Turkish Journal of Diabetes and Obesity / *Türkiye Diyabet ve Obezite Dergisi*
Original Article / Özgün Araştırma

Random SNP Events for Diabetes and Their Molecular Interaction Neighborhood

Ertuğrul DALGIÇ

Zonguldak Bülent Ecevit University School of Medicine, Department of Medical Biology, Zonguldak, Turkey

Cite this article as: Dalgıç E. Random SNP Events for Diabetes and Their Molecular Interaction Neighborhood. Türk Diyab Obez 2019;2: 99-105.

ABSTRACT

Aim: Genomics studies provide a collection of Single Nucleotide Polymorphisms (SNPs) which are significantly associated with various diseases and other conditions, including type 2 diabetes mellitus (T2DM). Frequency of T2DM associated SNP events could be investigated by genome scale randomizations. Based on mapped genes for SNP events, molecular interaction neighborhood could also be analyzed.

Material and Methods: Random SNP events were generated for the human genome. Frequencies of different unique T2DM associated SNP events were analyzed. Mapped genes for the SNPs were collected and their direct molecular interaction neighborhood was analyzed. Insulin Signaling (IS) Pathway was also checked to observe if it was targeted by the T2DM associated SNPs.

Results: Having at least a single T2DM associated SNP randomly, was observed to be likely. The effect of random SNP events expanded, when network neighborhood was considered. Some SNPs and their mapped genes were more frequently targeted than others. Although IS Pathway members were rarely targeted, network neighborhood also expanded the influence on IS Pathway.

Conclusion: Randomly expected variations in individual genomes are likely to affect diabetes susceptibility. Consideration of network level relationships enlarge the effect of the genomic variations.

Key Words: *Diabetes, Single nucleotide polymorphism, Systems biology, Biological networks, Systems medicine*

Rastgele Diyabet SNP Olayları ve Moleküler Etkileşim Komşuluğu

ÖZET

Amaç: Genomik çalışmalar, tip 2 diabetes mellitus (T2DM) dahil olmak üzere, birçok hastalık ve diğer fenotiplerle önemli ilişkileri olan Tek Nükleotid Polimorfizmleri koleksiyonu sunmaktadır. T2DM ilişkili SNP olaylarının frekansı genom düzeyinde rastgeleleştirme analiziyle incelenebilir. SNP olayları ile eşleştirilen genlere dayanarak, moleküler etkileşim düzeyindeki etkiler incelenebilir.

Gereç ve Yöntemler: İnsan genomu için rastgele SNP olayları oluşturuldu. Farklı T2DM ilişkili SNP olaylarının frekansları incelendi. SNP olaylarıyla eşleştirilmiş genler elde edildi ve bu genlerin doğrudan moleküler etkileşim komşuları incelendi. Ayrıca İnsülin Sinyalleşmesi (IS) Yolağının, T2DM ilişkili SNP olaylarının hedefinde olup olmadığı kontrol edildi.

Bulgular: En az bir adet T2DM ilişkili SNP'nin rastgele olarak gözlemlenmesi olası olarak bulundu. Ağ komşuluğu göz önüne alındığında, rastgele SNP olaylarının etkisi genişledi. Bazı SNP'ler ve bunlarla eşleştirilmiş olan genler, diğerlerine göre daha sıkça hedeflendi. IS Yolağı üyeleri nadiren hedeflendi, ancak ağ komşuluğu bu yolağa olan etkiyi de genişletti.

Sonuç: Bireysel genomlarda rastgele beklenen varyasyonlar diyabet duyarlılığını muhtemelen etkiler. Ağ düzeyi etkileşimler genomik varyasyonların etkisini genişletir.

Anahtar Sözcükler: *Diyabet, Tek nükleotid polimorfizmi, Sistem biyolojisi, Biyolojik ağlar, Sistem tıbbı*

ORCID: Ertuğrul Dalgıç / 0000-0003-0536-4447

Correspondence Address / Yazışma Adresi:
Ertuğrul DALGIÇ
Zonguldak Bülent Ecevit University School of Medicine,
Department of Medical Biology, Zonguldak, Turkey
Phone: +90 (372) 261 31 70 • E-mail: ertugruld@beun.edu.tr

DOI: 10.25048/tjdo.2019.47

Received / *Geliş tarihi* : 21.05.2019
Revision / *Revizyon tarihi* : 14.08.2019
Accepted / *Kabul tarihi* : 22.08.2019

INTRODUCTION

Single Nucleotide Polymorphisms (SNPs) are responsible for the vast majority of genetic variations between individuals. On average, a person has about 4 million SNPs, when compared to reference human genome (1). Therefore, most of the genetic differences among individuals could be attributed to SNPs, which could play an important role in determining the susceptibility to different diseases. Genome-Wide Association Studies (GWASs) revealed SNPs with statistically significant association to some human diseases (2). However, there is an enormous number of SNP events associated with diseases, hence, the biological understanding and translational use of such information is not straightforward (3).

