Hypertensive rat genome sequence expected to uncover genetic basis of human hypertension

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Chronic high blood pressure, also known as hypertension, is a serious health risk factor that afflicts more than 25% of all adults worldwide, but the molecular basis of the disease remains poorly understood. In a study published online today in *Genome Research*, scientists have sequenced the genome of the spontaneously hypertensive rat, building a rich catalog of genetic variants that will help researchers to understand causes of the disease in humans.

The spontaneously hypertensive rat (SHR) strain is the most widely studied animal model of human hypertension. Research on this strain has identified many genomic regions that likely harbor genetic variants that are responsible for the hypertension phenotype, however without a complete sequence of the hypertensive rat genome, it has been difficult to resolve many of these genomic changes and explore their molecular consequences.

Taking advantage of new technologies that are rapidly driving down the cost of DNA sequencing, an international team of researchers led by Timothy Aitman of the MRC Clinical Sciences Centre and Imperial College London have sequenced the first genome of a mammalian disease model with second-generation sequencing technology. By comparing the SHR genome sequence with that of the rat reference genome sequence, Aitman and colleagues generated a nearly complete catalog of SHR genomic variants that could contribute to hypertension

and other phenotypes. They also found that genes known to be abnormally expressed in SHR are especially enriched for sequence variants.

The group expected that the genome sequence would reveal mutations disrupting a number of genes in the SHR strain, however the number of mutated genes they found was quite surprising - 788 genes are mutated in SHR compared to the reference genome, including 60 that are deleted altogether. "So many major differences in protein sequence were unexpected because of the previous belief that differences in a small number of genes and proteins would be responsible for the phenotypic differences between such rat strains," said Aitman.

Of the 788 mutated genes identified in the SHR genome, many are related to cellular functions such as ion transport and plasma membrane localization, as well as immunological and neurological processes. The authors suggest that defects in these functional categories may be causally associated with the known phenotypes of this strain.

Aitman explained that their characterization of genetic variation in the hypertensive rat would be invaluable for complete elucidation of the causes of hypertension and related traits at the molecular level in hypertensive rat. "This in turn will pave the way for greater understanding of the genetic basis of hypertension in humans," Aitman noted, "a problem that has proved remarkably difficult to study in humans directly."

More information: Atanur SS, Birol I, Guryev V, Hirst M, Hummel O, Morrissey C, Behmoaras J, Fernadez-Suarez XM, Johnson MD, McLaren WM, et al. The genome sequence of the spontaneously hypertensive rat: Analysis and functional significance. Genome Res. doi:10.1101/gr.103499.109

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