Gene Biomarkers in Congenital Hyperinsulinism

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Abstract: Congenital hyperinsulinism (CHI) is a rare type of disease that causes a severe drop in blood sugar in infants. This disease prevents reaching enough sugar to the child’s brain and causes lifelong and permanent damage. This study aims to investigate gene biomarkers in congenital hyperinsulinism. In this study, after reviewing the texts and searching for the bioinformatics databases of NCBI, Genecards, Swiss-prot, Diseasome, etc., the genes involved in the disease based on at least one of the methods in-vivo, in-vitro, and in-silico has been extracted as candidate genes. The expression data obtained from each group was standardized compared to the control group to compare the results in case and control groups. Then, the connection network of expression data of candidate genes in patients and healthy people were drawn separately with the help of MATLAB software (Version 9.1), and the correctness of these networks and determined biomarkers were checked using the rectome and diseasome database. All statistical calculations were done using R and Matlab software. In the present study, the essential genes of CHI disease were identified using 5 central criteria, including maximum neighborhood component, degree, closeness, radiality, and betweenness. Based on the results of the central criteria method, INS-PRKACA-PRKACB-PRKACG-AKT1 genes had the most repetitions. According to the identification of the most effective genes related to CHI disease in the present study, it is suggested that further studies need to be designed at the in vitro and clinical levels on the identified effective genes as diagnostic biomarkers of CHI disease.

Keywords: Congenital Hyperinsulinism, Gene Biomarker, Predictive biomarkers, GDA score, Bioinformatics databases.

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1. INTRODUCTION

Hypoglycemia in children has a plasma glucose level less than 2.8 mmol/l. This condition can be a potential threat to a person’s health, calling for careful evaluation and serious intervention to enable correct diagnosis of its cause and prevent brain damage and other complications.1,2 Congenital hyperinsulinism (CHI) is a rare disease that causes newborns and children to have low blood sugar due to abnormal insulin secretion. In a healthy person, insulin is secreted when blood sugar levels reach high levels, but in infants and children with CHI, even if they have low blood sugar, insulin is produced and secreted abnormally.3 Endogenous insulin-induced hypoglycemia is defined in patients with pancreatic tumors, which Whipple’s triad can recognize, including hypoglycemic symptoms, low plasma glucose concentration, and relief of general symptoms following resolution of hypoglycemia.4,5 Whipple’s triad is used today in modern guidelines for the diagnosis and management of hypoglycemia and its complications to differentiate patients with true hypoglycemia and to determine those in need of being investigated for the cause of hypoglycemia.4 The prevalence of this disease is between 1 in every 30,000 to 50,000 live births.6 In Iran, until 2014, about 3 cases of this disease have been reported in infancy.7,8 The incidence rate of this disease is about 1 in every 40,000 cases in Northern Europe. Disruption in the Sulfonylurea receptor-1 (SUR1) gene has been diagnosed in less than 60% of patients with CHI. Therefore, the incidence rate of this disease is high in areas of the world where consanguineous marriage is high, such as Saudi Arabia and areas where Ashkenazi Jews live; this rate in Saudi Arabia has been reported to be about 1 in every 2500 births.9 Most cases of the disease are sporadic.10 However, a study reported that, more than 67% of them already had this disease in their family.8 Computational bioinformatics includes computer programs in genomic and biological studies aiming to understand better the genetic basis of disease, unique adaptations, desirable properties, or differences between populations.9 Bioinformatics is an interdisciplinary knowledge that includes methods and software for understanding biological information. Bioinformatics, as a multidisciplinary field of knowledge, combines computer science, statistics, mathematics, and engineering to analyze and interpret biological information.11-13 Biomarkers related to the disease provide information about the possible effects of treatment on the disease (predictive biomarkers), the presence of the disease (diagnostic biomarkers), and how a disease develops regardless of the type of disease (prognostic biomarkers).14 Predictive biomarkers provide information about possible responses to a specific type of treatment, while prognostic biomarkers provide information about disease progression, whether the patient is treated or not.15-17 The present study aims to investigate gene biomarkers in congenital hyperinsulinism.

