Evolutionary comparison finds new human genes

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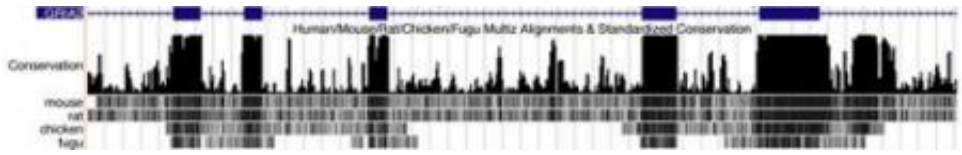

Over millions of years of evolution, a gene called GRIA2 has continued to do it's job of making a receptor for neurotransmitters. The portions of the gene that code for amino acids that make up a protein change in different ways from other parts of the genome, so computer algorithms can use these distinctive patterns of evolutionary change to identify new genes that have been missed by other methods. A portion of GRIA2 is shown here in an alignment of the genomes of several species, beneath a graph of the computer analysis. Peaks in the graph identify exons (regions that are expressed), separated by introns (non-coding regions). When a cell reads the gene to make a protein the introns are edited out. Credit: Provided/Siepel

Using supercomputers to compare portions of the human genome with those of other mammals, researchers at Cornell have discovered some 300 previously unidentified human genes, and found extensions of several hundred genes already known.

The discovery is based on the idea that as organisms evolve, sections of genetic code that do something useful for the organism change in different ways.

The research is reported by Adam Siepel, Cornell assistant professor of biological statistics and computational biology, Cornell postdoctoral researcher Brona Brejova and colleagues at several other institutions in the online version of the journal *Genome Research*, and it will appear in the December print edition.

The complete human genome was sequenced several years ago, but that simply means that the order of the 3 billion or so chemical units, called bases, that make up the genetic code is known. What remains is the identification of the exact location of all the short sections that code for proteins or perform regulatory or other functions.

More than 20,000 protein-coding genes have been identified, so the Cornell contribution, while significant, doesn't dramatically change the number of known genes. What's important, the researchers say, is that their discovery shows there still could be many more genes that have been missed using current biological methods. These methods are very effective at finding genes that are widely expressed but may miss those that are expressed only in certain tissues or at early stages of embryonic development, Siepel said.

"What's exciting is using evolution to identify these genes," Siepel said. "Evolution has been doing this experiment for millions of years. The computer is our microscope to observe the results."

Four different bases -- commonly referred to by the letters G, C, A and T -- make up DNA. Three bases in a row can code for an amino acid (the building blocks of proteins), and a string of these three-letter codes can be a gene, coding for a string of amino acids that a cell can make into a protein.

Siepel and colleagues set out to find genes that have been "conserved" -- that are fundamental to all life and that have stayed the same, or nearly

so, over millions of years of evolution.

The researchers started with "alignments" discovered by other workers -- stretches up to several thousand bases long that are mostly alike across two or more species. Using large-scale computer clusters, including an 850-node cluster at the Cornell Center for Advanced Computing, the researchers ran three different algorithms, or computing designs -- one of which Siepel created -- to compare these alignments between human, mouse, rat and chicken in various combinations.

Over millions of years, individual bases can be swapped -- C to G, T to A, for example -- by damage or miscopying. Changes that alter the structure of a protein can kill the organism or send it down a dead-end evolutionary path. But conserved genes contain only minor changes that leave the protein able to do its job. The computer looked for regions with those sorts of changes by creating a mathematical model of how the gene might have changed, then looking for matches to this model.

After eliminating predictions that matched already known genes, the researchers tested the remainder in the laboratory, proving that many of the genes could in fact be found in samples of human tissue and could code for proteins. The researchers were sometimes able to identify the proteins by comparison with databases of known proteins. The discovered genes mainly have to do with motor activity, cell adhesion, connective tissue and central nervous system development, functions that might be expected to be common to many different creatures.

The entire project, from building and testing the mathematical models to running final laboratory tests, took about three years, Siepel said. The work was supported by the National Cancer Institute, a National Science Foundation Early Career Development Grant and a University of California graduate research fellowship.

Source: Cornell University