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GENE LOSS IN HUMANS

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Humans are estimated to have about 20,000 genes, but several hundred of these can be 'lost' in some individuals within the population because of the presence of variants such as nonsense SNPs, frame-shift SNPs and indels, as well as larger copy number variations (CNVs). Olson has proposed a "less is more" theory: that gene loss, usually thought of as disadvantageous, can sometimes be advantageous and even an important engine of evolutionary change. We have known of a few examples of evolutionarily advantageous gene loss in humans for some time, including Caspase-12 and Actinin-3 where loss leads to increased sepsis resistance and improved athletic endurance, respectively; or in chimpanzee, inflammatory response genes such as IL1F7 and IL1F8. With data from personal genome sequences as well as the 1000 Genomes Project, we can now evaluate the evolutionary importance of loss-of-function variants in recent human history in a more systematic fashion. Overall, variants that cause gene loss are evolutionarily disadvantageous as expected, illustrated by decreased allele frequency or lower population differentiation compared with near-neutral variants such as synonymous substitutions. The pilot phase of the 1000 Genomes Project is providing a catalog of the majority of loss-of-function variants present at a frequency of ~5% or above in three populations from Africa, East Asia or Europe, and we will report on the current evaluation of the evolutionary significance of these and their implications for personalized medicine.

Keywords: Gene loss, Human evolution, Natural selection, Loss-of-function variants