NEWS

Embryo selection based on polygenic traits is still premature

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Ethical concerns around "designer babies" are heightened across the globe in the wake of infants apparently born with a CRISPR-edited genome. While less controversial, screening embryos based on polygenic traits prior to in vitro fertilization (IVF) is possible, thanks to single-cell genomics and progress in complex trait genetics. But the actual benefit expected from polygenic selection techniques has not been established. In a recent article in *Cell* (https://doi.org/10.1016/j.cell.2019.10.033) Karavani et al. use genetic modeling, simulations, and a unique nuclear family data set to show that embryos with the highest polygenic scores for height and IQ yield only minimal gains—just 2.5 cm or 2.5 IQ points with current IVF technology—and can easily be outweighed by environmental factors. Gain is defined as the difference between the value of the predicted trait for an embryo with the average polygenic score, compared with the highest-scoring embryo. The researchers first modeled the gain based on a normal distribution of polygenic scores and the variance, or predictive power, of a polygenic score. The team used their model to simulate polygenic scores and gain based on genotypic and phenotypic data from three cohort studies. Simulated embryos were based on 102 actual couples and 500 randomly matched couples. The quantitative model and the simulations based on real data yield nearly the same gain for both height and IQ. When variance of the polygenic score and number of embryos were varied in the model and simulations, neither significantly improved the predicted gain. An upper bound of 80% is expected for height variance, which increases the gain to 5.5 cm. For IQ, quadrupling the variance doubled the gain to 6 IQ points. When the number of embryos increased from 10 to 1000, gain increased by a factor of 1.7. Karavani and colleagues then compared the model for height with a data set of 28 nuclear families with an average of 10 children, showing that realized gain does not follow the quantitative model. In only seven of the families did the tallest offspring also have the highest polygenic score, whereas in five cases the embryo predicted to become the tallest actually resulted in below-average height. This is the first study in which the limitations of polygenic embryo selection have been empirically analyzed. Because targeted use of preimplantation genetic diagnosis is not currently regulated in the United States, the authors conclude that oversight over the use of such technologies may be needed.
—A. N. Grennell, News Editor

Inaccessible genetic variants unlocked with nanopore sequencing

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While short tandem repeats (STRs) usually occur in noncoding regions of the genome, expansions of STRs in coding sequences can lead to pathogenic genetic variants associated with many neuropsychiatric disorders. For example, expansion of a CGG motif in the *FMR1* gene leads to fragile X syndrome, one of the most commonly identified genetic causes of autism and cognitive disability. Recent evidence suggests that repeat variability and DNA methylation modulate the disease phenotype, but quantifying STRs with current methods is challenging. In a recent study in *Nature Biotechnology* (https://doi.org/10.1038/s41587-019-0293-x) Giesselmann et al. demonstrate a new technique for nanopore sequencing of STRs that accurately quantifies expansion length and identifies epigenetic markers simultaneously, and can be adapted to any other genomic region of interest. Nanopore sequencing directly senses megabase-long nucleotide sequences by threading fragmented DNA through nanopores in a silicon chip via electrophoresis while observing changes in electrical current across the nanopore. The researchers detected and analyzed STRs in the *FMR1* in stem cells derived from patient tissue as well as cells derived from patients with a $(G_4C_2)_n$-repeat in the *C9orf72* gene, which is the most common genetic cause of frontotemporal dementia and amyotrophic lateral sclerosis. To make nanopore sequencing suitable for reliable detection of STRs, Giesselmann and colleagues developed a hidden Markov model to accurately count numerous repeats in the raw nanopore signal, and then increased the signal from STR regions of interest by two orders of magnitude, relative to the rest of the genome, with CRISPR–Cas nuclease–based chemical tagging. The team named their new technique STRique (short tandem repeat identification, quantification, and evaluation). Initial proof-of-concept experiments successfully counted several different $(G_4C_2)_n$-repeat lengths produced synthetically on plasmids. When applied to *FMR1*, STRique found a wide distribution in the length of the STR region, from ~250 to more than 1000 repeat counts. Even different cells from the same patient showed variation in repeat counts. Nanopore sequencing is also sensitive for epigenetic markers, like CpG methylation states, which the team validated with positive and negative controls of two different STRs studied. Using STRique, the researchers found little methylation on *C9orf72* but all *FMR1* STRs were highly methylated, indicating the gene has been silenced. The authors conclude that with the inclusion of appropriate CRISPR–Cas enrichment, STRique can be adopted to any other region of interest on the entire genome, and can immediately integrate genetic and epigenetic signals associated with that region.
—A. N. Grennell, News Editor

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