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Researchers find clues to common birth defect in gene expression data

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Researchers at MassGeneral Hospital for Children (MGHfC), The Jackson Laboratory and other institutes have uncovered 27 new candidate genes for congenital diaphragmatic hernia (CDH), a common and often deadly birth defect.

Their sophisticated data-filtering strategy, which uses gene expression during normal development as a starting point, offers a new, efficient and potentially game-changing approach to gene discovery.

Babies born with CDH—representing one in every 3,000 live births—have a hole in the diaphragm that separates the abdominal cavity from the chest cavity, and may die due to poor growth of the lung.

Patricia K. Donahoe, M.D., director of the Pediatric Surgical Research Laboratories at MGHfC, explained, "That hole can be fixed surgically if CDH has been diagnosed in time. But even surgery does not rescue the infants' impaired lung development, which often leads to fatal respiratory complications." Patients who survive into adulthood "tend to have a lot of ongoing health issues," she noted.

Donahoe and her colleagues Meaghan Russell, Ph.D., and Mauro Longoni, M.D., and Jackson Laboratory Professor Carol J. Bult, Ph.D., a computational biologist, led the research, published in the *Proceedings of the National Academy of Sciences*. The team had two goals: to identify the genes and gene networks that cause the hole in the diaphragm in order to develop new diagnostics and preventive treatments, and to learn

more about how healthy lungs form to boost lung development in post-operative infant patients.

Bult and her Jackson colleague Julie Wells, Ph.D., generated gene expression profiles—snapshots of gene activity—for embryonic mouse diaphragms at multiple stages of development. Using algorithms designed by the JAX-MGH team, they used these data to then predict genes likely to contribute to diaphragm defects.

Bult said, "We asked which genes in our developmental data sets work together in common pathways, and which of these pathways contain previously known CDH genes from human studies and mouse models?"

To build gene networks, the researchers used the Mouse Genome Informatics (MGI) data base resource based at The Jackson Laboratory. MGI, freely available to the research community, maintains the most comprehensive collection of mouse genetic and genomic information.

The researchers' filtering strategy identified 27 new candidate genes for CDH. When the investigators examined the diaphragms of knockout mice for one of these candidate genes—pre-B cell leukemia transcription factor 1 or Pbx1—they found previously unreported diaphragmatic defects, confirming the prediction.

The next step in the project is to screen patients for mutations in Pbx1 using the collection of CDH patient data and DNA that MGHfC and Children's Hospital Boston have been accumulating for years in collaboration with hospitals from around the world.

The research reported in the paper opens the door "not only to further research to explore the effects of the other 26 CDH candidate genes," Bult said, "but to a disease gene identification and prioritization strategy for CDH, an approach that can be extended to other diseases and

developmental anomalies."

Provided by Jackson Laboratory