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The Software Development and Design Based Approach in Assessing the Probability of Essential Hypertension Disease

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Abstract

Background and objectives: Software design and development for cardiovascular genetics laboratories.

Materials and methods: Integrated development environment-Delphi 7.0, Pascal language. In this program were laid down results of a retrospective analysis of hypertensive patients hospitalized in the Department of Arterial Hypertension (AH) of the Republican Specialized Center of Cardiology (RSCC) for the period from 2011 to 2013 y., passed the clinical and genetic testing according to the plan of Research Project ADCC-15.13.1. The study included 100 healthy volunteers and 800 patients with I-II grade of essential hypertension EH, all of them were Uzbek males in the mean age of 48.3 ± 8.1 yrs. The study was approved by the medical ethical committee of the center of cardiology, Tashkent Uzbekistan. Informed consent was obtained from each individual recruited.

Results: We have attempted to develop «CDS» application for the genetics cardiology department. For support parameters, we took the results of SNP-genotyping cardiovascular markers, biochemical, clinical parameters, as well as nutritional status. We have developed «GeneSecure» platform with «CDS» for IBM Pentium, Windows OS.

Conclusion: The polygenic nature of EH and incomplete update patient records significantly reduce diagnostic effect of the CDS. However, in some cases, the CDS are not always able to clearly determine the synergistic and intergenomic effect of analyzed genes. These issues occur when the volume of new data exceeds the amount of filer memory, leading to the appearance of these areas, which are very difficult to manage.

Keywords: Electronic Medical Records (EMR); Clinical Decision Support (CDS); Single Nucleotide Polymorphisms (SNP); DNA Database; Essential Hypertension (EH)

Introduction

It is known that the gene impact on the development of essential hypertension (EH) can range from low to high risk. In this regard, it is logical to suppose that the use of a genetic test is an important aspect of modern predictive medicine. However, cardiologist and clinical genetics consultation for the analysis of these large data is not enough today. A potential solution to this problem might be «CDS» application that can synchronize the genetic and clinical information in the context of essential hypertension pathology. At present there are 2,500 clinical genetic tests available to physicians [1,2]. Therefore be unreasonable to expect that the physician is able to remember each genetic test for each state in conjunction with the main clinical features of the patient [3]. Today, these conservative operations can take the clinical decision support system «CDS». These advanced systems usually operate within the electronic medical records «EMR», DNA databases and «CDS» dispatcher [4]. The demand for such systems is gradually increasing in hospitals and medical centers, especially in the cardiac profile. It is known that the gene impact on the development of essential hypertension (EH) can range from low to high risk. In this regard, it is logical to suppose that the use of a genetic test is an important aspect of modern predictive medicine [5]. However, cardiologist and clinical genetics consultation for the analysis of these large data is not enough today. A potential solution to this problem might be «CDS» application that can synchronize the genetic and clinical information in the context of essential hypertension pathology.

The aim of the present study was to develop the software design for cardiovascular genetics laboratories.

Materials and Methods

In this program were laid down results of a retrospective analysis of hypertensive patients hospitalized in the Department of Arterial Hypertension (AH) of the Republican Specialized Center of Cardiology (RSCC) for the period from 2011 to 2013, passed the clinical and genetic testing according to the plan of Research Project ADCC-15.13.1. The study included 100 healthy volunteers and 800 patients with I-II grade of EH, all of them were Uzbek males in the mean age of 4.3 ± 8.1 yrs. The study was approved by the medical ethical committee of the center of cardiology, Tashkent Uzbekistan. Informed consent was obtained from each individual recruited.

The software development and design

Integrated development environment-Delphi 7.0, Pascal language. For support parameters, we took the results of SNP-genotyping cardiovascular markers, biochemical, clinical parameters, as well as nutritional status.

Genetic cardiovascular risk prediction

Continuous variables were expressed as mean± standard deviation and categorical variables as percentages. Differences in continuous variables between cases and controls were examined using the

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unpaired Student's t-test, where the Mann-Whitney U-test was used in case of abnormal distribution. Deviations from the Hardy-Weinberg equilibrium and differences in allele distributions between the two groups were assessed by the chi-square test with 1 degree of freedom, whereas differences in genotype distributions were assessed by the chi-square test with 2 degrees of freedom. Associations between alleles or genotypes and EH were sought using odds ratios (OR) with 95% confidence intervals and ROC curve analysis. The significance level for all the analyses was set at $p<0.05$. Statistical analyses were performed using Microsoft Office Excel 2007 and Statistica v6.0 (StatSoft, USA) software.

