	-3.345	2.863	2.904	0.019	0.017	Non	Non	N	LoN	LoN	Common
LSM5	LSM8	-0.869	-0.119	2.729	-3.598	-2.848	0.006	0.022	Non	Non	P	LoP	LoP	Common
FUS	HNRNPK	1.153	1.203	-1.987	3.140	3.190	0.013	0.011	Non	Non	N	LoN	LoN	Common
LSM3	LSM7	-0.608	-0.693	2.414	-3.022	-3.107	0.013	0.013	Non	Non	P	LoP	LoP	Common
HNRNPA1	IVNS1ABP	2.408	1.104	-1.383	3.791	2.487	0.004	0.034	P	Non	Non	GoP	Other_Pos	Common
HNRNPA2B1	HNRNPA3	0.915	0.825	-2.486	3.401	3.311	0.010	0.009	Non	Non	N	LoN	LoN	Common
HNRNPH1	SMN2	-1.056	0.239	2.679	-3.734	-2.440	0.005	0.042	Non	Non	P	LoP	LoP	Common
HNRNPK	HNRNPA3	0.780	1.712	4.744	-3.964	-3.032	0.003	0.015	Non	Non	P	LoP	LoP	Common
HNRNPK	MBNL1	-0.441	-0.239	4.218	-4.660	-4.457	0.001	0.001	Non	Non	P	LoP	LoP	Common
HNRNPK	SRSF11	0.869	1.915	4.634	-3.765	-2.720	0.004	0.024	Non	Non	P	LoP	LoP	Common
HNRNPK	QKI	-1.415	-0.239	2.884	-4.299	-3.123	0.002	0.012	Non	Non	P	LoP	LoP	Common
YBX1	HNRNPA0	-1.649	-0.360	3.507	-5.156	-3.867	0.001	0.005	Non	Non	P	LoP	LoP	Common

Gene 1	Gene 2	SMA	ALS	Normal	Z-score difference		P value		Correlation condition			Groups		Disease
		Z-score	Z-score	Z-score	SMA	ALS	SMA	ALS	SMA	ALS	Normal	SMA	ALS	
YBX1	SNRPB	0.566	0.199	-2.090	2.655	2.288	0.028	0.048	Non	Non	N	LoN	LoN	Common
POLR2C	PRMT5	-0.650	0.159	2.965	-3.615	-2.806	0.006	0.022	Non	Non	P	LoP	LoP	Common
POLR2E	POLR2G	0.360	0.199	3.149	-2.789	-2.950	0.022	0.017	Non	Non	P	LoP	LoP	Common
POLR2E	POLR2I	-0.566	-0.608	3.610	-4.175	-4.217	0.002	0.001	Non	Non	P	LoP	LoP	Common
POLR2E	POLR2J	-1.056	-0.736	2.924	-3.980	-3.661	0.002	0.006	Non	Non	P	LoP	LoP	Common
POLR2E	POLR2L	0.119	-1.307	2.474	-2.355	-3.781	0.046	0.004	Non	Non	P	LoP	LoP	Common
SFPQ	SRRM1	-1.777	1.307	3.964	-5.741	-2.657	0.000	0.028	Non	Non	P	LoP	LoP	Common
SFPQ	SMN2	0.079	-1.529	2.428	-2.349	-3.957	0.045	0.003	Non	Non	P	LoP	LoP	Common
SFPQ	SNRPD2	-0.360	-0.566	-3.283	2.924	2.718	0.019	0.024	Non	Non	N	LoN	LoN	Common
SMN2	SNRPD2	0.360	0.736	-2.428	2.788	3.165	0.023	0.012	Non	Non	N	LoN	LoN	Common
SNRPD1	SNRPE	0.040	-0.040	5.476	-5.436	-5.515	0.000	0.000	Non	Non	P	LoP	LoP	Common
SNRPD2	SNRPF	-0.040	-1.987	2.679	-2.718	-4.666	0.023	0.001	Non	N	P	LoP	GoN	Common
SNRPD3	PABPC1	0.482	1.987	-2.056	2.538	4.043	0.035	0.003	Non	P	N	LoN	GoP	Common
SNRPE	STRAP	0.079	1.056	4.339	-4.260	-3.283	0.002	0.010	Non	Non	P	LoP	LoP	Common