Diabetes Mellitus is an important health problem across the World (4). Type II Diabetes Mellitus (T2DM) is a chronic disease, whose effect is expected to rise in near future (5). Majority of the diabetes cases in adults is T2DM (4). Molecular understanding of T2DM is crucial for diagnosis and therapy. Studies such as GWAS, provide important genetic variations that are significantly linked to T2DM. For highly polygenic diseases like T2DM, the genetic susceptibility of an individual is based on a complex combination of many variants (3).

Thousands of T2DM patients were analyzed in GWASs and many SNPs were identified to be associated to T2DM, and such information are kept in databases such as European Bioinformatics Institute (EBI) GWAS Catalog (6). Integrative analysis of GWAS datasets for T2DM was shown to provide novel potential regulatory mechanisms for T2DM (7).

Understanding the biological mechanisms underlying T2DM could be improved by using GWAS results in combination with complex molecular interactions. Systems Biology aims to understand biological events from interconnections of molecules and its translational perspective is known as Systems Medicine (8). Computational analysis of large datasets such as interactomes, could improve understanding of disease mechanisms and their treatment (8, 9). Analysis of interactomes could improve the mechanistic understanding of diseases (9). Molecular interaction network neighborhood of T2DM Associated SNPs were not previously analyzed. In addition to large-scale interaction datasets, molecular pathways also provide import insights into cellular events. Insulin Signaling (IS) Pathway is closely linked with insulin resistance and diabetes (10). In this study, SNP events were analyzed together with large-scale interaction datasets and IS pathway data for a Systems Medicine perspective on diabetes. T2DM associated SNPs were shown to be possibly hit randomly and their effect on genes were shown to be expanded by interaction neighborhood.

MATERIAL and METHODS

SNP and Interaction Datasets

Curated T2DM associated SNP dataset was downloaded from EBI GWAS Catalog on 21 March 2019 (6). There was a total of 1486 SNP entries. EBI GWAS data was based on Human Genome Assembly GRCh38.p12. Therefore, chromosome sizes for GRCh38.p12 were obtained from National Center for Biotechnology Information (NCBI) Nucleotide database (https://www.ncbi.nlm.nih.gov/nucleotide). 14 entries had SNP-SNP interaction data, which was treated as independent SNP events. 2 entries with the Pubmed ID 28254843, had multiple SNP events reported together. These SNP events were also treated as independent events. 2 SNP entries with no reported chromosome locus were ignored. 12 entries with no mapped gene information were also ignored. In addition, there were also redundant SNP events in the dataset. Overall, there were 1008 unique chromosome locations in the T2DM associated SNP dataset. Each unique chromosomal locus had only one unique SNP event, therefore there was a total of 1008 T2DM associated SNPs.

Biological General Repository for Interaction Datasets (BioGRID) interactions (Release 3.5.170) were downloaded on 27 March 2019 (11). BioGRID Interactome dataset had physical protein interactions as well as genetic interactions for various organisms, among which, only human data were selected. NCBI Gene IDs of the proteins were collected and then converted to Gene Symbols by using Human Genome Organization Gene Nomenclature Committee (HGNC) dataset (12). HGNC dataset was downloaded on 28 March 2019. BioGRID Human Interactome dataset had 308773 unique interactions based on Gene Symbols. Human IS Pathway members were collected from Kyoto Encyclopedia of Genes and Genomes (KEGG) database on 03 April 2019 (13-15). There was a total of 136 genes in the KEGG IS Pathway.

Randomization and Network Analysis

Chromosome location data was used for randomization. Mitochondrial and Y chromosomes were absent in the EBI GWAS Catalog curated T2DM associated SNP dataset, therefore, they were omitted during randomization. An individual human genome was expected to have about 4 million SNPs (1). Using uniform distribution, 4 million random locations (single nucleotide positions) across the 23 chromosomes (haploid genome, which had a length of 3,031,042,417 base-pairs) were chosen. Sequence level probabilities were ignored; once a chromosomal locus was chosen randomly, it was assumed to have an SNP event neglecting the different substitution possibilities.

