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Virtual Screening SNP-Polymorphisms of Genes Determining the High Level of General Non-Specific Reactivity of Organism

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Abstract

As a result of a bioinformatic search using resources of NCBI PubMed Central, PDB, KEGG, and SNP authors have developed a database of genes associated with phenotypic manifestations of general non-specific reactivity level (GNRL). Out of 164 genes primarily relevant by search criteria for a detailed analysis there are selected 23 genes, divided into four groups: genes associated with the synthesis and reception of neurotransmitters (1); genes associated with membrane transport of electrolytes (2); genes associated with the synthesis of interleukins (3); and genes associated with certain metabolic response (4). After studying the SNP-polymorphisms annotations in the database NCBI-SNP, 10 genes and 20 SNP- polymorphisms were identified as the most likely candidates for the potential formation of phenotypic manifestations for GNRL. Further analysis of the degree of influence the conformational variability of amino acid chains in forming the secondary structure of proteins on their likely functional properties allows to select as promising the next 6 SNP: rs1851048 and rs 6777055 in the *cacna2d3* gene, encoding the voltage gated Ca^{2+} channels; rs2562456 in *znf-ld* gene of zinc-containing transcriptional regulator of DNA methylation; rs6923492 and rs362962 in *grm1* gene of metabotropic glutamate receptor; and rs6314 in *htr2a* gene, coding for serotonin receptor type 2A.

Keywords: pain, general non-specific reactivity of an organism, genetics, SNP-polymorphisms, bioinformatics.

Introduction

In earlier studies it was justified a property of integrative manner for general nonspecific reactivity level (GNRL) of the organism, which manifests itself in a functional unity of all organism systems through the central coordination of the extent of their sensitivity, reactivity and activity [1-3]. Currently the GNRL actively is used as a criterion for estimation of predicting and modulation of the functional states of the human organism and animal species [4-6].

For the further research in this direction it must be better detailed the study of the genetic prerequisites for the GNRL formation. As the universal indicator of the GNRL in the animals experiment and in the human study is a pain threshold, the problem of genetic determinism of the GNRL, at least initially, can be reduced to the search for genes associated with phenotypic variability of pain sensitivity.

By its biological origin, pain is one of the most important signals that inform organism about the damage of tissues and trigger a whole range of defensive reactions designed to minimize the and eliminate the damage [7]. Genetic factors contribute significantly to individual differences in the tolerance thresholds and psychophysical perception of painful sensation during the formation of responses to pain stimuli of different nature. The spread of individual differences in pain sensitivity is a challenging task for medical diagnostics and may have a separate value in the mechanisms of the chronic pain syndromes development [8-10].

The genetic approach to the pain study by use of model organisms identified the molecular nature of the nociceptive stimulus transformation, regulatory mechanisms associated with changes in neuronal activity, and the important role of immune system cells in the nociceptive pathways stimulation.

In humans, the genetic contribution to the formation of pain sensitivity is the most studied through the use of twin method, by comparing the ratio of the pain threshold between monozygotic and dizygotic twins. It was received the confirmation of the genetic contribution to sensitivity to the most painful stimuli. The observations showed that consanguineous marriages cause changes in pain threshold [11]. So, it was revealed the predominant genetic determinancy of painful sensation in regard to the cold - 60% compared to 26% of the determinism of the pain threshold to the heat perception [12]. In addition to experimentally induced pain, several studies have been devoted to the study of the genetic variation contribution in severity and susceptibility to pain at chronic diseases [13-15]. It was found that in formation of chronic pain syndrome a determining factor is genetically determined reactivity of the organism (especially structures of central nervous system) [7]. Twin studies demonstrated heritability from 52% to 68% of painful sensations in the back and from 35% to 58% of pain in the neck, which proves the genetic contribution to formation of the nociceptive sensation [9].

The complexity of human studies consists in the difficulty of creating similar environmental living conditions, phenotypic and genotypic homogeneity of the research objects. In this regard, animal experiments are important component in the study of genetic mechanisms in pain and analgesia. Experimental animal studies are strong evidence of pain and analgesia heritability [10, 16], the correlation between the pain threshold and psycho-emotional status [17].