SNRPE	LSM5	0.780	0.159	3.507	-2.727	-3.348	0.026	0.008	Non	Non	P	LoP	LoP	Common
SNRPE	SNRPG	-1.203	0.159	3.425	-4.628	-3.266	0.001	0.009	Non	Non	P	LoP	LoP	Common
SNRPF	LSM7	-1.588	1.777	4.286	-5.875	-2.509	0.000	0.036	Non	Non	P	LoP	LoP	Common
SNRPG	LSM3	0.780	0.524	3.302	-2.522	-2.779	0.034	0.023	Non	Non	P	LoP	LoP	Common
DDX39B	THOC6	0.319	0.736	-2.018	2.337	2.754	0.047	0.025	Non	Non	N	LoN	LoN	Common
SRSF11	PUF60	0.360	-0.040	-2.818	3.178	2.779	0.012	0.022	Non	Non	N	LoN	LoN	Common
SRSF11	ARL6IP4	-0.524	-0.566	-3.006	2.482	2.441	0.036	0.038	Non	Non	N	LoN	LoN	Common
QKI	RALY	3.309	3.309	-0.983	4.291	4.291	0.001	0.002	P	P	Non	GoP	GoP	Common

Gene 1	Gene 2	SMA	ALS	Normal	Z-score difference		P value		Correlation condition			Groups		Disease
		Z-score	Z-score	Z-score	SMA	ALS	SMA	ALS	SMA	ALS	Normal	SMA	ALS	
IVNS1ABP	HNRNPUL1	-0.650	1.056	-1.312	0.662	2.368	0.312	0.046	Non	Non	Non	Non_DCPPIs	Other_Pos	ALS
CLK1	SRSF3	0.650	0.079	2.486	-1.836	-2.407	0.089	0.039	Non	Non	P	Non_DCPPIs	LoP	ALS
DDX5	YBX1	-0.279	2.227	-1.115	0.836	3.341	0.263	0.009	Non	P	Non	Non_DCPPIs	GoP	ALS
DHX9	USP39	0.961	-0.319	2.666	-1.705	-2.985	0.097	0.015	Non	Non	P	Non_DCPPIs	LoP	ALS
DHX9	HNRNPA1	-2.408	2.728	-0.873	-1.535	3.602	0.126	0.005	N	P	Non	Non_DCPPIs	GoP	ALS
DHX9	RBM4	0.524	-0.736	1.927	-1.403	-2.663	0.151	0.026	Non	Non	Non	Non_DCPPIs	Other_Neg	ALS
PUF60	PABPC1	-0.360	0.869	-2.018	1.658	2.887	0.113	0.019	Non	Non	N	Non_DCPPIs	LoN	ALS
FUS	SRRM1	-0.279	1.915	-2.163	1.885	4.078	0.085	0.002	Non	Non	N	Non_DCPPIs	LoN	ALS
FUS	SFPQ	0.279	0.693	-1.609	1.888	2.302	0.083	0.048	Non	Non	Non	Non_DCPPIs	Other_Pos	ALS
HNRNPA1	TRA2B	1.255	1.649	-0.923	2.177	2.572	0.060	0.030	Non	Non	Non	Non_DCPPIs	Other_Pos	ALS
HNRNPA2B1	SRSF3	0.119	1.529	-1.887	2.006	3.416	0.068	0.008	Non	Non	Non	Non_DCPPIs	Other_Pos	ALS
HNRNPA2B1	SNRPB2	0.441	-0.279	2.360	-1.919	-2.639	0.083	0.027	Non	Non	P	Non_DCPPIs	LoP	ALS
HNRNPC	YBX1	-1.360	2.143	-0.695	-0.665	2.838	0.313	0.021	Non	P	Non	Non_DCPPIs	GoP	ALS
HNRNPD	SREK1	-0.869	2.408	0.089	-0.959	2.319	0.241	0.047	Non	P	Non	Non_DCPPIs	GoP	ALS
HNRNPK	RALY	-2.063	0.040	-2.258	0.194	2.297	0.438	0.048	N	Non	N	Non_DCPPIs	LoN	ALS
HNRNPK	YBX1	-0.079	2.227	-1.312	1.233	3.539	0.180	0.006	Non	P	Non	Non_DCPPIs	GoP	ALS
HNRNPK	PCBP2	1.008	-0.869	1.694	-0.686	-2.563	0.303	0.031	Non	Non	Non	Non_DCPPIs	Other_Neg	ALS