Randomizations were done for 50000 iterations. For each randomization case (random genome), any hits at the 1008 T2DM associated SNP chromosomal locations were collected. Gene symbols for mapped genes for each locus were gathered. Hits at the IS Pathway genes were also obtained. Lastly, direct neighbors of mapped genes were collected from the BioGRID Human Interactome.

In addition to the SNP randomization analysis, network neighborhood effect for the mapped genes of the 1008 T2DM associated SNPs (T2DM associated genes) was analyzed. 510 of 1074 unique T2DM associated genes were present in the BioGRID Human Interactome, which had a total of 16395 genes. Degree value (connectivity) of a gene was defined as the number of direct interacting partners (neighbors) of the genes in the Interactome. Degree values of T2DM associated genes was compared to random sets of genes with the same size collected from the members of the Interactome. Median and maximum degree values of 510 T2DM associated genes were compared to random gene sets of the same size. Randomizations were used to generate a distribution and one sided p-values were calculated for median and maximum degree values (i.e., percentage of random iterations in which random gene set median degree value was greater than or equal to the median degree value of T2DM associated genes).

RESULTS

Random Hits at T2DM Associated SNPs

Random human genomes, which were defined to have random SNPs, were checked for overlaps with T2DM Associated SNPs. The frequency distribution of the number of T2DM Associated SNPs for randomized genomes was analyzed. For more than half of the random cases, the genome was expected to have at least one T2DM Associated SNP (Figure 1A). The fraction of random genomes with T2DM Associated SNPs decreased towards higher number of hits. Only 1% of the random cases had 5 or more SNP hits. Next, the frequency distribution of the mapped genes for the randomly targeted T2DM Associated SNPs was analyzed. A similar trend was observed for the mapped genes; at least one gene was hit for the majority of random genomes (Figure 1B). Since a single SNP can affect more than one gene, the effect at the gene level was greater. 9% of the random cases had 5 or more unique gene hits. Different SNP events could be mapped to common genes, therefore some genes could be influenced by random SNP events more than once for a single randomization case. However, this was observed very rarely in this study (around 0.1% of random cases). Therefore, there was no difference between the distribution of unique gene hits vs. total gene hits.

When a gene was influenced by an SNP event, it can then influence its interacting neighbors in the cell. Because of this, BioGRID Human Interactome was used to collect the direct neighbors of the mapped genes. When the frequency distribution of the mapped gene neighborhood was analyzed, an approximately 100-fold greater effect could be observed (Figure 1C). 52% of the random cases had 5 or more unique gene hits when the neighborhood was considered. There were 300 or more gene hits for 1% of random genomes. Therefore, potential effects of randomly hit T2DM Associated SNPs are greater when interaction networks were considered. For 8% of random cases, some genes were influenced more than once for a single randomization case.

Connectivity of 510 T2DM associated genes was also analyzed separately, besides randomizations. Degree values of these genes were not significantly different from random sets of the same size in the network (Figure 1D). Randomization based one sided p-values for median and maximum degree values were 0.71 and 0.27.

IS pathway member genes were mostly not directly targeted by randomly hit T2DM Associated SNPs (Figure 2A). For only 0.9% of random genomes, IS pathway was hit. However, when the network neighborhood was considered, 26.5% of random genomes had at least a single IS pathway gene hit. There could be as many as 20 or more IS Pathway member genes affected (Figure 2B). Therefore, molecular networks also increase the influence of random hit SNPs to IS pathway.

Frequently Targeted Genes

Randomly hit T2DM Associated SNPs affected 1074 genes at least once. However, some genes were targeted more frequently than others. CDKN2B-AS1, AL157937.1, RF00019, CDKAL1, IGF2BP2, and KCNQ1 were uniquely targeted for more than 1% of randomizations. 666 of 7526 unique genes in the T2DM Associated Gene Neighborhood based on BioGRID Human Interactome, were uniquely targeted for more than 1% of randomizations. Only 4 genes; ESR2, TRIM25, ELAVL1, and HNRNPL, were uniquely targeted for more than 10% of randomizations.

