New Clues to Human Longevity

Brian D. Piening[1,2*†]

What is the key to a long lifespan? A number of prior and ongoing projects have intensely studied centenarians (>100 years old) and supercentenarians (>110 years old) with hopes of unlocking genetic and/or biochemical secrets as to why a subset of humans live an exceptionally long and disease-free life *(1, 2)*. This is a highly challenging area of study in humans, given their long average lifetimes relative to the animal kingdom and the significant environmental variability that individuals experience over the course of these lifetimes.

One pathway of keen interest for lifespan modulation consists of human growth hormone (GH) and insulin-like growth factor (IGF), in which mutations in the *IGF1* locus have been shown to be enriched in centenarians *(3)*. Recently, in the June 16 issue of *Science Advances (4)*, Ben-Avraham et al. identified a new longevity-associated allele consisting of a splice isoform of the GH receptor (*GHR*) lacking exon 3 (*d3-GHR*). These authors showed that homozygous *d3-GHR* status was enriched in male centenarian populations across 4 independent cohorts, with homozygous male carriers living on average 10 years longer than wildtype counterparts. Remarkably, homozygous *d3-GHR* male carriers were an inch taller in the study. To be clear, this is not a particularly rare polymorphism, as approximately 25% of individuals are carriers of at least 1 *d3-GHR* allele.

How soon or if these findings can be translated into a novel therapeutic remains to be seen, and the male-specific nature of *d3-GHR* longevity is not yet understood. Phenotypically, the authors showed that in cultured cells homozygous *d3-GHR* was associated with lower basal cell proliferation and extracellular-signal-regulated kinase (ERK) activation; yet, both proliferation and ERK signaling were significantly enhanced upon stimulation with GH, raising the intriguing possibility that a lower threshold for GH stimulation in elderly *d3-GHR* homozygotes may provide some protections against metabolic disease, carcinogenesis, or more complex pleiotropies. The identification of protective effects for *d3-GHR* for specific morbidities will likely require building extensive cohorts of genotyped individuals of all ages, a goal that will surely expand our understanding of human longevity genetics.

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References

1. Sebastiani P, Solovieff N, Dewan AT, Walsh KM, Puca A, Hartley SW, et al. Genetic signatures of exceptional longevity in humans. PLoS One 2012;7:e29848.
2. Gierman HJ, Fortney K, Roach JC, Coles NS, Li H, Glusman G, et al. Whole-genome sequencing of the world's oldest people. PLoS One 2014;9:e112430.
3. Suh Y, Atzmon G, Cho MO, Hwang D, Liu B, Leahy DJ, et al. Functionally significant insulin-like growth factor I receptor mutations in centenarians. Proc Natl Acad Sci USA 2008;105:3438–42.
4. Ben-Avraham D, Govindaraju DR, Budagov T, Fradin D, Durda P, Liu B, et al. The GH receptor exon 3 deletion is a marker of male-specific exceptional longevity associated with increased GH sensitivity and taller stature. Sci Adv 2017;3:e1602025.

[1] Molecular Genomics Laboratory, Providence Portland Medical Center, Portland, OR; [2] Earle A. Chiles Research Institute, Robert W. Franz Cancer Research Center, Providence Portland Cancer Center, Portland, OR.
* Address correspondence to this author at: Molecular Genomics Laboratory, Providence Portland Medical Center, 4400 N.E. Halsey St., Building 3, Portland, OR 97213. Fax 503-893-7658; e-mail brian.piening@providence.org.
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Human Genes: *IGF1*, insulin-like growth factor 1; *GHR*, growth hormone receptor.