CVD risk factor thresholds

Assessment of endothelial function: Flow-mediated dilation of the brachial artery has been widely used as a simple and noninvasive method of determining endothelial function. The diameter of the brachial artery was measured from two-dimensional ultrasound images, with a 7.5 MHz linear array transducer and a standard EnVisor-C system. In each study, scans were taken at rest and during reactive hyperemia. Reactive hyperemia was calculated as the maximum flow recorded in the first 60 sec after cuff deflation divided by the flow during the baseline scan [6].

Echocardiography: Central hemodynamic parameters and left ventricular mass were estimated using M-mode echocardiography. Left ventricular mass was indexed to body surface area (g/m^2) to calculate LVM index, and left ventricular hypertrophy was defined as an LVM index of ≥ 125 g/m^2 [7].

Ambulatory blood pressure monitoring: Daily blood pressure profile was assessed by 24-hour ambulatory blood pressure monitoring using the TONOPORT V system (GE Medical Systems, Freiburg, Germany).

Results

We have highlighted the adaptive accompaniment of «CDS», being based on standardized protocols and benchmarks for the diagnosis and treatment of essential hypertension [8]. As a result of 3 year- study, we have developed «GeneSecure» software package supporting «CDS» technologies within the EMR, supply module status CardioHealth and access to a local DNA database (Figure 1).

In order to «CDS» was technologically effective in the clinical process, we have combined all the working units within the EMR and local DNA database on less on the how it was possible. This triangulation has allowed to stratify and prioritize patient information as to determine the dynamics of the EH clinical development (Figure 2).

Figure 1: The adaptive interface of CDS on «GeneSecure» platform.

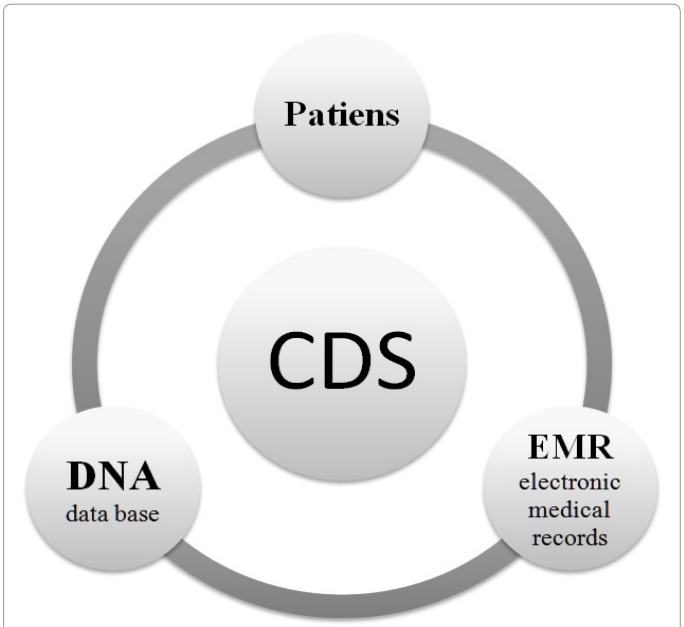

Figure 2: The triangulation CDS within the local network.

We have included in the «CDS» auxiliary options such as a reminder of the planned actions, correction of errors when entering clinical data, warnings about rare genotypes, epidemiological analysis of population warning intergenic interaction of mitochondrial and nuclear DNA, notification of the synergetic effect of genes on the increasing blood pressure. The developed «CDS» capable of processing clinical data in conjunction with the genetic information for 25 variables. This ability allows the «CDS» apply the logic and assess risks through the filter of environmental factors, genomic information, electronic medical history and family history of the patient. Thus the «CDS» allows the clinician to focus on treating the patient rather than to analyze and interpret complex genomic information is usually beyond his training. Similarly the «CDS» will allow clinicians with minimal training in the field of genetics, use of genetic information with low accuracy. For example, individuals with mutations in genes of RAAS system, SNS, ENDOTHEL has a risk of developing hypertension in more than 50%. The knowing of this information can allow taking measures to reduce this risk through weight control, physical activity and a balanced diet. We have studied genotype of 21 gene of cardiovascular continuum and identified 6 diagnostically significant genes (Table 1).