Only 5 of the 136 KEGG IS pathway members; PRKAG2, BRAF, SOCS2, GCK, and GYS2, were directly hit by SNPs. However, when the network level influence was considered, 29 KEGG IS pathway members were affected; IKBKB, SHC1, PRKAR2A, CRK, CRKL, SREBF1, MAPK1, MAPK3, MAPK9, CALM1, MTOR, PPARGC1A, MAP2K1, AKT1, RAF1, MAPK8, PRKAA1, GRB2, GSK3B, HRAS, RPTOR, TSC2, TSC1, CALM3, PRKCZ, PPP1CA, CBL, PRKACA, and KRAS. Majority of the IS pathway were not targeted by T2DM associated SNPs.

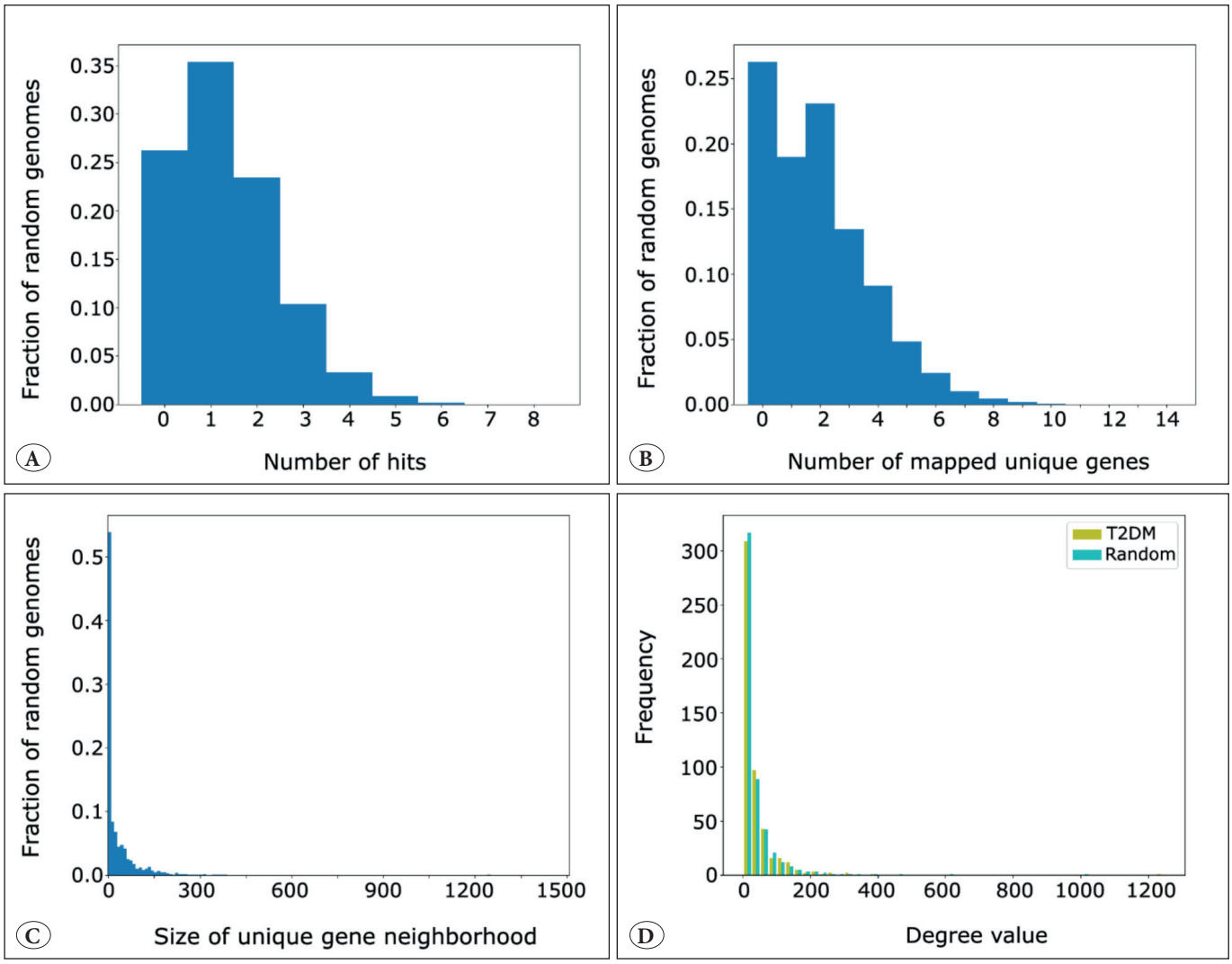

Figure 1: Frequency distributions of SNPs, genes, and degree values. **A)** Distribution of random genome fraction vs. number of hits at T2DM SNPs. **B)** Distribution of random genome fraction vs. number of mapped unique T2DM associated genes. **C)** Distribution of random genome fraction vs. unique gene neighborhood size (number of unique interaction partners). **D)** Frequency distribution of degree values for T2DM associated genes compared to random list (average of random values were shown).