2. MATERIALS AND METHODS

The present analytical study datas were extracted from NCBI, SWISS prot, Genecards, and Disaesome bioinformatics databases from samples of 417 CHI patients and 400 healthy individuals. The genes involved in the disease were extracted based on at least one in vivo or in vitro and silico method and were considered Candidate Genes. To investigate the network connection of genes involved in CHI disease and to calculate essential factors, genes involved in the disease were determined using the text mining method. Then, this disease’s target gene was ranked using the Gene-Disease-Association-score (GDA score). Expression data were collected after determining the candidate genes from related studies. The expression data obtained from each group was standardized compared to the control group to compare the results of the two experimental and control groups. Then, the communication network of expression data of candidate genes was drawn in sick and healthy individuals separately using MATLAB (Version 9.1), and the structural parameters of communication networks of expression data were calculated and compared. Significant parameters were introduced as potential biomarkers, and using rectome and disaesome databases, the validity of these determined networks and biomarkers was checked for a second time.

2.1. Statistical analysis

All statistical calculations in this research were done using R and Matlab. Advanced descriptive and analytical statistical methods were used to analyze the data. Moreover, machine learning methods based on advanced bioinformatics algorithms were used to calculate features and network data analysis to extract biomarkers related to the structural characters of the network.

3. RESULTS

This study used the GDA score to define and rank the essential genes for disease diagnosis and treatment. The essential genes were identified using 5 criteria: degree, closeness, radiality, betweenness, and the maximum neighborhood component. Here, 5 genes, i.e., PRKACA - INS - AKT1 - PRKACG - PRKACB, had the most repetitions based on all the results of the above 5 central criteria methods. In this study, the communication network between candidate genes and the structural focus criteria of the network were calculated to determine essential genes and proteins (Figure 1).
The results indicated that regarding the maximum neighborhood component (MNC) and radiality indices, the most effective biomarker of the CHI disease network is related to INS, and the least effective is GCG. Regarding the degree index, the most effective biomarker of the CHI disease network is related to INS, and the least effective is related to PTPN1. As for the closeness criterion, the most effective biomarker of the CHI disease network is related to INS, and the least effective is IRS1. Regarding the betweeness criterion, a gene with the highest score may have the most significant effect on the transmission of information in the biological network compared to other vertices of the network, and their removal from the network disrupts the entire network communication. Based on this criterion, the most effective biomarker of the CHI disease network is related to INS, and the least effective is related to PTPN1 (Table 1).

<table>
<thead>
<tr>
<th>Gene name</th>
<th>full name</th>
<th>Chromosomal location</th>
<th>The highest level of expression</th>
<th>Diseases related to this gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>INS</td>
<td>Insulin</td>
<td>11p15.5</td>
<td>Pancreas (RNAseq)</td>
<td>Permanent neonatal DM/MODY/DM1/ hyperproinsulinemia</td>
</tr>
<tr>
<td>PRKACA</td>
<td>protein kinase cAMP-activated catalytic subunit alpha</td>
<td>19p13.12</td>
<td>Cardio-skeletal muscles (RNAseq)</td>
<td>primary pigmented nodular adrenocortical disease/fibrolamellar carcinoma/mixed fibrolamellar hepatocellular carcinoma</td>
</tr>
<tr>
<td>PRKACB</td>
<td>protein kinase cAMP-activated catalytic subunit beta</td>
<td>1p31.1</td>
<td>Brain (RNAseq)</td>
<td>primary Pigmented nodular adrenocortical disease/cervical (non)keratinizing squamous cell carcinoma/ carney complex variant</td>
</tr>
<tr>
<td>PRKACG</td>
<td>protein kinase cAMP-activated catalytic subunit gamma</td>
<td>9q21.11</td>
<td>Testicle (RNAseq)</td>
<td>Bleeding disorder/ primary Pigmented nodular adrenocortical disease/Stormorken syndrome/Friedreich ataxia/ thrombocytopenia absent radius syndrome</td>
</tr>
<tr>
<td>AKT1</td>
<td>AKT Serine/Threonine Kinase 1</td>
<td>14q32.33</td>
<td>Adipocyte, adrenal gland, breast (RNAseq)</td>
<td>Proteus syndrome/ breast, ovarian, and colorectal cancer/schizophrenia</td>
</tr>
</tbody>
</table>