Currently, it is known, at least 23 genes associated with experimentally induced pain, clinical pain or anesthesia [10]. Studies on the inbred line of mice, suggest that there are at least five genetically different basic types of nociception and hypersensitivity: basic thermal nociception (1), spontaneous reactions to noxious chemical stimuli (2) thermal sensitivity (3) mechanical hypersensitivity (4), and the afferent input of independent hypersensitivity (5). At the same time, variations genes that regulate the processing of nociceptive stimuli at various levels of the nervous system, may affect the perception of several types of stimuli. Thus, in addition to the system of cellular perception of nociceptive stimuli it is possible that a single gene can affect the coding and processing of multiple types of stimuli [18]. Thus, it is likely the existence of multiple genetic variants of the perception of painful sensation [19, 20].

Objective

To create a database of genes involved in the formation of the level of general nonspecific reactivity of the human organism, taking into account the phenomenon of point polymorphisms and select based on virtual screening genes, the most promising for the establishment of an appropriate diagnostic kit.

Material and Methods

In carrying out the bio information retrieval, to create a structured and easy-to-use database it was searched and analyzed the information in open sources: e-source NCBI, PubMedCentral, PDB, KEGG and SNP. The search is performed by following keywords: pain, pain threshold, nociception, and the specific genes in combination with a single nucleotide polymorphism, gene polymorphism. The analysis has been selected more than 400 sources for 10-year period.

For the database design, we chose shell Microsoft Access, the layout of the database was obtained using Microsoft Visio Program ("Microsoft Corp"., USA). To build the database were used the following criteria: adequacy, completeness, stability. Given these criteria, were formed the following fields to the database: the full name of the gene, standard abbreviations and commonly used synonyms, a direct function of the encoded protein, the presence of polymorphisms, functional annotation of SNPs (impact on the direct function of the encoded protein), a functional effect on the reactivity (in the including probability) sources.

Results and Discussion

As a result of the analysis and construction was obtained the following data base (Fig. 1).