HNRNPU	PRPF8	0.279	-1.008	1.665	-1.387	-2.673	0.151	0.028	Non	Non	Non	Non_DCPPIs	Other_Neg	ALS
HNRNPU	IVNS1ABP	0.239	1.255	-1.174	1.413	2.429	0.142	0.039	Non	Non	Non	Non_DCPPIs	Other_Pos	ALS
HNRNPU	WBP4	0.239	-2.614	0.535	-0.297	-3.149	0.415	0.013	Non	N	Non	Non_DCPPIs	GoN	ALS
HNRNPU	TRA2A	0.400	-0.566	1.847	-1.447	-2.413	0.150	0.039	Non	Non	Non	Non_DCPPIs	Other_Neg	ALS
HNRNPU	NONO	0.482	2.728	0.456	0.026	2.272	0.499	0.046	Non	P	Non	Non_DCPPIs	GoP	ALS

Gene 1	Gene 2	SMA	ALS	Normal	Z-score difference		P value		Correlation condition			Groups		Disease
		Z-score	Z-score	Z-score	SMA	ALS	SMA	ALS	SMA	ALS	Normal	SMA	ALS	
HNRNPU	POLR2J	-1.307	-2.227	0.599	-1.906	-2.826	0.082	0.022	Non	N	Non	Non_DCPPIs	GoN	ALS
HNRNPU	RPS26	-0.869	2.143	-1.392	0.522	3.535	0.345	0.008	Non	P	Non	Non_DCPPIs	GoP	ALS
HNRNPU	TRA2B	0.360	0.961	-1.675	2.034	2.636	0.071	0.029	Non	Non	Non	Non_DCPPIs	Other_Pos	ALS
HNRNPU	SMN2	-0.239	-1.915	0.449	-0.687	-2.363	0.304	0.048	Non	Non	Non	Non_DCPPIs	Other_Neg	ALS
HNRNPU	RBM39	0.119	1.987	-0.679	0.798	2.666	0.277	0.030	Non	P	Non	Non_DCPPIs	GoP	ALS
MYOD1	PABPN1	0.869	2.728	-1.234	2.104	3.963	0.062	0.003	Non	P	Non	Non_DCPPIs	GoP	ALS
NCBP1	IVNS1ABP	2.227	1.056	4.025	-1.799	-2.970	0.093	0.018	P	Non	P	Non_DCPPIs	LoP	ALS
NHP2L1	SAP18	0.040	-1.255	2.271	-2.232	-3.526	0.053	0.007	Non	Non	P	Non_DCPPIs	LoP	ALS
NONO	WBP4	0.869	-3.309	0.159	0.710	-3.468	0.292	0.009	Non	N	Non	Non_DCPPIs	GoN	ALS
NONO	YBX1	0.159	2.063	-0.315	0.474	2.379	0.360	0.040	Non	P	Non	Non_DCPPIs	GoP	ALS
NONO	SMN2	-0.239	-2.143	1.481	-1.720	-3.624	0.107	0.005	Non	N	Non	Non_DCPPIs	GoN	ALS
YBX1	IVNS1ABP	-0.736	3.503	-0.939	0.203	4.442	0.444	0.001	Non	P	Non	Non_DCPPIs	GoP	ALS
YBX1	SREK1	-1.471	2.989	-1.600	0.129	4.589	0.462	0.001	Non	P	Non	Non_DCPPIs	GoP	ALS
YBX1	SNRPD1	-0.400	1.649	-1.269	0.869	2.918	0.253	0.017	Non	Non	Non	Non_DCPPIs	Other_Pos	ALS
POLR2C	POLR2G	1.415	-1.056	2.884	-1.469	-3.940	0.136	0.003	Non	Non	P	Non_DCPPIs	LoP	ALS
RBM4	RBM22	-0.079	1.649	-1.286	1.207	2.935	0.189	0.018	Non	Non	Non	Non_DCPPIs	Other_Pos	ALS
RPS13	RPS26	0.360	-1.588	1.705	-1.346	-3.294	0.165	0.009	Non	Non	Non	Non_DCPPIs	Other_Neg	ALS
SRSF5	SAP18	0.608	2.507	-0.300	0.907	2.807	0.245	0.023	Non	P	Non	Non_DCPPIs	GoP	ALS
SRSF5	SNRPF	-1.153	1.777	-0.873	-0.280	2.650	0.425	0.029	Non	Non	Non	Non_DCPPIs	Other_Pos	ALS