### 4. DISCUSSION

CHI is the inappropriate secretion of insulin in the presence of low plasma glucose levels, which leads to severe and persistent hypoglycemia in infants and children. In CHI, due to the inhibitory effect of insulin on lipolysis and ketogenesis, ketone body formation is suppressed, thus leading to an increased risk of brain damage. Thus, rapid diagnosis and
immediate management of CHI are necessary to prevent brain damage and long-term neurological complications in children.22 Today, progress in molecular genetic sciences, imaging techniques, medical treatments, and surgery outcomes has increased the recovery rate in patients with CHI.23 The recently discussed biomarkers have helped to solve the difficulties and heterogeneities of CHI disease pathophysiology and can be a way to improve clinical tools for researchers and doctors. This study used bioinformatics to investigate essential genes for diagnosing and treating CHI. Based on this, the essential genes were identified using 5 centrality criteria, i.e., degree, closeness, radiality, betweenness, and maximum neighborhood component. Here, 5 genes, i.e., INS - PRKACA - PRKACB - PRKACG - AKT1, had the most repetitions based on all the results of the above 5 central criteria methods. The INS gene provides instructions for the production of the hormone insulin, which is necessary to control the glucose level in the blood.24 Also, INS as a growth factor plays a role in the differentiation process of stem cells into brain and nerve cells.25,26 The present study showed that INS is the most effective biomarker related to CHI, in line with the results of other studies.27 In a study conducted on patients with congenital hyperinsulinism, they found that a large percentage of infants with this disease have ventricular hypertrophy, which may be related to the severity of CHI at the time of diagnosis, making the previous care of these patients even more severe.28 The results showed that PRKACA is the second most effective biomarker related to CHI. This gene encodes one of the catalytic subunits of protein kinase A, which exists as a tetrameric holoenzyme with two regulatory subunits and two catalytic subunits in its inactive form.29 Also, the results showed that PRKACB is the third most effective biomarker related to CHI. The protein encoded by this gene is a serine/threonine protein kinase family member. PKA consists of two regulatory subunits and two catalytic subunits. The encoded protein is a catalytic subunit of cAMP-dependent protein kinase, mediating cAMP signaling.30 In this study, PRKACG was reported as the third most effective biomarker associated with CHI. Also, the results showed that AKT1 is the fifth effective biomarker related to CHI in this study. Previous studies have suggested the role of AKT1 kinase in the cell-to-cell communication of neurons, nerve cells’ survival, and memory formation. The AKT1 gene belongs to a group of genes known as oncogenes. If oncogenes are mutated, they have the potential to turn normal cells into cancerous ones.31,32

5. CONCLUSION

The results of the present study showed that the most effective genes related to CHI include INS-PRKACA-PRKACB-PRKACG-AKT1. Thus, in the future, additional studies at the laboratory and clinical levels can be designed on the determined effective genes as diagnostic biomarkers of CHI disease. Besides, by investigating the communication paths in the gene communication network of CHI disease, one can recognize and study the communication in the disease and the interaction of this disease with other diseases, which can help to understand more about the mechanism of the disease.

6. AUTHOR’S CONTRIBUTION STATEMENT

Dr. Hossein Seidkhani, designed the model and the computational framework and analyzed the data. Dr. Reza Valizadeh, Critical revision of the manuscript for intellectual content, administrative, technical, and material support.

7. CONFLICT OF INTEREST

Conflict of interest declared none.

8. REFERENCES


