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HUMAN GENOMICS

Known and unknown

The tidal waves of data from high-throughput sequencing enable new attempts to address vexing questions of inheritance and evolution. One of the most sought after insights has been a direct and accurate measure of the human mutation rate. A group of researchers — including the 1000 Genomes Project investigators — have now applied their sequence resources to the problem.

Conrad *et al.* report the generation of complete genome sequences from lymphoblastoid cell lines of two parent–offspring trios: one of European origin and one of African origin. Single-base substitutions in the offspring were classified as either germline *de novo* mutations or mutations that occurred in the cell line at some later point. Extensive validation of mutation status was performed using a third generation in the European pedigree and separate blood samples in the African pedigree. The authors found the mutation rate to be 1.17×10^{-8} in the three European samples and 0.97×10^{-8} in the three African samples — estimates that are in keeping with previous studies. For perspective, many of the same authors noted in a previous work (see Further reading) that this corresponds to about two *de novo* mutations in the coding regions per zygote.

Whereas most previous studies produced sex-averaged mutation rates, Conrad and colleagues were able to provide separate estimates of male and female germline mutation rates. In these two trios, the rates were significantly different: 92% of mutations on the male background in one and 36% in the other. These numbers suggest that sex-specific mutation rates vary much more widely between families than expected, but larger sample sizes are, of course, needed confirm this. The findings have implications for the increasing numbers of studies that are applying high-throughput sequencing to trios or families in search of disease-causing mutations — the ease of determining the pathogenicity of putative mutations may vary widely between families or even within families.

> “These numbers suggest that sex-specific mutation rates vary much more widely between families than expected”

Like previous estimates of mutation rate, other variables affect the conclusions of this study. Rates were measured in cell lines that have been created and passaged multiple times in culture, very likely inducing mutations — the authors point out that anyone using cell lines must account for such mutations. They were also unable to quantify the effect of paternal age or environmental factors. In the immortal words of Donald Rumsfeld, “we know there are some things we do not know. But there are also unknown unknowns, the ones we don’t know we don’t know.” Conrad and colleagues have made a valiant effort at addressing the known unknowns, only to turn up previously unknown unknowns, which is what makes science exciting.

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ORIGINAL RESEARCH PAPER Conrad, D. F. *et al.* Variation in genome-wide mutation rates within and between human families. *Nature Genet.* **43**, 712–714 (2011)
FURTHER READING Awadalla, P. *et al.* Direct measure of the de novo mutation rate in autism and schizophrenia cohorts. *Am. J. Hum. Genet.* **87**, 316–324 (2010)