TRA2B	IVNS1ABP	2.227	1.712	4.088	-1.861	-2.376	0.086	0.043	P	Non	P	Non_DCPPIs	LoP	ALS
SMN2	HNRNPUL1	0.079	-2.507	1.304	-1.224	-3.811	0.183	0.005	Non	N	Non	Non_DCPPIs	GoN	ALS
SMN2	SNRPB2	-0.400	1.203	-1.115	0.714	2.318	0.297	0.046	Non	Non	Non	Non_DCPPIs	Other_Pos	ALS

Gene 1	Gene 2	SMA	ALS	Normal	Z-score difference		P value		Correlation condition			Groups		Disease
		Z-score	Z-score	Z-score	SMA	ALS	SMA	ALS	SMA	ALS	Normal	SMA	ALS	
SMN2	SNRPD3	-0.319	2.408	-1.159	0.840	3.567	0.263	0.006	Non	P	Non	Non_DCPPIs	GoP	ALS
SMN2	SNRPG	0.040	1.649	-0.784	0.823	2.433	0.271	0.041	Non	Non	Non	Non_DCPPIs	Other_Pos	ALS
SMN2	GEMIN7	-0.441	3.139	-0.808	0.367	3.947	0.395	0.002	Non	P	Non	Non_DCPPIs	GoP	ALS
SNRPA1	SNRPD1	0.400	-1.987	1.410	-1.009	-3.397	0.231	0.008	Non	N	Non	Non_DCPPIs	GoN	ALS
SNRPA1	SNRPF	2.507	-0.915	1.356	1.151	-2.271	0.200	0.047	P	Non	Non	Non_DCPPIs	Other_Neg	ALS
SNRPB	CD2BP2	-0.199	1.588	-0.906	0.707	2.494	0.293	0.038	Non	Non	Non	Non_DCPPIs	Other_Pos	ALS
SNRPB	SNRPD2	0.319	-2.852	1.132	-0.812	-3.984	0.272	0.003	Non	N	Non	Non_DCPPIs	GoN	ALS
SNRPB	GEMIN7	0.279	-0.400	2.018	-1.739	-2.418	0.106	0.041	Non	Non	P	Non_DCPPIs	LoP	ALS
SNRPC	SRRM1	-1.153	0.441	-2.195	1.042	2.637	0.224	0.030	Non	Non	N	Non_DCPPIs	LoN	ALS
SNRPD2	PRPF8	0.869	-1.203	1.383	-0.513	-2.586	0.344	0.031	Non	Non	Non	Non_DCPPIs	Other_Neg	ALS
SNRPD3	SNRPN	1.415	-1.712	0.661	0.754	-2.373	0.284	0.043	Non	Non	Non	Non_DCPPIs	Other_Neg	ALS
SNRPE	PRPF8	-1.008	2.989	-1.937	0.929	4.925	0.249	0.001	Non	P	Non	Non_DCPPIs	GoP	ALS
SNRPE	LSM4	-0.159	-1.915	1.226	-1.384	-3.140	0.157	0.013	Non	Non	Non	Non_DCPPIs	Other_Neg	ALS
SNRPF	SRRM1	-0.825	1.360	-2.629	1.805	3.990	0.092	0.003	Non	Non	N	Non_DCPPIs	LoN	ALS
SNRPF	PUF60	1.415	1.153	3.507	-2.092	-2.354	0.062	0.041	Non	Non	P	Non_DCPPIs	LoP	ALS
SNRPF	RBM8A	-0.239	1.529	-1.321	1.083	2.850	0.218	0.021	Non	Non	Non	Non_DCPPIs	Other_Pos	ALS
SRSF11	RBM39	0.961	0.400	2.780	-1.819	-2.379	0.091	0.044	Non	Non	P	Non_DCPPIs	LoP	ALS
RBM39	SAP18	1.153	1.915	-0.647	1.800	2.561	0.098	0.033	Non	Non	Non	Non_DCPPIs	Other_Pos	ALS
RBM39	ARL6IP4	-1.471	0.040	-3.120	1.648	3.159	0.112	0.011	Non	Non	N	Non_DCPPIs	LoN	ALS

* Common: both SMA & ALS

Table 14. Network properties of 'RNA splicing' for genes derived from DCPINs of SMA and ALS

