containing phytochromes. This result was not observed under surface-water conditions, suggesting that these photoreceptors are specifically useful for acclimatization to light-limited environments.

The authors' work provides insights into the evolutionary adaptation of marine diatoms to the light in their environment. Diatom phytochromes function effectively as an optical depth sensor, providing information on their vertical position in the water column. This is particularly advantageous in regions with strong seasonal or daily vertical mixing, where diatoms experience rapid changes in light conditions.

Although diatoms are key contributors to aquatic biochemical cycles, they are not the only photosynthetic phytoplankton in these habitats. So are diatom phytochromes unique from an evolutionary standpoint? All land plants have phytochromes, but chlorophyte algae, their closest aquatic relatives, have completely done away with these red-sensing photoreceptors[2]. Indeed, these species have few characterized red-light responses and depend on blue-sensing photoreceptors to regulate their physiology[7]. Phytochromes have been detected in many other algal lineages that are not related to plants; however, these proteins do not share the same structure as plant phytochromes, suggesting a different evolutionary origin[2]. Indeed, several studies report that aquatic phytochromes respond to light across the visible spectrum and have a poor ability to detect red and far-red light[8,9].

Duchêne and colleagues' work provides strong support for this hypothesis, but emphasizes a key point — even in the diatom lineages, the environment has a strong effect on the selective evolution of phytochromes. The ability to sense and respond to spectral light variations probably confers a competitive advantage to phytochrome-containing diatoms, particularly in regions at high latitudes that have dynamic light regimes.

The questions raised by this study could also be asked about other environmentally relevant lineages. For instance, brown algae (such as kelps) dominate intertidal and subtidal areas globally and have an enormous ecological effect on these areas[10], but the prevalence and distribution of phytochromes for this lineage have not yet been reported. Uncovering whether there are similar (convergent) evolutionary patterns in other algal lineages would reveal a widespread role for phytochromes as regulators of aquatic photobiology.

Marina Cvetkovska is in the Department of Biology, University of Ottawa, Ottawa, Ontario K1N 6N5, Canada.
e-mail: mcvetkov@uottawa.ca

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Genome editing

Embryo editing for disease is unsafe and unproven

Shai Carmi, Henry T. Greely & Kevin J. Mitchell

Mathematical modelling suggests that it is theoretically possible to reduce risk of common diseases using heritable genome editing. Scientists argue that the technology involves considerable risk and uncertain benefits. **See p.637**

The possibility of editing the genomes of human embryos has been widely discussed, particularly since the discovery of the CRISPR–Cas9 gene-editing tool. The revelation in late 2018 that a Chinese scientist, He Jiankui, had edited embryos that became living babies created a huge wave of controversy[1]. On page 637, Visscher *et al*.[2] describe a mathematical model that argues that just a handful of edits could reduce the risk of various disorders dramatically — in a theoretical scenario in which heritable, large-scale genome editing is feasible and safe. Although the authors' claims are logical and thought-provoking, their model relies on several speculative assumptions and glosses over unknown, but predictable, serious risks. Given the broad interest in this topic, the work will probably be discussed widely and might ultimately affect policy. It raises both scientific and ethical issues, which we discuss here.

Most traits and common diseases, such as heart attack, stroke, cancers and diabetes, are polygenic — meaning that they are influenced by thousands of DNA variants. Over the past 15 years, hundreds to thousands of variants associated with disease risk have been discovered for almost every common polygenic medical condition[3]. Although the risk associated with each variant is tiny, an individual's overall burden of these variants can be used to assess their disease risk, and those at high risk can be offered extra monitoring or preventive measures[4].

A more radical approach pushes disease prevention to *in vitro* fertilization (IVF): embryos with low polygenic risk would be selected for transfer and hoped-for gestation[5]. This approach has been available in the United States since 2019, but the expected reductions in disease risk are modest, at best — even if the clinical, ethical and social concerns[5] are dismissed.

An even more radical proposal is to modify the genome of a target embryo in pre-specified ways. Genome editing has already been successfully piloted for the treatment of rare genetic conditions[6] but, except for He Jiankui's experiments[1], it has been done in only somatic tissue (cells of the body), not cells of the germ line (reproductive cells) or embryos. Heritable genome editing is illegal in much of the world, owing in part to concerns about off-target effects and other unpredictable negative consequences[1]. In their paper, Visscher *et al*. ask, in a hypothetical scenario in which these problems do not exist, what health gains could theoretically be achieved?

