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HUMAN GENETICS

Dissecting deleterious mutation complexity

> deleteriousness as a systems property rather than as an intrinsic feature of individual genes or proteins

Deleterious mutations are predicted to disrupt gene function and to reduce organismal fitness. A surprising result from various genome sequencing studies of healthy humans is the high prevalence of deleterious mutations, including mutations that occur in a homozygous state. Two new studies characterize the burden of deleterious variants in different populations and provide rationale for their tolerance based on protein network topology.

In the first study, Fu *et al.* sought to characterize the burden of deleterious mutations in different human populations, particularly to address discrepancies in the literature as to whether inter-population differences exist. They mined available exome sequencing data from 6,515 African American (AA) and European American (EA) individuals.

From the identified single-nucleotide variants (SNVs) they calculated PhyloP scores: this approach estimates SNV deleteriousness by assessing the degree to which that SNV has been evolutionarily avoided across a 36-species eutherian–mammalian phylogeny. Importantly, the authors reduced bias by modifying the PhyloP approach to exclude the human reference genome from the cross-species phylogeny (so that the genuinely deleterious SNVs that by chance are represented in the human reference genome will not cause an underestimation of the deleteriousness of the same SNVs in the sample populations). Using this approach, they found that the number of deleterious alleles per individual was slightly but significantly higher for EAs than AAs, primarily owing to EAs harbouring more SNVs in a homozygous state. Simulations showed that the differences in deleterious SNV distributions between EAs and AAs is largely accounted for by weakly deleterious mutations that increased in frequency as a result of population bottlenecks as humans left Africa and dispersed throughout the world.

As one explanation for discrepant published results, Fu *et al.* propose that opposing patterns of variation arise from focusing attention at the level of populations versus individuals. For example, population bottlenecks decrease the number of deleterious variants in the population but increase the per-individual load of deleterious variants.

In the second study, Garcia-Alonso *et al.* sought a functional understanding of how the load of deleterious mutations carried by humans is compatible with normal health. Using exome sequencing data from healthy individuals in the 1000 Genomes Project and from an additional 252 healthy Spanish individuals, they identified variants that score for deleteriousness according to the SIFT and PolyPhen programs.

They then examined the proteins affected by these deleterious variants for their connectivities in a protein–protein interaction network, finding that these proteins (particularly those from homozygously mutated genes) occupy peripheral positions in the network and have few connections. Furthermore, when considering the combinations of proteins affected in individuals, removing these sets of proteins from the network had a less disruptive effect on the network than removing random combinations of proteins. Overall, these results may explain why the observed mutations do not result in serious consequences to cellular or organismal physiology. By contrast, when analysing known disease-associated variants — either germline variants underlying Mendelian diseases or somatic mutations in chronic lymphocytic leukaemia — the proteins occupy more central positions in the network, and their mutation is hence more disruptive to the network. This study therefore highlights the value of considering deleteriousness as a systems property rather than as an intrinsic feature of individual genes or proteins.

As a potential intersection of these studies, it will be valuable to investigate the functional implications of the differences in deleterious variant distributions between human populations.

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ORIGINAL RESEARCH PAPERS Fu, W., *et al.* Characteristics of neutral and deleterious protein-coding variation among individuals and populations. *Am. J. Hum. Genet.* **95**, 421–436 (2014) | Garcia-Alonso, L. *et al.* The role of the interactome in the maintenance of deleterious variability in human populations. *Mol. Syst. Biol.* **10**, 752 (2014)