Gene Symbol	Gene ID	Description	Degree		Clustering coefficient	
			SMA	ALS	SMA	ALS
ACIN1	22985	apoptotic chromatin condensation inducer 1	4	0	0.167	0.000
ARL6IP4	51329	ADP-ribosylation factor-like 6 interacting protein 4	1	2	0.000	1.000
CD2BP2	10421	CD2 (cytoplasmic tail) binding protein 2	4	1	0.000	0.000
CLK1	1195	CDC-like kinase 1	0	1	0.000	0.000
CPSF7	79869	cleavage and polyadenylation specific factor 7, 59kDa	1	0	0.000	0.000
DDX39B	7919	DEAD (Asp-Glu-Ala-Asp) box polypeptide 39B	2	1	0.000	0.000
DDX5	1655	DEAD (Asp-Glu-Ala-Asp) box helicase 5	3	3	0.000	0.000
DHX9	1660	DEAH (Asp-Glu-Ala-His) box helicase 9	3	5	0.000	0.000
DNAJC8	22826	DnaJ (Hsp40) homolog, subfamily C, member 8	1	0	0.000	0.000
FUS	2521	FUS RNA binding protein	2	3	1.000	0.333
GEMIN7	79760	gem (nuclear organelle) associated protein 7	0	2	0.000	0.000
HNRNPA0	10949	heterogeneous nuclear ribonucleoprotein A0	4	2	0.000	0.000
HNRNPA1	3178	heterogeneous nuclear ribonucleoprotein A1	5	3	0.000	0.333
HNRNPA2B1	3181	heterogeneous nuclear ribonucleoprotein A2/B1	3	3	0.000	0.000
HNRNPA3	220988	heterogeneous nuclear ribonucleoprotein A3	4	2	0.333	0.000
HNRNPC	3183	heterogeneous nuclear ribonucleoprotein C (C1/C2)	3	1	0.000	0.000
HNRNPD	3184	heterogeneous nuclear ribonucleoprotein D (AU-rich element RNA binding protein 1, 37kDa)	2	1	0.000	0.000
HNRNPH1	3187	heterogeneous nuclear ribonucleoprotein H1 (H)	2	1	0.000	0.000
HNRNPK	3190	heterogeneous nuclear ribonucleoprotein K	9	8	0.056	0.036
HNRNPU	3192	heterogeneous nuclear ribonucleoprotein U (scaffold attachment factor A)	2	10	0.000	0.067
HNRNPUL1	11100	heterogeneous nuclear ribonucleoprotein U-like 1	1	2	0.000	0.000

Gene Symbol	Gene ID	Description	Degree		Clustering coefficient	
			SMA	ALS	SMA	ALS
IVNS1ABP	10625	influenza virus NS1A binding protein	2	6	0.000	0.133
LSM3	27258	LSM3 homolog, U6 small nuclear RNA associated (S. cerevisiae)	4	2	0.000	0.000
LSM4	25804	LSM4 homolog, U6 small nuclear RNA associated (S. cerevisiae)	2	1	0.000	0.000
LSM5	23658	LSM5 homolog, U6 small nuclear RNA associated (S. cerevisiae)	2	2	0.000	0.000
LSM7	51690	LSM7 homolog, U6 small nuclear RNA associated (S. cerevisiae)	4	2	0.000	0.000
LSM8	51691	LSM8 homolog, U6 small nuclear RNA associated (S. cerevisiae)	4	1	0.000	0.000
MBNL1	4154	muscleblind-like splicing regulator 1	2	1	0.000	0.000
