The genomic keys to sickle-cell therapy

Because it is caused by a single point genetic mutation, sickle-cell disease represents an ideal opportunity for gene and RNA therapy. Ambroise Wonkam lays out the promise and challenges ahead.

Although the first clinical case of sickle-cell disease was described 111 years ago, progress in drug development has been slow. Only two medications have been approved in the United States and Europe: hydroxyurea (HU) 20 years ago, and crizanlizumab more recently. Only HU is available in African countries. Limited clinical acceptance of the drugs provides further impetus for developing therapies.

Sickle-cell disease is the result of a single nucleotide substitution in the gene that codes for a protein involved in producing haemoglobin (Hb) — the protein that constitutes 70% of red blood cells and transports oxygen to all organs. In sickle-cell disease, the abnormal, sickled Hb (HbS) tends to polymerize in red blood cells. That process causes the cells to become deformed and to take on a sickle shape. Such cells are most often destroyed, leading to anaemia. In addition, sickled red blood cells tend to obstruct blood vessels, resulting in damage to multiple organs. In Africa, at least 50% of children with untreated sickle-cell disease die before the age of 5.

Because it is caused by a single point mutation, sickle-cell disease is an ideal target for gene therapy. There are two key ways to accelerate the development of curative therapies for the disease through genomics research. The first is to explore the missing heritability of fetal haemoglobin (HbF) in Africa: currently, 80% of gene variants accounting for heritability of HbF are still to be identified. In the womb, HbF is the dominant form of haemoglobin. After birth, the level of HbF decreases as adult haemoglobin A (HbA) replaces it.

The mechanism that controls the switch from HbF to HbA is dependent on specific variations in a few genes. Because the presence of HbF in red blood cells blocks HbS polymerization, interventions that allow individuals with the disease to continue to produce HbF can result in a longer life expectancy. The most common way to promote HbF production is to block proteins that inhibit HbF expression. One such option is inhibition of the gene that codes for the protein BCL11A, which modulates the switch from HbF to HbA at birth[1].

Variants already identified in HbF-modulating loci (for example, in BCL11A), however, explain no more than roughly 20% of HbF levels in African individuals with sickle-cell disease[2], compared with up to 50% of the variation in HbF in Europeans — possibly because other HbF-controlling loci or variations are yet to be discovered in Africans. The genome-wide association studies (GWAS) that discovered known modulators of HbF, such as BCL11A, were performed in populations of European ancestry[3]. These studies used GWAS arrays designed for that population and thus did not necessarily capture Africa's high genetic diversity.

Although people of African ancestry comprise only about 2.5% of GWAS participants globally, they account for nearly 8% of the trait and disease associations[4]. The high GWAS yields in the few studies that included Africans are due to the high genetic diversity in this group, the oldest of humanity's populations. With more than 300,000 years of human genomic evolutionary history in Africans, and only a small group of individuals having originally moved out of Africa (the ancestors of present-day Europeans and Asians), most of the human genome variations stayed behind. Consequently, millions of genetic variants, some of which are yet to be characterized, either occur more or less frequently in Africans or are specific to this population — which makes detailed identification of gene variants for disease or trait associations easier. Indeed, research to uncover the missing heritability of HbF-promoting loci in populations of African ancestry could provide druggable targets for effective promotion of HbF.

The second genetic approach to sickle-cell disease therapy involves RNA. Small non-coding RNAs called microRNAs (miRNAs) gum up the production of proteins by binding to the transcription machinery in a cell. They could be used to target the entire pathway of HbF production — particularly to suppress the expression of HbF-inhibitor proteins, such as BCL11A — which would have a much stronger effect than targeting a single gene. Research that identifies more candidate miRNAs that act on HbF production will provide an attractive route for future sickle-cell therapies that mimic HU-induced HbF production[5]. Mediation of HbA or HbF production through the injection of messenger RNA, a process used in COVID-19 vaccines, could provide another RNA-based technique for sickle-cell therapy.

Although the success and equitability of such genomic research is questionable, we can take encouragement from the faster-than-expected development of the COVID-19 vaccine. Such research should be accompanied by a mechanism, overseen by international agencies such as the World Health Organization, to ensure its benefits are equitably distributed, through the establishment of centres of excellence for sickle-cell disease care — particularly in Africa. Responsibility will also lie with funding bodies, such as the Cure Sickle Cell Disease Initiative of the US National Institutes of Health. Such work could serve as a model for developing therapies for other monogenic diseases. The time has come for an ambitious global genomic-research programme to uncover more genomic keys to sickle-cell disease therapy.

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"Sickle-cell disease is an ideal target for gene therapy."

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1. Esrick, E. B. *et al. N. Engl. J. Med.* **384**, 205–215 (2021).
2. Mtatiro, S. N. *et al. PLoS ONE* **9**, e111464 (2014).
3. Menzel, S. *et al. Nature Genet.* **39**, 1197–1199 (2007).
4. Gurdasani, D., Barroso, I., Zeggini, E. & Sandhu, M. S. *Nature Rev. Genet.* **20**, 520–535 (2019).
5. Walker, A. L. *et al. Blood* **118**, 5664–5670 (2011).