**The moral argument for heritable genome editing requires an inappropriately deterministic view of genetics**

Gyngell and colleagues consider that the recent NCOB report does not go far enough: heritable genome editing (HGE) is not just justifiable in a few rare cases, instead there is a moral imperative to undertake it. We agree there is a moral argument for this, but in the real world it is mitigated by the fact that it is not usually possible to ensure a better life. We suggest that a moral imperative for HGE can currently only be concluded if one first buys into an overly deterministic view of a genome sequence and the role of variation within in it in the aetiology of disease: most diseases cannot simply be attributed to specific genetic variants that we could edit away. Multiple poorly understood genetic and environmental factors interact to influence the expression of diseases with a genetic component, even well understood ‘monogenic’ disorders. Population level genome analyses are now demonstrating that many genetic “mutations” are much less predictive than previously thought(1). Furthermore, HGE might introduce new risks just as it reduces old ones; or remove protections not yet clearly delineated.

**How can we know that edits would result in a ‘better’ life?**

In order to use HGE responsibly, we would need to be confident that it would improve the welfare of the resultant person. There are currently no examples where we know at a molecular level exactly what HGE will do, and can be completely confident there are no off-target or unintended effects. Genome editing technologies are often inefficient and sometimes imprecise(2, 3), and there is no ‘normal’ genome to aim for. The potential harms of HGE to future children are currently so unknown that it is far from clear that using HGE would enhance the welfare of the resulting child. For some ‘mendelian’ conditions the lifetime chance of manifesting the associated disease is lower than the chance of never doing so(4): HGE of such variants could not be classed as a moral imperative. In some families with, for example, a dominantly inherited cancer risk, people who test negative for the ‘disease-causing’ variant in their family may still experience the associated cancer and HGE might not confer the hoped-for immunity from disease. Multiple poorly understood factors influence how genetic conditions are expressed within families, and population studies indicate that the predictive value of many genetic “mutations” varies significantly depending on the context in which they were ascertained(1). Until we better understand what determines the penetrance of such genomic variants, HGE is premature.

**The value of ‘genetic relatedness’**

Gyngell *et al* accept that many people have a strong preference for genetically related offspring. But what does this mean? Approximately 99.9% of the genetic code is the same in everyone(5); the degree to which we share variation in the remaining 0.1% is therefore at stake. This consists of some four to five million variants per person; 100,000 of these will be rare(6) and so our knowledge of their clinical significance is usually limited, and is often purely hypothetical. Their impact will depend on their context within a genomic background, and the influence of environmental factors, some of which will be stochastic(7, 8). Attempting to predict the effect of each variant separately in a pointillist fashion oversimplifies this issue(9), and means that once we stray beyond considering HGE for well-understood, highly penetrant single gene disorders, we quickly cease to know what we might be doing. Furthermore, the more extensively we undertake HGE in a given embryo, the more we reduce the ‘genetic relatedness’ that forms a key part of the given rationale for this technology. Efforts to correct ‘normal’ properties (such as a 1 in 3 lifetime risk of developing cancer), or to influence complex traits like intelligence, will ultimately undermine the genetic relatedness that HGE is sold as preserving.

**Polygenic risk distracts from the case for HGE**

Polygenic risk is generated by a combination of variants scattered throughout the genome, most of which are not co-inherited. A child of a parent with a high polygenic risk of a particular condition will inherit only some of these and also inherit a complement of protective and susceptibility factors from their other parent, creating a completely new polygenic risk profile for that child. Most importantly, many variants used in gauging polygenic risk are *markers* of disease risk, rather than agents of pathogenesis themselves, presumably lying physically close to the ‘real’ contributors to disease. Applying HGE to these markers would be entirely futile as well as potentially harmful(10). Other variants are double-edged, for example, a variant in *HBB* might cause sickle cell trait whilst also conferring relative protection against malaria. Research to date has largely focussed on finding susceptibility factors for disease rather than protective factors, so many variants may have ‘positive’ effects on health of which we are unaware.

Gyngell and colleagues acknowledge that HGE for polygenic risk is ‘a long way away from being plausible’. We argue that presenting HGE as a potential mitigator for polygenic risk unduly distracts from the most compelling arguments for HGE, which relate to the very unusual situations where a parent would inevitably pass on a severe, fully penetrant disorder every time they had a genetically related child. However, we think that these situations are rarer than Gyngell *et al* suggest, and we are concerned that arguing a more widespread moral imperative for HGE might skew a public discourse- that already verges on inappropriate genetic determinism- in the wrong direction. We would like to encourage more debate about HGE in these extremely rare cases, without diluting the arguments by including HGE for polygenic, multifactorial or poorly penetrant conditions.

**Summary**

We agree that ready availability of technically perfect HGE might create responsibilities to use it in certain extremely unusual cases. We argue that polygenic risk is an inappropriate substrate to edit against, and that even for monogenic disorders, the relationship between the presence of a genomic variant and the expression of a disease is often more complex than the popular discourse around genomics might suggest. HGE may have an important role when considering the tiny number of people who do not have other routes to having genetically related children unaffected by severe, highly penetrant genetic conditions. Here, we need to look at the status we give to ‘genetic relatedness’, and the potential risk of off-target or unknown effects when using HGE that might undermine the aspiration to result in a ‘better’ life.

**References**

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