MYOD1	4654	myogenic differentiation 1	1	2	0.000	0.000
NCBP1	4686	nuclear cap binding protein subunit 1, 80kDa	1	1	0.000	0.000
NHP2L1	4809	NHP2 non-histone chromosome protein 2-like 1 (S. cerevisiae)	2	1	0.000	0.000
NOL3	8996	nucleolar protein 3 (apoptosis repressor with CARD domain)	1	0	0.000	0.000
NONO	4841	non-POU domain containing, octamer-binding	0	4	0.000	0.333
PABPC1	26986	poly(A) binding protein, cytoplasmic 1	2	2	0.000	0.000
PABPN1	8106	poly(A) binding protein, nuclear 1	1	1	0.000	0.000
PCBP2	5094	poly(rC) binding protein 2	1	1	0.000	0.000
PNN	5411	pinin, desmosome associated protein	3	0	0.000	0.000
POLR2C	5432	polymerase (RNA) II (DNA directed) polypeptide C, 33kDa	2	2	0.000	0.000
POLR2E	5434	polymerase (RNA) II (DNA directed) polypeptide E, 25kDa	5	4	0.100	0.000
POLR2F	5435	polymerase (RNA) II (DNA directed) polypeptide F	1	0	0.000	0.000
POLR2G	5436	polymerase (RNA) II (DNA directed) polypeptide G	2	2	1.000	0.000
POLR2I	5438	polymerase (RNA) II (DNA directed) polypeptide I, 14.5kDa	1	1	0.000	0.000
POLR2J	5439	polymerase (RNA) II (DNA directed) polypeptide J, 13.3kDa	3	2	0.333	0.000

Gene Symbol	Gene ID	Description	Degree		Clustering coefficient	
			SMA	ALS	SMA	ALS
POLR2L	5441	polymerase (RNA) II (DNA directed) polypeptide L, 7.6kDa	1	1	0.000	0.000
PPIG	9360	peptidylprolyl isomerase G (cyclophilin G)	1	0	0.000	0.000
PQBP1	10084	polyglutamine binding protein 1	1	0	0.000	0.000
PRMT5	10419	protein arginine methyltransferase 5	1	1	0.000	0.000
PRPF19	27339	pre-mRNA processing factor 19	3	0	0.000	0.000
PRPF6	24148	pre-mRNA processing factor 6	2	1	0.000	0.000
PRPF8	10594	pre-mRNA processing factor 8	3	4	0.000	0.000
PUF60	22827	poly-U binding splicing factor 60KDa	3	4	0.000	0.167
QKI	9444	QKI, KH domain containing, RNA binding	3	2	0.000	1.000
RALY	22913	RALY heterogeneous nuclear ribonucleoprotein	3	2	0.000	1.000
RBFOX1	54715	RNA binding protein, fox-1 homolog (C. elegans) 1	1	0	0.000	0.000
RBM22	55696	RNA binding motif protein 22	0	1	0.000	0.000
RBM39	9584	RNA binding motif protein 39	4	4	0.167	0.167
RBM4	5936	RNA binding motif protein 4	3	2	0.000	0.000
RBM5	10181	RNA binding motif protein 5	2	0	0.000	0.000
RBM8A	9939	RNA binding motif protein 8A	1	1	0.000	0.000
RPS13	6207	ribosomal protein S13	1	1	0.000	0.000
RPS26	6231	ribosomal protein S26	0	2	0.000	0.000