Size of the neighborhood in the BioGRID Human Interactome varied substantially for the T2DM Associated SNPs (Figure 3). Mapped genes for the 336 of the 1008 SNPs were absent in the network. Among the 672 SNPs which had at least a single mapped gene in the Interactome, 327 were less connected then the average degree of the Interactome, which was 18.83. 99% of the SNPs had less than 226 neighbors. Some SNPs had very high number of neighbors. rs846178 SNP with chromosomal location of 4:2483888, which was mapped to RNF4, had 1249 neighbors in the Interactome. rs7685296 SNP with the chromosomal location of 4:152332969, which was mapped to FBXW7, had 376 neighbors. rs17405722 SNP with the chromosomal location of 17:42390483, was mapped to STAT3 and CAVIN1. STAT3 had 258, CAVIN1 had 104 neighbors; they both had 354 unique neighbors. rs3130501 and rs3132524 SNPs at chromosome 6 locations 31168676 and 31168937, which were both mapped to POU5F1, had 318 neighbors. While the network level effect of many T2DM associated SNPs could be very limited (less than average degree), some SNPs could have larger effect.

DISCUSSION

In this study, random SNPs were analyzed in order to gain insight on T2DM susceptibility. SNP events, which were previously significantly linked to T2DM were used. Having at least one T2DM associated SNP event had a probability higher than 50%. Because of the complexity of the disease, having SNPs cannot be directly converted to disease occurrence. Prevalence of T2DM is about 8% in

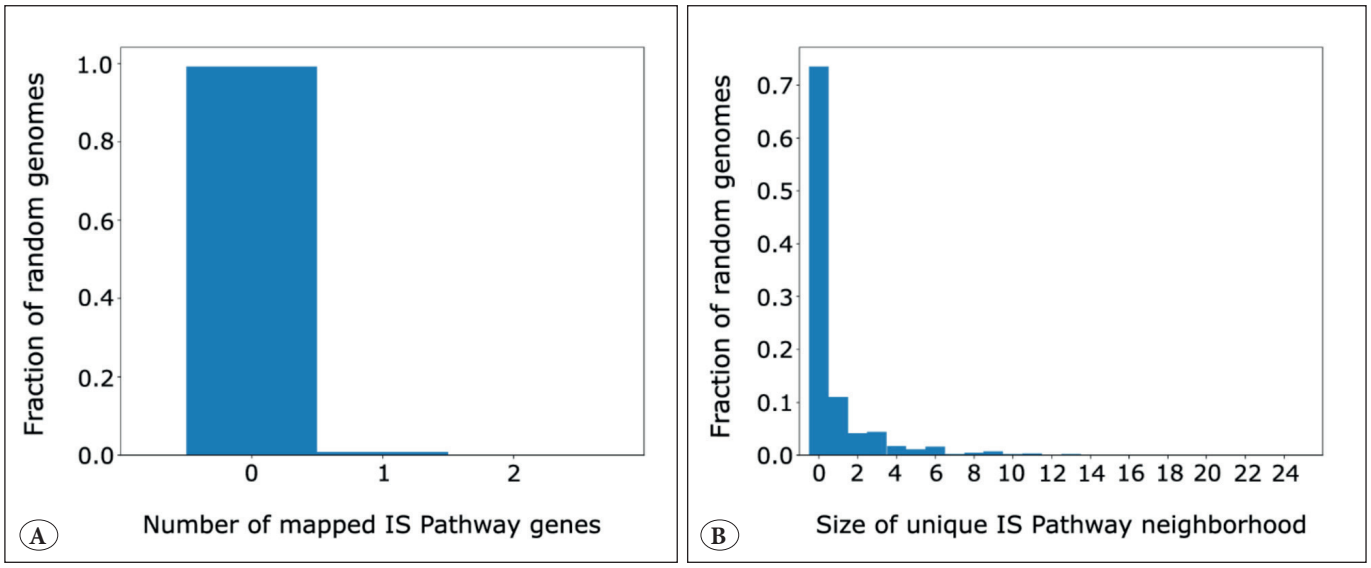

Figure 2: Frequency distributions of IS Pathway members and their neighborhood. **A)** Distribution of random genome fraction vs. number of hits at IS Pathway members. **B)** Distribution of random genome fraction vs. unique IS Pathway neighborhood size (number of unique interaction partners of IS Pathway members).