Visscher and colleagues' main claim is that disease risk can be reduced by introducing into the genomes of embryos 'rare protective alleles' — genetic variants that are uncommon in the population but are thought to protect against disease. The existence of such alleles is well established[7] — for example, rare loss-of-function alleles in the genes *PCSK9* and *ANGPTL3* reduce cholesterol levels and cardiovascular illness[8]. This is, in fact, the strategy taken by He Jiankui in his attempts to grant embryos some protection against HIV. Given that most people do not carry them, rare protective alleles provide, in theory, a general target for decreasing disease risk — a one-size-fits-all 'genomic prophylactic'.

The model proposes that editing only ten rare protective alleles per disease is expected to lead to dramatic reductions in risk, between 2-fold and 60-fold, for common conditions

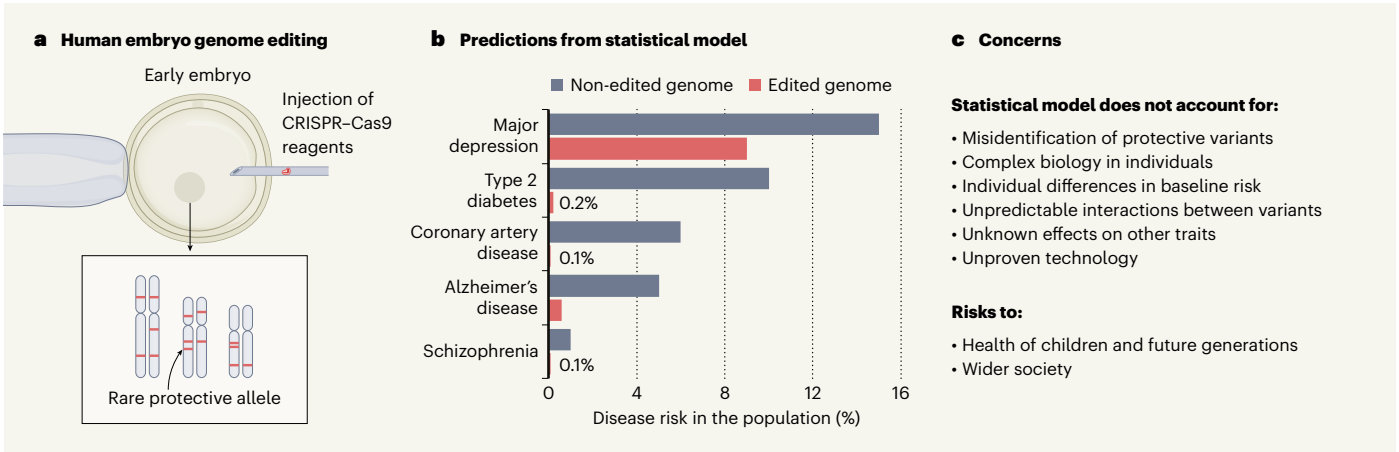

Figure 1 | Heritable gene editing to protect against disease. **a**, Editing the genomes of human embryos *in vitro* using CRISPR–Cas9 is highly controversial. Visscher *et al.*[2] propose that introducing a handful of genetic variants referred to as rare protective alleles into the genomes of embryos could, in theory, protect against common diseases. **b**, The authors' mathematical model, based on population statistics, predicts that introducing just ten rare protective variants into the genome could greatly reduce disease risk. **c**, However, this technology is associated with efficacy, safety and ethical concerns. The assumptions on which the model relies are not proven, and the biological outcomes are unknown and could vary between individuals. Heritable editing could be harmful to individuals and future generations, and there could be negative societal consequences, such as the widening of health inequalities.

such as type 2 diabetes, coronary artery disease, schizophrenia, Alzheimer's disease and major depression (Fig. 1). It also predicts very large reductions in traits that predispose people to some diseases, such as high blood levels of low-density lipoprotein cholesterol or triglycerides.

But mathematical models are only as good as the assumptions they are based on, and this model depends on five key ones. First, the model assumes that genome-editing techniques will be able to modify DNA with perfect accuracy. Although current CRISPR-based therapeutics show great promise, total precision will require further advances.

Second, the success of the proposed approach relies on accurate identification of genetic variants that have a causal effect. Visscher *et al.* suggest that causal protective alleles could be systematically identified from genetic-association studies. However, these studies do not identify causal alleles, but only common genetic variants that are linked with the variants that cause the disease or trait. Mapping causal variants has been a slow process so far[9], and for many traits, even some of the most well-investigated ones, there is contradicting evidence about the causal genetic mechanism[10].

Third, Visscher *et al.* assume that the protective effects of different variants are independent and will add up. Human genetics research suggests that often, the effects of common risk variants can be summed at the population level[11], but there are many examples of dependence or interaction between variants. When two protective alleles affect the same biochemical pathway, introducing both is not expected to double the risk reduction. In the absence of data on people carrying several rare protective variants, additivity is not guaranteed.