We have developed two independent solutions for the «CDS»: 1) Modeling of the EH risk assessment - risks, events, actions and their consequences over time, 2) Drawing up recommendations based on mutations in six genes of SNP.

We took into account the fact that the food-induced gene expression variability significantly affects the increase in blood pressure. As a result, we developed «CardioHealth» application with support «CDS» technology to assess nutritional status [9]. Considering the mineral status indicators, waist circumference, blood pressure BP, body mass Index BMI, triglycerides, salt sensitive, HDL-C and glucose, this module «CDS» is able to assess the risk of heart remodeling and the risk of cardiovascular disease in metabolic syndrome.

During the CDS testing, we were obtained epidemiological data of clinical development EH in the Uzbek population. For example, 91.2% of participants with EH were structural changes in the heart with a

Systems	Genes	Negative genotypes	DC
ENDOTHEL	B2BKR / +9/-9	9+/+9	0.6
	eNOS / 4a/4b	4a/4b	2.1
SNS	ADRB3 / Trp64Arg	T/T	3.6
	β2-AR / Gln27Glu	Glu27Glu	2.4
RAAS	ACE / I/D	D/D	1
	CYP11B2 / C344T	T/T	1.8

Table 1: Genetic panel.

disease duration of 5.4 ± 4.41 years (LVMI 159.8 ± 35.55). The highest blood pressure was recorded on a level of 220/130 mm Hg (0.5% of the sample). The highest level of total cholesterol, total cholesterol recorded in 2 patients at the level of 327 mmol/l at the age of 52 years. Only 13% of patients from the whole sample had a weight within the normal range (BMI 23.43 ±1.17). Registration of the genotyping results has identified an association RAAS system genes (*CYP11B2*/ S344T; ACE/I/D) with the risk of violations of water-salt metabolism, ENDOTHEL system genes (B2BKR/+9/-9; eNOS /4a/4b) with the risk of endothelial dysfunction, SNS system genes (ADRB3/Trp64Arg; B2-AR/Gln27Glu) with insulin resistance development risk.

As a result of «CDS» system testing revealed significant deficiencies. First of all it concerned the lack of coordination between the EMR, the DNA database and «CDS» dispatcher due to the autonomy of some clinical modules architecture. Another problem has been related with the understanding and use of the tool. Is not uncommon the «CDS» conclusion does not coincide with the findings of the clinician. Perhaps the reason for this controversy is the effect of syntropy and differences between the standards of norms of laboratory parameters, or forms of treatment standards in the care process.

Conclusion

Thus, the carrier state of TT-damaging genotype of *CYP11B2* gene and DD-genotype of ACE gene have been identified in 39% and 25% cases, respectively. The CDS showed a tendency to a violation of water-salt metabolism in patients with TT- genotype of *CYP11B2* gene and DD- genotype of the gene ACE gene via multivariate analysis. This displacement may be observed due to renal dysfunction caused by *CYP11B2* and ACE genes regulation, the mechanism of Na^+ - exchange through diuresis.

The detected connection of 4a/4b-genotype (eNOS gene) and 9+/+9 (B2BKR gene) with the development of endothelial dysfunction in 24% and 8% cases respectively, is most likely due to coupling of the polymorphic marker and site mutation leading to a change of NO production by endothelial cells.

Also the CDS has identified Glu/Glu - homozygous connection of β2-AR gene and high body mass index (BMI) with impaired glucose tolerance and systolic blood pressure in obese patients. The identified association of T/T-genotype of ADRB3 gene and Glu/Glu-genotype of β2-AR gene with the developing insulin resistance risk in 50% and 8% cases respectively confirmed that these genes mediate the physiologic effects of adrenaline.

However, in some cases, the CDS are not always able to clearly determine the synergistic and intergenomic effect of analyzed genes. These issues occur when the volume of new data exceeds the amount of filer memory, leading to the appearance of these areas, which are very difficult to manage. The polygenic nature of EH and incomplete update patient records significantly reduce diagnostic effect of the CDS.

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Financial and Competing Interest's Disclosure

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