How will we use gene editing to treat human disease?

No issue in biotechnology raises as many eyebrows as the prospect of GMPs—genetically modified people—even though the technology for effective and safe human germ line editing is not close yet. The capability is predicted to be still be a few years away but we are getting closer. Scientists in China in 2015 were the first to successfully edited a human embryo and in 2016 the first CRISPR clinical trial was approved in the country. With each time that someone hits a new milestone in genome editing, scientists, bioethicists, and people of all walks begin passionately discussing the pros and cons of designer babies.

It can be fun to contemplate the societal implications of enabling future parents to choose superficial traits of their offspring such as eye color, hair texture, stature, or skin pigmentation, but that's not the ultimate promise of gene editing on humans. Instead, it's the possibility of ending countless cases of human suffering. Let's explore some potential applications of human germ line editing that have more tangible therapeutic advantages that are likely to receive widespread support in our society.

Dominant genetic diseases

Huntington disease is a good example of what is called a dominant genetic condition. There also are certain familial forms of amyotrophic lateral sclerosis (ALS, Lou Gehrig disease) that are inherited with dominant genetics. Dominance means that just one abnormal gene copy, or *allele*, will cause a disease, even though the individual carries two alleles of every gene (one from mom and one from dad). Dominant conditions occur even when a person has a normal copy of the disease. On the other hand, recessive conditions require two abnormal alleles to produce disease, usually because lack of an enzyme due an abnormal allele is compensated by the normal allele.

This happens when the abnormal allele merely produces no enzyme, while amount of enzyme produced by the normal allele is adequate to the meet the cell's needs. But there's an abnormal gene for an enzyme in the membranes of the mitochondria—the power plants of the cell—that does worse than simply not make the enzyme. The enzyme is a powerful antioxidant called SOD1 (its gene is called *ALS1*) and molecules of the abnormal form clump together. It even causes normal versions of SOD1 to clump. This leads to ALS and since nerve cells are disrupted from the clumping, rather from a lack of functional SOD1 enzyme, it's inherited with dominant genetics.

With Huntington's disease, the reason for dominance is the presence of multiple copies of a genetic sequence within the abnormal allele, but in both Huntington's disease and ALS a couple desiring children might have a pretty good rationale to opt for germ line editing. The basic strategy is this: embryos would be produced through *in vitro* fertilization (IVF), using the woman's ova and the man's sperm, the same method used for couples that are infertile.

The Huntington disease gene could then be edited out of any embryo that is to be implanted in the mother. Although a fertilized ovum begins as one cell, it immediately splits into a two-cell entity called a blastomere and is a multi-cell structure called a blastocyst when it is optimal for implantation in the uterus after around day 5. In this very early period of development, not only are there many cells, but the cells

are changing and dividing rapidly, and gene editing technology would have to do its work (in this case replacing a Huntington gene) in the same way in every cell without disrupting the development process.

As noted earlier, the technology is not there yet, so we're imagining a time in the future, but a reasonable argument is that it will always be easier simply to screen embryos. If one or both parents have Huntington disease, but due to just one copy of the gene then they *could* produce normal embryos and those could be selected for implantation. The problem comes in, however, if at least one of parents is homozygous for a dominant disease, meaning that he or she has two copies of the abnormal gene. In this case, 100 percent of embryos made by IVF will have the Huntington gene. Embryo screening would thus not be helpful and the benefit-to-risk balance for the children might weigh in favor of germ line editing.

A game of probabilities

What about using embryo screening when a certain fraction of a couple's embryos should be normal, such as when neither parent has two abnormal copies of the gene for a dominant disease. If we consider one normal parent and another with Huntington disease due to one abnormal allele, theoretically 50 percent of the offspring should be normal; 25 percent of both parents had one abnormal gene. Why not just make a large batch of embryos and use the good ones.

The problem is that there are limits to how many embryos can be produced in each round of IVF. To produce multiple ova, a prospective mother already has to be stimulated with fertility drugs and health risks increase the more aggressive one makes the treatment. For various reasons, not all of the embryos are optimal for implantation, and of those that are implanted not all of them take.

Even if you could fertilize 10 embryos in one try, a couple could get really unlucky and have all of them with the Huntington gene, despite the probability being 50 percent, just as a coin toss could come out tails ten times in a row. In genetics, the Mendelian predictions are accurate only for really large litters. For a couple with a dominant disease, sure, they could do embryo screening and could come up with the few good candidates for implantation, and it could all work out. But the numbers game will not come out that way for everyone and the situation is similar when it comes to recessive diseases, since crossing two healthy carriers still leaves a 25 percent risk and the coin toss phenomenon holds sway.

For any of these situations, the prospect of germ line editing would beckon in an era that could be on the horizon when the technology is ready and safe. But this would also bring up the question of how can or should we go? Where should we draw the line between disease prevention and enhancements whose potential benefits may or may not outweigh any risk of ill-effects of the procedure, even if the risk is judged to be minimal.

Most of society is probably on the same page when it comes to enhancing human embryos to retain tails, grow a third eye, have wings, or anything else we might imagine. But what about making future generations more resistant to HIV or other viruses, or for that matter bacterial infections? Fewer people might oppose using germ line editing for that purpose compared with eliminating the much more certain fate connected with Huntington disease, and especially ALS. But a good number might also embrace the prospect.

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