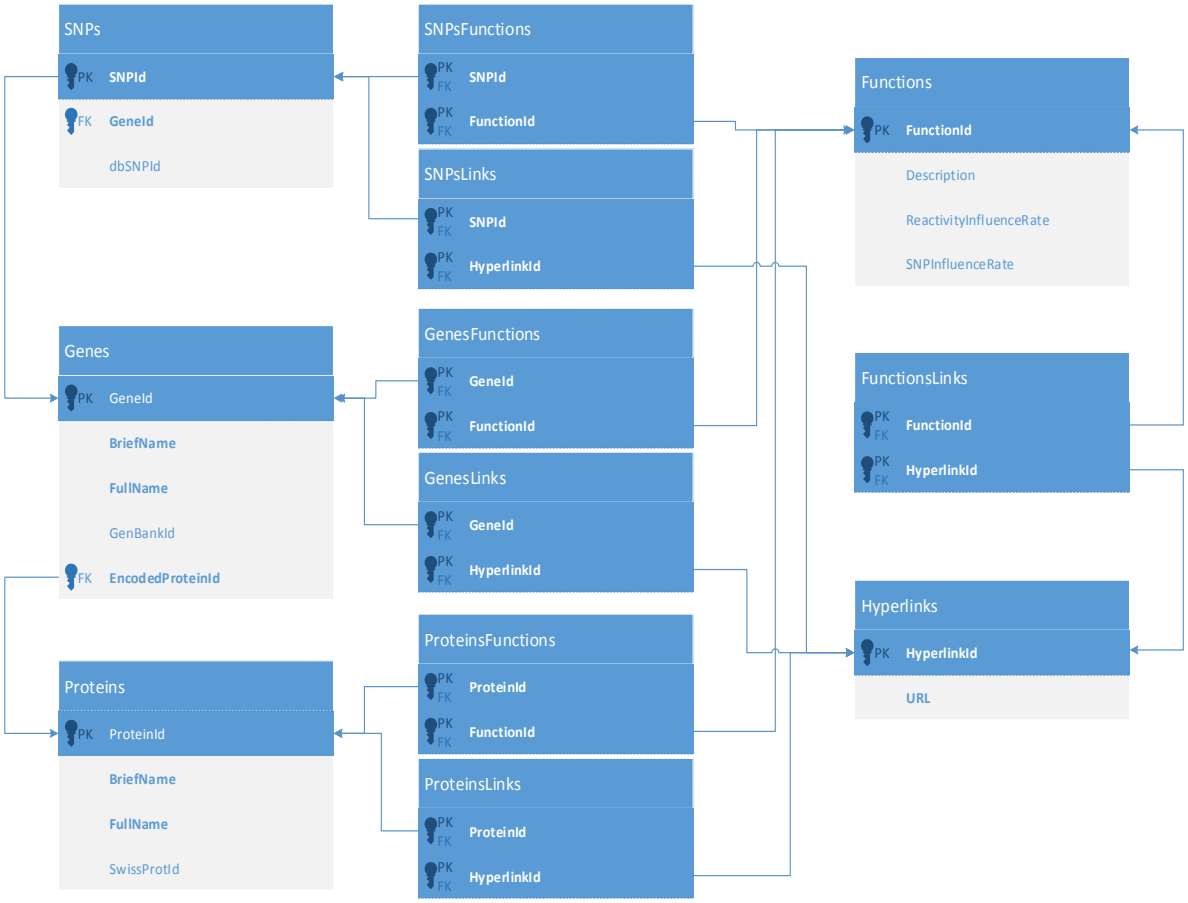

Figure 1. A working block diagram of a database of genes associated with phenotypic characteristics of pain perception in the shell of MS Vision

As a result, in the database are recorded 164 genes from the human genome that met the combination of characteristics: the proven facts of pain perception variations until the increased frequency of various chronic pain syndromes (1) and the availability of the annotated SNPs associated with these phenotypic variations (2). After exclusion of one-time mention, which did not find confirmation in future studies, and cases of describing rare inherited syndromes or cases of detection of variation only in situations of severe visceral pain (cancer surgery, traumatic operational effects, etc.) for the subsequent analysis were chosen 23 major genes (Table 1).

Table 1: A list of major genes associated with phenotypic characteristics of pain perception and reactive response of the human organism to the pain perception

Gene	Encoded Protein	Variation of Phenotype	Ref
The genes associated with the synthesis and reception of neurotransmitters			
adrb2	Adrenergic receptor β2	Visceral pain, vascular reactions	[21-23]
comt	Catechol-O-methyltransferase	Somatic and visceral pain	[15,24-26]
gch1	GTP cyclohydrolase 1	The exchange of biogenic amines, somatic and visceral pain	[14, 27, 28]
grm1	Glutamate receptor 1	Pain sensitivity and tolerance of pain	[29]
hcrtr2	Orexin B	Headache	[30, 31]
htr2a	Serotonin receptor 2A	Chronic pain syndromes	[32, 33]
mc1r	Melanocortin-1 receptor	Experimental pain, dependent conditions	[26]
oprd1	Opioid receptor, delta 1	Experimental pain	[34]
oprm1	Opioid receptor, mu 1	Experimental pain, dependent conditions	[35-37]
p2rx7	Ca^{2+}-permeable cationic channels	Chronic pain syndromes	[38]
slc6a4	Serotonin transporter	Chronic pain syndromes, experimental pain	[39, 40]
trpa1	Transient receptor potential A1	Experimental pain	[34]
trpv1	Transient receptor potential V1	Experimental pain	[34]
Genes associated with membrane transport of electrolytes			
cacna1a	P/Q type neuronal calcium channel	Headache	[30]
cacna2d3	Voltage gated Ca^{2+} channels	Chronic pain syndromes, experimental pain	[41, 42]
kcns1	Voltage gated K^+ channels	Chronic pain syndromes, experimental pain	[43]
scn9a	Voltage gated Na^+ channels	Chronic pain syndromes, experimental pain	[44]
Genes associated with the synthesis of interleukins			
il10	Interleukin-10	Chronic pain syndromes	[45, 46]
il1b	Interleukin-1β	Chronic pain syndromes	[47, 48]
il6	Interleukin-6	Chronic pain syndromes	[49]
Tnfa	Tumor necrosis factor, α	Chronic pain syndromes	[50, 51]

