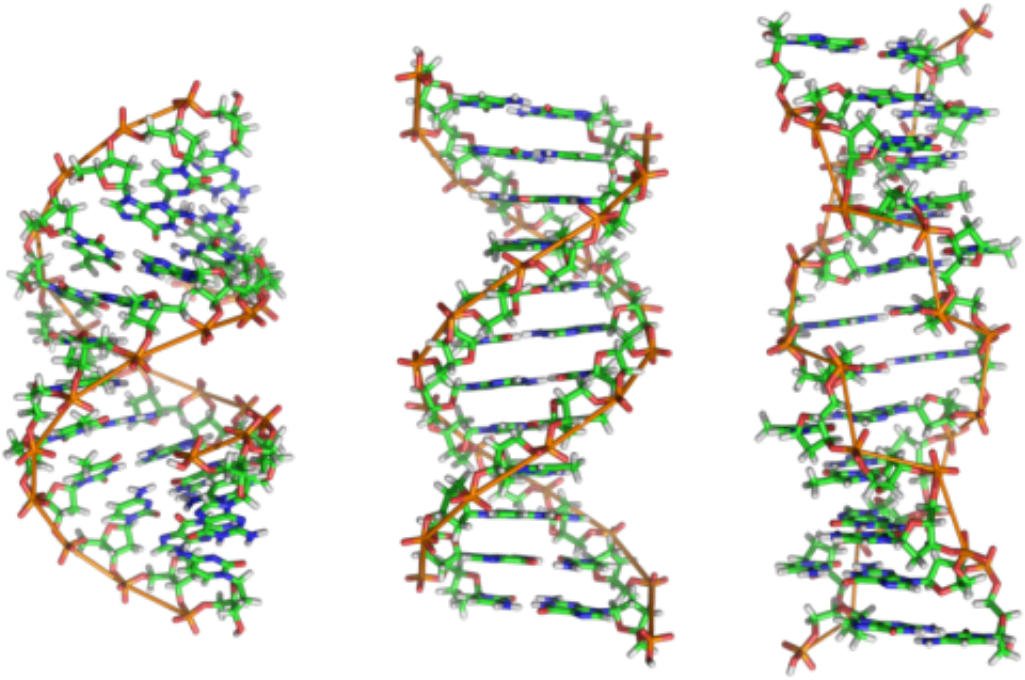
Icelandic genome offers clues to human diversity, gene-disease links

March 26 2015, by Melissa Healy, Los Angeles Times



From left to right, the structures of A-, B- and Z-DNA. Credit: Wikipedia

Scientists who sequenced the entire genomes of 2,636 people in Iceland have produced a trove of information about the nature, location, and frequency of human genetic variations.

The new research not only sheds light on the range of human genetic variability; it helps equip researchers to draw more direct lines between genes and diseases.

In a package of articles published Wednesday in the journal *Nature Genetics*, a private consortium of researchers found genetic abnormalities long thought to doom their host to early death to be more common than has been believed. They also discovered new genetic contributors to such varied afflictions as Alzheimer's disease, liver disease and atrial fibrillation.

The effort, underwritten by Amgen's DeCode Genetics, a biopharmaceutical company based in Reykjavik, Iceland, offers scientists insight to the human genome that will expand their ability to investigate the genetic bases of human diseases.

By sequencing the full genomes of more than 2,500 Icelanders and comparing the results with less extensive genotype data from more than 104,000 other Icelanders, the teams identified more than 20 million genetic variants in the Icelandic population.

They then cross-checked that information against Iceland's extensive genealogical and health care information records, which would document diagnoses, chronicle treatment response and allow researchers to see how a single disease might run through generations of a given family.

As they did so, the role of many of those genetic variations in diseases became evident. Future researchers are likely to find more such links as they comb through the genetic and genomic data released by the project.

Armed with the new findings, "we can turn the tables," said DeCode President Kari Stefansson, a senior author on all four articles published by *Nature Genetics*.

In addition to starting with a known disease and hunting for its origins in a population's genetic material - a needle-in-a-haystack approach called

the genome-wide association study - scientists can use the genetic clues found by DeCode to replicate some recognizable diseases in animals, said Stefansson.

When scientists can watch exactly how illness emerges from a specific genetic variation, he told reporters, the result will be a more intimate understanding of what goes wrong in human disease. Such knowledge will probably speed the process of finding targeted treatments for those afflictions, he said.

Stefansson said approach would also improve the identification of genetic variations that confer protection from diseases.

Some of the genetic transcription errors found in the Icelandic population may not be as deadly as once believed, the new research suggests.

One of the articles published Wednesday looked for genetic "knockouts" - gene deletions that scientists had thought would do irreparable harm to the individual bearing such a variation. The team identified 1,171 genetic "knockouts," and found more than 8,000 Icelanders who have completely lost the function of at least one gene.

Genes responsible for our ability to discriminate between smells were the most commonly knocked-out class of genes. The team found far fewer knock-outs in genes that are expressed highly in the brain, suggesting that a gene deletion there would be more harmful.

As scientists mine these data, they're likely to glean new insight on which genes are indispensable and which are linked to disease.

Linda D. Brooks, program director of the National Human Genome Research Institute's program on genetic variation in Bethesda, Md., said

the Icelandic genome project is particularly valuable for its ability to detect uncommon genetic variations that contribute - sometimes in conjunction with better known mutations - to diseases or help protect against them.

Such findings will further the goals of the Obama administration's precision medicine initiative, said Brooks, who was not involved in the DeCode initiative.

By helping paint a fuller picture of the genetic factors that give rise to - or confer protection from - disease, the Icelandic findings will help scientists devise disease-risk estimates that are fine-tuned to individuals, said Brooks. That, in turn, will allow patients and their physicians to take steps to prevent those diseases or treat them in a targeted way, she said.

While Iceland's small and homogeneous population was a factor in making such genetic discoveries possible, the benefits of DeCode's findings are not limited to Icelanders, said Harvard genetic scientist Steven McCarroll, who was not involved in the research leading to the four Nature Genetics articles.

By first finding a genetic variant and only then looking for its manifestation, McCarroll said, DeCode's scientists have uncovered a relationship that is likely to be found universally in humans, however different their genetic lineage may be.

"The things that they're learning about what genes contribute to disease are generally biologically true," said McCarroll, who was not involved in the research leading to the four Nature Genetics articles.

McCarroll praised Iceland - and other countries, including Sweden, Finland and Estonia - that are committed not only to providing excellent national health care but to maintaining comprehensive records on

matters pertaining to citizens' health, including kinship relations and, now, genetic information.

"Countries like Iceland are really going to be the leaders in the genomic medicine movement," said McCarroll. Meanwhile, countries such as the United States, with its fragmented health care system and patchwork of decentralized record-keeping, "are going to be playing catch-up," he said.

If U.S. scientists were to undertake a similar project, the nation's genetic diversity "would be a towering strength," McCarroll said.

Brooks of the NHGRI also underscored the importance of conducting large-scale genome-sequencing projects, not just in small, ethnically homogeneous countries such as Iceland, but in the United States.

"You really want to include people of all different ethnicities," said Brooks. "There's a lot of genetic variance in the U.S. population that is not in Icelanders." Beyond that, she said, such studies conducted in the United States would help tease out the role of environmental factors - including diet, exercise patterns, pollution and other toxic exposures - that can influence gene expression, and which may not be present in Iceland.

More information: DOI: 10.1038/ng.3247,
DOI: 10.1038/ng.3246,
DOI: 10.1038/ng.3243,
DOI: 10.1038/ng.3171,
DOI: 10.1038/sdata.2015.11