Fourth, alleles that are protective in one environment today might not be protective in other environments, today or in the future. In fact, evidence is mounting that common risk variants have highly variable effects across environments and life circumstances[12]. And in the future, edited protective alleles will be unhelpful for conditions that have been eliminated from the population or have become easily treatable.

Finally, the model assumes that the degree of risk reduction would be the same across the relevant population, but it would inevitably vary. Some embryos might already be at low risk of disease because they are carrying target protective alleles. Others might be at low or high risk because of their burden of common variants.

Perhaps more important than questions of efficacy, heritable editing has serious safety risks that Visscher and colleagues downplay. They assume that risks from the editing process itself can be tolerated, mostly thanks to hoped-for future methodological improvements. However, safety is far from guaranteed[13], and risks to children must be taken especially seriously. Genomic interventions, particularly in the process of embryonic development, can result in unexpected outcomes. For example, early use of genetic testing of embryos to screen for chromosomal abnormalities before implantation inadvertently worsened IVF outcomes[14]. In embryo editing, the stakes are extremely high. Unlike somatic editing, any errors will affect every cell and organ in the future child, including during prenatal development.

> **"It is the responsibility of researchers, public-health professionals and policymakers to weigh the benefits against the risks."**

Even if editing itself is technically safe, heritable genome modification might result in unpredictable and undesirable long-term side effects. Harmful consequences could arise from edits to misidentified causal alleles. More generally, alleles that are protective for one condition can have 'pleiotropic' effects, meaning they can increase the risk of other conditions, including undesired traits or disorders[15,16]. Indeed, worsening of overall health has clearly been seen in livestock bred to have improved food-production traits[17]. Focusing on introducing rare alleles raises the concern that they might have been selected against throughout evolution[18] – in other words, they might be rare for a reason.

Visscher and colleagues do concede that the risks of pleiotropy could reduce 'fitness' (that is, the likelihood of survival and fertility) in future generations. However, they do not clearly describe the possible outcomes or adequately address the harms that could occur to real people.

Finally, there is the likelihood of unpredictable interactions arising from new combinations of variants that are not present in the existing population[16]. Thus, even if genome editing could be made technically foolproof, the authors' statistical models do not capture predictable but unknown harms that might still occur to specific individuals when permanent and heritable changes are introduced into the genome.

There are also ethical concerns over human germline editing. Heated arguments are ongoing around issues such as unnaturalness, stigmatization, discrimination, inequality, reproductive autonomy, reproductive norms and values, parent–child relationships, disability rights and religion[1]. Indeed, the widespread national bans of the technique are

probably driven more by these concerns than by worries about technical safety and efficacy. Visscher and colleagues discuss these ethical issues, but the debate is likely to continue.

Public-health interventions are often associated with risks but are nevertheless advocated. For example, many standard medical screening tests are recommended despite being known to harm some people through side effects or false positive results. It is the responsibility of researchers, public-health professionals and policymakers to weigh the benefits against the risks — particularly when the risks are high, as in the case of heritable editing. The authors calculate that this technology will be so low risk and so effective in every individual that deploying it on a large scale might be justified, even for individuals who start out at low absolute risk of disease. But both the assumptions of universally high effectiveness and of low risk are questionable.

The paper argues that it is useful to discuss the implications of heritable polygenic editing — both positive and negative — before such technology becomes practically possible. We do acknowledge the value of thought experiments. And we agree that introducing a handful of rare protective alleles is a more promising approach than the naive elimination of common risk-increasing alleles. The results of the model are provocative; heritable editing might well be worth exploring in non-human animal models, to test whether the underlying assumptions hold in real life. But given how far scientists are from understanding and mitigating the associated risks, we wonder whether describing its prospects so confidently is responsible.

The technology presented here requires major advances in genome-editing techniques, in identifying causal variants on a genome-wide scale and in mapping the full range of interactions between alleles and traits. These advances might not be achieved any time soon. Meanwhile, other technologies in reproductive genetics are already available or are around the corner, including embryo, fetus and newborn whole-genome sequencing. Each comes with profound clinical, ethical and societal questions. Upcoming population-scale genome-sequencing efforts raise further urgent questions of privacy, stigmatization and discrimination. Is it wise to distract stakeholders, including the public, with a technology that is still a long way off at best, and might never actually be safe?

Shai Carmi is in the Braun School of Public Health and Community Medicine, The Hebrew University of Jerusalem, Jerusalem 9112102, Israel. **Henry T. Greely** is in the Center for Law and Biosciences, Stanford Law School, Stanford, California 94305, USA. **Kevin J. Mitchell** is in the Smurfit Institute of Genetics, Trinity College Dublin, Dublin 2, Ireland.
e-mails: shai.carmi@huji.ac.il; hgreely@stanford.edu; kevin.mitchell@tcd.ie

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