Human multigene disorders: functional analysis of known associated genes.

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Many of human pathologies are known to be associated with more or less stringent genetic component. However, only a few of them could be determined as single-gene mendelian phenotypes. The modern approaches of predicting of the so-called "disease" or "disease-associated" genes normally produce the large multigene loci and numerous putatively associated alleles with unknown functional effect. The mechanism of such involvement of these genes to nonmendelian human disorders remains mostly insufficiently studied. The disease-associated genetically determined variants were found in numerous human genes. Some genes are indispensable to embryonic function, so that deleterious mutations result in embryonic lethality and go unrecorded in humans. In other cases, abolition of gene function may normally have no effect on the phenotype because other nonallelic genes also supply the same function (genetic redundancy). Thus, we have performed a comparative functional analysis of the most significantly detected disease-associated human genes known from modern biomedical publications. We have selected the subset of genes of interest meta-query biomedical publications analysis. More than 2000 genes were included in the final dataset and their genetic effects on human pathologies were quantitatively estimated. We have ranked genes of interest according to the significancy of their association with such human multigene pathologies, as Parkinsons's disease, Alzheimer disease, colorectal, breast and lung cancer etc. Our integrated database included also data on normal- and pathology-based tissue expression levels of these genes. We have shown that genetically associated genes could be divided into subgroups according to their disease specificity and also on their expression

pattern. The promiscuitent genes were shown to be probably involved into various non-related human pathologies. Functional analysis allowed us to show that this subset was enriched with metabolic enzymes and related factors. The expression level of these genes varied non-specifically among normal and pathological tissues. The subgroups of specific disease-associated genes were divided according to their association with expression patterns. The lowly on non-expressed in tissue of pathology genes were revealed and enriched with cell signalling involved factors. By the way, we have also proposed the probable misannotation in genes, associated with some diseases and provided the functionally relevant candidate genetic markers basing on the analysis of these loci. Our initial analysis provides useful information for putative functional mechanisms involved in origin and progression of such severe human pathologies, like cancers, neurodegenerative disorders and others. Thus, the integrative approach and the constructed database could be useful for further biomedical studies.