Reply: Loss-of-function genetic diseases and the concept of pharmaceutical targets

Ségalat makes several interesting points regarding the relevance of monogenic disorders in the identification and validation of novel drug targets. Nonetheless, we feel that the comments are overly conservative. It is not the logic of our argument that is criticized by Ségalat; it is rather the practical applicability of our approach to drug and target discovery. Our approach is not exclusive, and we did not intend to imply that it would be applicable to all disease states. Our point is simply that monogenic disorders can be of value in understanding the underlying pathophysiology of many common diseases, and if so they should not be overlooked. Multiple examples of major drug programmes that are already in progress that stem from, or are influenced by, human monogenic molecular results, support our conclusion. We have suggested that more effort and resources should be placed in this arena of human genetics, to complement the current enthusiasm for whole-genome SNP-association testing, and that the potential value of such genetics for new drug target validation should always be considered. We have also noted in our article that the distinction between 'monogenic' and 'complex genetics' is more operational than theoretical, but feel that this is still a useful distinction as long as the limitations of this dichotomization are respected.

Ségalat notes that the physiology of the ascertained monogenic disorders (whether molecularly characterized or not) has typically been evaluated already with respect to important common diseases. This is not in dispute. But, as we note, these represent only a fraction of all possible monogenic phenotypes, and are probably biased towards rare, not common, medical phenotypes. The null or loss-of-function allelic consequences in most human genes remain totally uncharacterized. For example, disregarding the olfactory receptors, there are approximately 370 G-protein coupled receptor (GPCR)-encoding genes, of which fewer than 40 have a defined monogenic phenotype. GPCRs are favourites of the pharmaceutical industry, and can sometimes be both agonized and antagonized by different chemistries. It is feasible that null alleles of uncharacterized GPCRs could lead to migraine, bipolar disorder, hypertension (or hypotension), obesity (or leanness) and so on. Clearly, highly penetrant dominant genetic disorders that mimic common medical conditions are not abundant, but recessive monogenic disorders that mimic common medical conditions are not easily ascertained by traditional medical genetics. Mutations in the leptin and leptin receptor genes are known in humans, but were only discovered by candidate-gene sequencing after these genes were implicated in obesity by mouse genetics. In fact, Ahituv *et al.*[1] and Cohen *et al.*[2] suggest that individually rare mutations in multiple genes could be additively important for understanding the total genetic burden of obesity and dyslipidemia.

Ségalat notes that, "…another major problem with genetic diseases is that they have no treatment." Although treatment remains elusive for many (but not all) genetic disease, our premise focused instead on the relevance of monogenic disorders to the treatment of a common disorders with similar physiology. We do not mean to imply that a mode of treatment can be suggested for the actual patients who suffer from the monogenic disorder: there might be in some cases, but that is not the point. Human genetics is being used as an analytical paradigm to dissect common disease pathways and to identify targetable steps. Gene therapy is a completely different issue: important, but unrelated to our logic.

We do not disagree with the comment that some important medical conditions might fail to yield to single-target-based therapeutics, and that some diseases are too complex for standard pharmaceutical treatment. Some approved, psychiatrically active drugs are already known to target multiple receptor types in the brain, which might be necessary for their action. However, the human genetics community is only beginning to analyse multi-locus phenotypes, and is still at the phase in which discovering a single locus that is relevant to a common disease phenotype is a major logistical and theoretical endeavor. Moreover, it is disingenuous to assume that the pharmaceutical industry will readily adapt to a multi-target or combined-therapy paradigm for all important indications, as these add major burdens of complexity and cost to compound development. The heavy onus placed on new pharmaceutical programmes to document mechanism of action, safety and efficacy, lead *de facto* to reductionist approaches, even when it is clear that multiple physiological pathways

are involved in a clinical phenotype. Our point is that human genetics, whether monogenic or complex, forms its interpretations from altered levels of gene function in the intact organism, and is thus less reductionist than other target validation methods that are commonly in use.

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1. Ahituv, N. *et al.* Medical sequencing at the extremes of human body mass. *Am. J. Hum. Genet.* **80**, 779–791 (2007).
2. Cohen, J. C. *et al.* Multiple rare alleles contribute to low plasma levels of HDL cholesterol. *Science* **305**, 869–872 (2004).