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Cutting through the genomic thicket in search of disease variants

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(Medical Xpress)—In the early stages of that vast undertaking known as the Human Genome Project, enthusiasm ran high. The enterprise would be costly and laborious but the clinical rewards, unprecedented. Once the complete blueprint of life was unlocked, the genetic underpinnings for a broad range of human maladies would be laid bare, allowing custom-tailored diagnosis and treatment and revolutionizing the field of medicine.

Or so it was thought.

Instead, "scientists were confronted with thousands of mutations in the collection of proteins in personal genomes, with no ready guide about what they meant in terms of health or disease," according to Sudhir Kumar, a researcher who directs the Center for Evolutionary Medicine and Informatics at Arizona State Unive rsity's Biodesign Institute.

Kumar explains that scientists and clinicians have turned to computer tools that sift meaningful variants from the glut of mutations they face. But the accuracy of these tools may be low, says Kumar.

Now Kumar, Li Liu and their colleagues describe a new technique that can reduce the rate of false positives in such tests, thereby increasing their reliability. The group's results recently appeared in the advanced online issue of the journal *Nature Methods*.

The new technique, labeled EvoD (for Evolutionary Diagnosis)

capitalizes in part on comparative genomics—an examination of DNA positions across evolutionary time and between diverse species—to analyze the likely significance of particular human gene variants. EvoD was shown to work much better for positions that are the most evolutionarily conserved in the protein-coding portion of the human genome—known as the exome.

As co-author Liu explains, researchers have taken a keen interest in mutations occurring at ultra-conserved sites in the exome, as these are usually the most critical in terms of protein function. Variants that are functionally damaging at such locations—where evolution is highly resistant to change—are likely to have profound effects on health, often producing so-called Mendelian diseases, which negatively impact health. EvoD performs better than existing methods in diagnosing these mutations.

The Center for Evolutionary Medicine and Informatics now provides EvoD as an online tool and genomic researchers have begun to use it already. The new technique and the tool pave the way for a deeper understanding of genomic variance and advances the quest for personalized disease diagnoses.

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