

Recombination hotspot stacks the DNA deck in finding a new diabetes susceptibility gene

November 3 2010

The autoimmune disease type 1 diabetes (T1D), also known as juvenile diabetes, is diagnosed in approximately 70,000 children worldwide per year. Genetics is increasingly being recognized as playing a significant role in susceptibility to the disorder, but outside a handful of genes, a clear understanding of the genetic architecture that underlies T1D has remained elusive. In a study published online today in *Genome Research*, scientists have identified a novel gene associated with diabetes in mice that is revealing new clues about genomic mechanisms that could underlie T1D susceptibility.

Genome-wide association studies (GWAS), genetic scans that look for variants that occur more frequently in people with a certain trait or disease, have recently uncovered more than 40 regions of the genome associated with T1D susceptibility. However, because of the diversity of the human population, isolating the genetic variants that actually cause the disease has been a challenge for researchers.

To avoid the complication of genetic diversity, a team of researchers in Australia have used <u>selective breeding</u> of a non-obese diabetic (NOD) mouse strain to narrow down one of 25 genomic regions associated with increased risk for diabetes to a single gene of unknown function, called *AK005651*. "We actually got a bit lucky in identifying a mouse gene that hadn't been studied before," said Thomas Brodnicki of St. Vincent's Institute of Medical Research, senior author of the study.

Brodnicki described how selective mouse mating in inbred strains



shuffles small pieces of DNA between mice, analogous to shuffling a deck of cards, that will reveal which piece of DNA encodes a disease-related gene. "In our case, a unique chromosome feature, called a recombination hotspot, stacked the DNA deck in favor of finding this gene," Brodnicki noted.

Genetic recombination is the process during cell division in which DNA regions are broken and rejoined, a mechanism beneficial in creating genetic diversity. However, there is also a risk that recombination will generate deleterious alleles. "This particular hotspot actually changed the identified gene's DNA makeup so that it altered diabetes onset in certain mice," Brodnicki said, explaining how the DNA sequence variations in *AK005651* were associated with decreased expression of the gene in the thymus and spleen of diabetic mice.

Brodnicki added that it is not yet clear if the mouse <u>diabetes</u> gene has an equivalent in humans, and exactly how the gene confers T1D susceptibility remains unknown. "Our work does demonstrate that recombination hotspots, which have been relatively neglected in recent genetic studies, should be investigated further for their ability to produce DNA changes in genes that can affect one's risk for developing common polygenic diseases, such as <u>type 1 diabetes</u>."

More information: Tan IKL, Mackin L, Wang N, Papenfuss AT, Elso CM, Ashton MP, Quirk F, Phipson B, Bahlo M, Speed TP, Smyth GK, Morahan G, Brodnicki TC. A recombination hotspot leads to sequence variability within a novel gene (AK005651) and contributes to type 1 diabetes susceptibility. *Genome Res* doi:10.1101/gr.101881.109

Provided by Cold Spring Harbor Laboratory



Citation: Recombination hotspot stacks the DNA deck in finding a new diabetes susceptibility gene (2010, November 3) retrieved 7 May 2024 from https://medicalxpress.com/news/2010-11-recombination-hotspot-stacks-dna-deck.html

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