Finding the sweet spot for clinical genomics

A review of genome sequencing strategies reveals cost-effective approaches for diagnosing hereditary disorders

Clinicians now have the capacity to comb through entire genomes in search of mutations underlying hereditary disorders, but a narrower approach may be a more efficient diagnostic strategy, according to new research.

Some children exhibit complex combinations of birth defects and symptoms that are difficult to diagnose. Whole-genome sequencing (WGS) allows clinicians to home in on the causative mutations by scanning through the complete nucleotide sequences of genes and the regulatory sequences that control them. But this is relatively expensive, and a strategy known as whole-exome sequencing (WES) offers a simpler alternative.

In WES, only the sequences of protein-coding genes are analyzed. This cuts the cost of sequencing and analysis in half, making it a good first step. "Most hospitals in Saudi Arabia go with WES first, and if that proves negative, they proceed with WGS," explains KAIMRC's Majid Alfadhel, who led a team to investigate whether this is the best strategy, or if starting with the broader dragnet of WGS might offer a more cost-effective road to a diagnosis.

To address this, they reviewed four years of WES and WGS data from King Abdulaziz Medical City in Riyadh. This center has produced a plethora of genetic diagnostics data, and Alfadhel and colleagues have already published 17 studies based on these data in 2020. Some of these were from 'solo' patients who were sequenced individually, but in most cases the clinicians performed 'trio' sequencing, which includes the patient's parents to more easily distinguish between harmless and potentially harmful mutations. A subset of the cases were 'trio plus' analyses, which also includes siblings.

Modern DNA sequencing instruments can deliver comprehensive information about genetic mutations, but clinicians are still learning how to use this technology to make diagnoses in the most efficient manner.

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Though each additional family member adds cost and delay to the analysis, the extra data should increase the 'hit rate' for identifying disease-related mutations, particularly with WGS. "But surprisingly, there was no difference in the hit rate between WES and WGS-solo, WGS-trio, or WGS-trio plus," says Alfadhel. Indeed, every single hit found with WGS could also be detected in the WES data, suggesting that more thorough reanalysis might be better than additional sequencing.

This work indicates that broader genome coverage generally does not deliver extra clinical value—in fact, it yields numerous enigmatic mutations that are impossible to interpret with current genetics knowledge. As a consequence, Alfadhel says that Saudi Arabia's clinical genetics teams "will do more WES- or WGS-solo than trio or trio-plus to conserve the budgets of our hospitals."

Alfares, A., Alsubaie, L., Aloraini, T., Alaskar, A., Althagafi, A. *et al.* What is the right sequencing approach? Solo VS extended family analysis in consanguineous populations. *BMC Med. Genomics* **13**, 103 (2020).