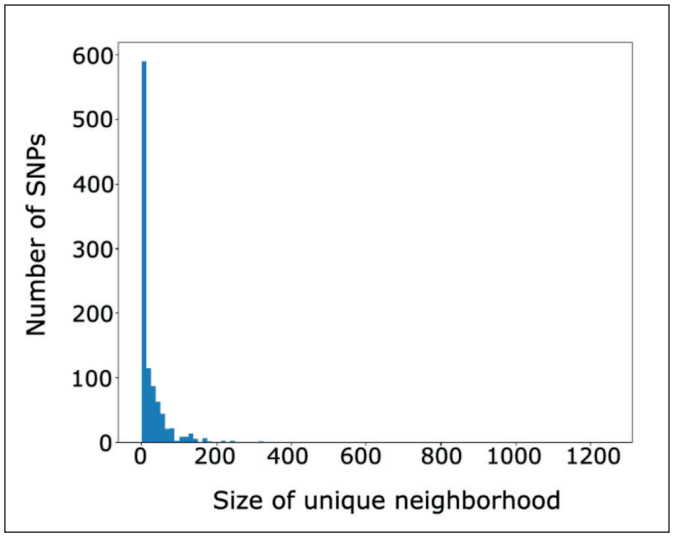

Figure 3: Frequency distribution of neighborhood size for T2DM SNPs (number of unique interaction partners of T2DM SNP mapped genes).

human population, however, there are various biological and environmental factors besides SNPs, affecting the progression of the disease (4). Hence, randomization based frequencies cannot be directly compared to prevalence in the population. As more GWASs were performed, databases will have bigger datasets linking more SNP events to various diseases including T2DM. Therefore, random frequency distributions observed in this study, are prone changes with updated datasets. SNP events were also assumed to be independent because of the insufficient number of SNP-SNP associations linked significantly to T2DM. Accumulation of more SNP-SNP interactions will improve future simulation studies.

Based on mapped genes for random SNP events, 6 genes were frequently targeted. Among these 6 genes, CDKN2B-AS1, AL157937.1 (ENSG00000236921), and RF00019 (ENSG00000201178) are not protein coding genes (16, 17). Therefore, the biological understanding of non-coding RNAs should improve for a better analysis of human diseases including diabetes. CDKAL1 is a protein coding gene, whose role in insulin production was shown (18, 19). IGF2BP2, which is a regulator of insulin like growth factor 2, was also linked to glucose and insulin levels (19, 20). KCNQ1 encodes for a potassium voltage-gated channel, which was also linked closely to insulin and glucose metabolism (21, 22). Therefore, frequently targeted genes were linked to glucose and insulin metabolism, which confirms their significance for T2DM.

ESR2, TRIM25, ELAVL1, and HNRNPL, were frequently targeted based on the Interactome neighborhood. Among the commonly hit network neighborhood genes, ESR2, coding for an estrogen receptor, was linked to obesity and diabetes (23, 24). TRIM25, coding for a ubiquitin ligase enzyme, was shown to suppress adipocyte differentiation, thus, it was also linked to obesity and diabetes (25). ELAVL1, an RNA-binding protein, was linked to diabetic nephropathy (26). HNRNPL, also an RNA-binding protein, was linked to glucose metabolism (27).

Some SNPs had very high number of neighbors in BioGRID Interactome, compared to others, such as rs846178 (mapped to RNF4) and rs7685296 (mapped to FBXW7). RNF4 is a ubiquitin ligase and molecular ubiquitination events were associated with diabetic nephropathy (28). FBXW7, also has a ubiquitin ligase related function, was shown to have role in glucose metabolism and linked to obesity and diabetes (29). These and other genes with high connectivity merit further investigation for their relevance to obesity and diabetes. Very few IS Pathway members were directly targeted by T2DM associated SNPs. Among these genes, SOCS2 was critically linked to diabetes (30). It was shown to be positively regulated by insulin and regulate Insulin Receptor activity negatively.

For better understanding of disease progression and susceptibility, System Medicine approaches such as random simulations are needed. Current study suggests that random simulations of SNP events could contribute substantially to our understanding of diabetes when integrated with biological large-scale datasets, such as molecular interactomes. Some SNPs and their mapped genes could be targeted more frequently, and they may have more molecular interaction neighbors. Therefore, clinical significance of these SNPs could be further investigated.

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