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New database to speed genetic discoveries

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A new online database combining symptoms, family history and genetic sequencing information is speeding the search for diseases caused by a single rogue gene. As described in an article in the May issue of *Human Mutation*, the database, known as PhenoDB, enables any clinician to document cases of unusual genetic diseases for analysis by researchers at the Johns Hopkins University School of Medicine or the Baylor College of Medicine in Houston. If a review committee agrees that the patient may indeed have a previously unknown genetic disease, the patient and some of his or her family members may be offered free comprehensive genetic testing in an effort to identify the disease culprit.

"PhenoDB is much more useful than I even thought it would be," says Ada Hamosh, M.D., M.P.H., a professor in the McKusick-Nathans Institute of Genetic Medicine at the Johns Hopkins University School of Medicine. "Bringing all of this information together is crucial to figuring out what our genetic variations mean." The database is designed to capture a bevy of standardized information about phenotype, which Hamosh defines as "any characteristic of a person"—symptoms, personal and family health history, appearance, etc.

Hamosh and others developed PhenoDB for the Baylor-Hopkins Center for Mendelian Genomics (BHCMG), a four-year initiative that, together with its counterparts at Yale University and the University of Washington, is charged with uncovering the genetic roots of every disorder caused by a single faulty gene. There are an estimated 3,000 inherited disorders that have been described phenotypically in scientific papers but whose genetic causes have not yet been pinpointed, Hamosh

says, but since many single-gene disorders are extremely rare, she suspects that many more have not yet made it into the literature.

The Centers for Mendelian Genomics have a powerful tool at their disposal, known as whole-exome sequencing. Just a few years ago, Hamosh explains, a geneticist trying to diagnose the cause of an inherited disease would have made an educated guess based on the patient's signs and symptoms about which gene might be at fault, and ordered a test of that gene. If the test came back negative for a mutation, she would order a test of a different gene, and so on. But whole-exome sequencing, in which about 90% of a person's genes are sequenced at one time, has been growing steadily cheaper, and it is this tool that the Centers will use to capture genetic sequencing information (whole-genome sequencing is the next step, but it remains too expensive for many uses, Hamosh notes, as it includes all of a person's DNA, most of which contains no genes).

However, making sense of the deluge of data yielded by whole-exome sequencing presents its own challenges. "The average person has tens of thousands of variations from the standard genetic sequence," Hamosh explains, "and we don't know what most of those variations mean." To parse these variations, she says, "one of the things that needs to change is that the lab doing the testing needs to have the whole phenotype, from head to toe." Researchers will then be better equipped to figure out which variations may or may not be relevant to a patient's illness. Another advantage of the database is that it enables colleagues at distant locations—such as Baylor and Johns Hopkins—to securely access the information and collaborate. Hamosh notes that the database enables different users to be afforded different levels of access—for example, a health provider will only be able to see the information he or she has entered—and that information is deidentified to protect patient privacy. In addition, providers must have patients' consent to be included in PhenoDB.

PhenoDB would be useful for any research project that seeks to match genomic information with its phenotypic effects, Hamosh says, and with that in mind, the Baylor-Hopkins Center for Mendelian Genomics has made the PhenoDB software available for free download at http://phenodb.net. She predicts that similar tools will soon be incorporated into electronic health records as well, so that "doctors will have patients' genomic information at their fingertips and can combine that with information about health history, disease symptoms and social situation to practice truly individualized medicine."

More information: onlinelibrary.wiley.com/doi/10 … /humu.22283/abstract

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