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PHARMACOGENOMICS

Know your GPCR mutations (and target them right)

Natural human genetic variations may cause patients to respond differently to the same medication. Therefore, understanding genetic variation in drug targets can maximize efficacy and reduce side effects. In a new study, a team led by M. Madan Babu present a comprehensive analysis of G protein-coupled receptor (GPCR) genetic variants and find that GPCRs targeted by marketed drugs show genetic variation within functional regions such as drug-binding sites.

GPCRs mediate the therapeutic effects of more than 30% of FDA-approved drugs. To assess how much variability is found among human GPCRs that are targeted by marketed drugs, the authors investigated data from the exome aggregation consortium (ExAC), which contains information on missense variations (MVs), loss-of-function variations (LoFs), and deletions and duplications (copy number variations; CNVs) from 60,000 individuals. Looking across 108 GPCRs, the authors found more than 14,000 variants, with any individual receptor having an average of 4 common and 128 rare variations. They analysed each of the MVs and found that 2,036 mutations in the 108 receptors fall within known functional sites, such as ligand binding, effector binding or post-translational modification sites.

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To explore the functional implications of such mutations, the authors then experimentally analysed the impact of three MVs near the ligand-binding pocket of the μ-opioid receptor (MOR) on G protein activation by the endogenous agonist endomorphine 1, morphine (full agonist), buprenorphine (partial agonist) and naloxone (antagonist). Whereas one variant (M153V) resulted in partial LoF and reduced the response to both full agonists and the partial agonist, another variant (K235N3) showed increased efficacy and potency of buprenorphine compared with the wild-type receptor. Another variant, V302I, showed gain-of-function effects with increased potencies of full agonists and increased efficacy of the partial agonist. This variant maintained G protein signalling when treated with the antagonist naloxone. This finding indicates that naloxone, which is used to treat opioid overdose, may exhibit poor efficacy in patients with this variant receptor.

The authors also considered the possible economic impact of the observed genetic variability in the MOR. Given the huge number of drugs targeting the MOR that are prescribed, if even a small fraction are ineffective or cause adverse reactions, the economic burden may be considerable.

However, “as it stands, no receptor variants are included in the labelling information of any GPCR drug target by any regulatory agency,” says Alexander Hauser, first author of this study. “This is likely going to change with increased sequencing efforts, bigger cohorts and better characterization of the variants”. Along with the study, the authors also present an online resource of GPCR genetic variants (gpcrdb.org), which they plan to update with new genome data sets as well as orthogonal data types. “There is still a lot to understand before we can fully embark on personalized medicine for GPCR-targeted drugs. However, we think the time is right to make a start”, concludes M. Madan Babu.

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ORIGINAL ARTICLE Hauser, A. S. *et al.* Pharmacogenomics of GPCR drug targets. *Cell* **172**, 41–54 (2017)
FURTHER READING Hauser, A. S. *et al.* Trends in GPCR drug discovery: new agents, targets and indications. *Nat. Rev. Drug Discov.* **16**, 829–842 (2017)