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**Genetics: An in-depth insight into human genetic variation (N&V)**

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An in-depth analysis of the exomes (protein-coding regions) of the human genome provides the most comprehensive catalogue of genetic variation in these regions to date. It is thought that the study, reported in this week's *Nature*, will improve efforts to identify clinically relevant genetic variation for human disease.

As part of the Exome Aggregation Consortium (ExAC), Daniel MacArthur and colleagues sequenced the exomes of 60,706 individuals of diverse geographic ancestry, including European, African, South Asian, East Asian and Latino populations. They identified around 7.4 million genetic variants, providing unprecedented resolution into low-frequency protein-coding variants in human populations. The authors analyse this dataset to characterize patterns of genetic variation worldwide, bringing resolution that has not been possible on smaller datasets of genetic variation. The density of genetic variation has allowed for resolution of multiple sequence variants at the same site (multiallelic variants), while the size of the dataset allows some of the first findings on mutational recurrence — rare mutations arising independently during the history of the populations.

ExAC provides an openly accessible reference database that has already proved useful as a clinical tool for evaluating purported Mendelian (single-gene) disease-causing variants, some of which are implausibly common in the population. The authors analysed 192 such variants reported in prior studies and found that only nine had sufficient data to support disease association. In a separate paper published in *Genetics in Medicine*, Roddy Walsh and colleagues evaluated genetic variation in one of the most common serious Mendelian disorders, cardiomyopathy (disease of the heart muscle). Their findings suggest that many genes and variants previously associated with a given cardiomyopathy are likely spurious, but that variant interpretation can now be significantly improved using ExAC.

In a third paper, published in *Nature Genetics,* Douglas Ruderfer and colleagues analyse rare copy number variation (a type of genome structural variation) within the ExAC dataset.

Previous research efforts have sought to catalogue genetic variation within the exome, but ExAC is the largest, most thorough initiative of its kind. In an accompanying News & Views, Jay Shendure concludes: "ExAC is both a technical and political achievement, requiring wrangling not only of data but also of investigators, consents and more from 14 studies — most of which were directed at the genetics of various common diseases."

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