Genes associated with certain metabolic response			
mt1x	Metallothionein	Dependent conditions	52
vldlr	Very low density lipoprotein receptor	Dependsent conditions	52
znf-ld	Transcriptional regulator of DNA methylation	Chronic pain syndromes, experimental pain	53

After the analysis of the SNP polymorphisms annotations in the database NCBI-SNP is selected 10 genes with interconnection variants of identified phenotype variations with non-synonymous SNP-semantic polymorphisms. For such polymorphisms have been described real variants of the amino acid in one of the positions of the amino acid sequence of the encoded protein, leading to a change of the spatial molecule conformation with the possible impact on its function. A list of these polymorphisms is presented in Table. 2, in which the above-described SNP polymorphisms were identified as relevant.

Table 2: A list of key genetic polymorphisms associated with phenotypic characteristics of pain perception and reactive response of the human organism on it

Gene	SNPs в NCBI-SNP			
	Number of records	**Only actual records**	**The most likely candidates**	**Effects on the phenotype**
adrb2	795	16	rs1800888 rs35336948	Sensitivity to drugs, the incidence of pain syndromes and cardiovascular diseases
comt	3980	29	rs9265 s74745580	General pain sensitivity and pain tolerance
grm1	74658	75	rs362829 rs6923492 rs362962	General pain sensitivity and pain tolerance
htr2a	15514	36	rs6314 rs2274639	The subjective pain tolerance
oprm1	28996	47	rs1799971 rs497976	The subjective pain tolerance, tendency to addiction
slc6a4	18642	41	rs28914822 rs25531	General pain sensitivity and pain tolerance
cacna2d3	180000	237	rs 6777055 rs1851048	General pain sensitivity and pain tolerance
il1b	2527	22	rs1143627 rs2853550 rs1799916	Tissue and general reaction to injury
Tnfa	802	11	s267600955	Tissue and general reaction to injury
znp-ld	11	1	rs2562456	The general reaction to the pain, and subjective pain tolerance

The analysis of the influence degree of the conformational variability of amino acid chains in the formation of the secondary structure of proteins on their likely functional properties allows to select as a promising the next 6 SNP: rs1851048 and rs 6777055 in *cacna2d3* gene, encoding the voltage gated Ca^{2+} channels; rs2562456 *znf-ld* gene of zinc-containing transcriptional regulator of DNA methylation; rs6923492 and rs362962 in *grm1*gene of metabotropic glutamate receptor; and Rs6314 in *htr2a* gene, encoding serotonin receptor type 2A.

Functional significance of each SNP seems to be concluded in alteration of peculiarities, which the encoded protein could express mediating specific manifestations of reactivity. The single

substitution in its amino acid chain lets to changes in affinity and/or activity of these receptors (GRM1 and HTR2A), channels (CACNA2D3), and gene regulators (ZNF-LD). These SNP variants could be used to develop the molecular diagnostics, allowing a high degree of reliability to detect genetically determined component of the general non-specific reactivity of the organism in the non-invasive study.

Conclusion

Bioinformatics analysis based on the full capture of the synonymous information from specialized databases of open access has allowed revealing twenty three genes with annotated SNP-polymorphisms linked to the variability of the pain perception and response of the organism to nociception. Due to the effect on the functional properties of the encoded proteins, up to ten of them can provide phenotypically significant properties of the organism in the composition of the GNRL phenomenon. The result is an actual list of the six SNPs with potentially high phenotypic variability, suitable for the manufacture of test systems for the prediction of a genetically determined component of GNRL.

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Примечания:

1. Типологические особенности системного ответа организма животных с различным уровнем общей неспецифической реактивности организма на стрессорно-повреждающие воздействия / В.Б. Писарев, В.В. Новочадов, А.Б. Мулик и др. // Вестник Волгоградского государственного медицинского университета. 1998. 54(4). С. 10-12.

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