SAP18	10284	Sin3A-associated protein, 18kDa	0	3	0.000	0.000
SF3A3	10946	splicing factor 3a, subunit 3, 60kDa	2	0	0.000	0.000
SFPQ	6421	splicing factor proline/glutamine-rich	7	4	0.190	0.333
SMN2	6607	survival of motor neuron 2, centromeric	5	10	0.100	0.044

Gene Symbol	Gene ID	Description	Degree		Clustering coefficient	
			SMA	ALS	SMA	ALS
SNRNP25	79622	small nuclear ribonucleoprotein 25kDa (U11/U12)	1	0	0.000	0.000
SNRPA1	6627	small nuclear ribonucleoprotein polypeptide A'	2	2	0.000	0.000
SNRPB	6628	small nuclear ribonucleoprotein polypeptides B and B1	3	5	0.000	0.000
SNRPB2	6629	small nuclear ribonucleoprotein polypeptide B	2	2	0.000	0.000
SNRPC	6631	small nuclear ribonucleoprotein polypeptide C	1	1	0.000	0.000
SNRPD1	6632	small nuclear ribonucleoprotein D1 polypeptide 16kDa	4	3	0.000	0.000
SNRPD2	6633	small nuclear ribonucleoprotein D2 polypeptide 16.5kDa	5	6	0.200	0.067
SNRPD3	6634	small nuclear ribonucleoprotein D3 polypeptide 18kDa	3	3	0.000	0.000
SNRPE	6635	small nuclear ribonucleoprotein polypeptide E	5	6	0.000	0.000
SNRPF	6636	small nuclear ribonucleoprotein polypeptide F	3	7	0.000	0.048
SNRPG	6637	small nuclear ribonucleoprotein polypeptide G	3	3	0.000	0.000
SNRPN	6638	small nuclear ribonucleoprotein polypeptide N	2	1	0.000	0.000
SREK1	140890	splicing regulatory glutamine/lysine-rich protein 1	4	2	0.333	0.000
SRRM1	10250	serine/arginine repetitive matrix 1	7	5	0.143	0.200
SRSF11	9295	serine/arginine-rich splicing factor 11	5	4	0.000	0.167
SRSF3	6428	serine/arginine-rich splicing factor 3	4	2	0.333	0.000
SRSF5	6430	serine/arginine-rich splicing factor 5	2	2	0.000	0.000
SRSF9	8683	serine/arginine-rich splicing factor 9	1	0	0.000	0.000
STRAP	11171	serine/threonine kinase receptor associated protein	1	1	0.000	0.000
THOC6	79228	THO complex 6 homolog (Drosophila)	1	1	0.000	0.000
TRA2A	29896	transformer 2 alpha homolog (Drosophila)	0	1	0.000	0.000
TRA2B	6434	transformer 2 beta homolog (Drosophila)	1	3	0.000	0.667

Gene Symbol	Gene ID	Description	Degree		Clustering coefficient	
			SMA	ALS	SMA	ALS
TXNL4A	10907	thioredoxin-like 4A	2	0	0.000	0.000
USP39	10713	ubiquitin specific peptidase 39	2	1	0.000	0.000
WBP4	11193	WW domain binding protein 4	1	2	0.000	1.000
XAB2	56949	XPA binding protein 2	1	0	0.000	0.000
YBX1	4904	Y box binding protein 1	3	9	0.000	0.000