

Distinct human mutations can alter the effect of medicine

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Credit: University of Copenhagen

Every person has a unique DNA sequence. Now, researchers from the University of Copenhagen and the MRC Laboratory of Molecular Biology in Cambridge have tried to quantify what these differences in the genome mean in the context of genes targeted by drugs.

In a new study published in the scientific journal *Cell*, they look at

certain [receptors](#) (GPCRs) in human cells. These protein receptors are the main targets of the biggest group of marketed modern medicine. By mining existing data sets, they have mapped the extent to which [mutations](#) occur within GPCR drug targets in individuals and studied what impact these mutations could have on the therapeutic effect of medicine.

"We estimate that an average of 3 percent of the population have receptors that contain mutations that can alter the effect of medicine," says first author Alexander Hauser from the Department of Drug Design and Pharmacology at the University of Copenhagen.

"This might mean that the medicine simply works less efficiently. It can also mean that the medicine does not work at all, or causes adverse effects on patients," adds Madan Babu from the MRC Lab of Molecular Biology in Cambridge, where Hauser conducted this research.

The researchers have analysed the mutations in human GPCRs by using whole genome sequencing data from the 1,000 Genomes project with about 2,500 participants, as well as exome data from the ExAC project with over 60,000 participants. They then used structural data to infer critical sites in GPCRs to uncover which mutations are more likely to alter the outcome of medicine.

"The 3 percent of the affected population is an average. For some important receptors, it is way more. For instance, the relevant mutations occur in 69 percent of people in the GLP1 receptor that is the target of diabetes medicine, and in 86 percent of people in the CNR2 receptor that is used as a target for medicine to relieve nausea induced by chemotherapy. But of course, we cannot know every person's genome, and so these are estimates based on the datasets available," says Alexander Hauser.

The researchers use their findings and sales data for the 279 GPCR-relevant drugs from the National Health Service in the U.K. to estimate how much money is spent on medicine with little or no effect. As a conservative estimate, they find the economic burden on the U.K. National Health Service to be at least £14 million annually, taking into account the number of people with mutations in both copies of the gene in important sites of the receptor target.

"The prevalence and potential impact of variation in [drug](#) response between individuals is a strong argument for further researching this field. It also constitutes a fine example of why personalised [medicine](#) might be the way forward; even when we are talking about common drugs," says Hauser.

More information: Alexander S. Hauser et al, Pharmacogenomics of GPCR Drug Targets, *Cell* (2017). [DOI: 10.1016/j.cell.2017.11.033](https://doi.org/10.1016/j.cell.2017.11.033)

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