# Critics cast doubt on recent longevity gene study findings

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(PhysOrg.com) -- A recent study of centenarians (reported in PhysOrg on July 1st) that linked a number of gene variants to longevity has now been questioned by other scientists, who suggest a DNA chip known as 610-Quad, used in the analysis, has a tendency to produce false-positives. The flaw in the chip, along with other concerns, has cast doubts on some of the major findings of the study.

The paper, published in *Science*, identified 150 genetic variants that may protect the body against disease and increase the chances of reaching 100 years or more. Even some of its critics admit the research was well-designed in almost all respects, and the researchers say they conducted "extensive quality-control procedures and cleaning of the data," and stand by their results.

One of the major components of the work, carried out by researchers at the Boston University School of Medicine, was a genome-wide association study (GWAS), which uses DNA analysis (SNP) chips to analyze DNA from many subjects to identify variants more common in the group of interest, called cases (in this study people over 100) than in controls. The variants seen more often in the cases are then considered to be linked to the trait being studied. The researchers built a model based on their genetic analysis, and found it could predict extreme longevity with 77 percent accuracy.

A single nucleotide polymorphism (SNP) chip is a tool now widely used in genome analysis. The chips are not perfect and are all known to

occasionally identify parts of DNA incorrectly, with each type of chip making different errors at different parts of the genome. If only one type of chip is used this can lead to false-positive results, and that is what some scientists, including geneticist David Goldstein of Duke University in Durham, North Carolina, suggest may have happened in the longevity gene study.

Goldstein said it is important to ensure cases and controls are analyzed in exactly the same way using exactly the same chip. If different chips are used for cases and controls the results found may be experimental artifacts rather than real differences. Goldstein added that using the same chip is standard practice for most GWAS research, and the "rigor that seems to be missing from this study is almost always found in others."

In the longevity gene study all the chips were made by the company Illumina, but they were not identical and some of the control and case samples were analyzed in different laboratories. According to the original paper most of the centenarians were analyzed using a 370 chip that looks at 370,000 genetic variations, while around 10 percent were analyzed using the 610-Quad chip that looks at 610,000 genetic variants. Some of the controls were analyzed with the 370 chip, others with the 610, and still others were analyzed using two other chips.

A geneticist from Iceland, Kari Stefansson, who founded deCode Genetics, also suggested a weakness in the research since the 610 chip has a "quirk" related to two of the strongest variants linked by the study to longevity: rs1455311 and rs1036819, in which it tends to always see the minor form (allele) of DNA but does not identify the major allele at those locations in the genome, even though it is usually present.

Stefánsson said when researchers are looking for unusual patterns in their cases, they could mistake these errors for a genetic link that does

not really exist. From his knowledge of the 610-Quad quirks he also took the data from the paper and calculated an estimate of centenarians who would have been analyzed with that chip. His result of eight percent is close to the actual figure of 10 percent.

Author of the original paper, biostatistician Paola Sebastiani of Boston University, said the reason was that the 370 chip went off the market during the study and using a different chip was "the best option for us in terms of costs and coverage." She also said the team found the same variants associated with longevity when a third laboratory repeated the analysis of control samples.

The flaw in the chip could be discounted if the analysis was re-run using the same DNA chip for controls and cases, but critics of the study say this should have been done before the paper was published in one of the top science journals. If the analysis were to be repeated it is possible the genetic associations found in the original paper will still hold, but until this is done they say the results found must remain in doubt.

After concerns were raised about the paper's findings the authors issued a statement acknowledging there had been "a technical error in the laboratory test used on approximately 10% of the centenarian sample that involved the two of the 150 variants." They said their preliminary analysis suggests the error would not affect the overall accuracy of the model, but they are closely re-examining the analysis.

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