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A novel embryo screening technique provides new insights into embryo biology and yields the first pregnancies following genome sequencing

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Study question

Can powerful next generation sequencing (NGS) techniques be adapted for the analysis of single cells, allowing unprecedented amounts of genetic information to be obtained from human embryos for diagnostic and research purposes?

Summary answer

A new NGS method was successfully developed, capable of simultaneously detecting monogenic disorders, diagnosing aneuploidy and quantifying mitochondrial DNA (mtDNA) mutations. The method was applied clinically, allowing identification and transfer of euploid embryos, resulting in healthy pregnancies. Additionally, a potentially important association between mtDNA content and blastocyst aneuploidy was discovered.

What is known already

Next generation sequencing, a class of methods involving the production of vast quantities of DNA sequence data, is revolutionizing genetic diagnostics. However, these techniques have not been applied to research involving human embryos, or to their clinical diagnosis, due to significant technical obstacles associated with analysis of single cells. Theoretically, NGS methods could allow simultaneous analysis of gene mutations and aneuploidy and could lead to reduced costs for patients requesting genetic diagnosis of their embryos.

Study design, size, duration

The NGS method was validated using single cells from cell-lines with known genetic defects (aneuploidies, cystic fibrosis mutations, or mitochondrial DNA defects) (n=30). Additionally, 45 embryos, previously shown to be abnormal using aCGH, were reanalysed in a blinded fashion. Subsequent clinical application involved testing of seven blastocysts from two patients.

Participants/materials, setting, methods

The method involved multiple displacement amplification followed by NGS using the Ion Torrent platform. Data was analysed with tools developed in our laboratory. The entire process could be completed within 16 hours, allowing fresh embryo transfer. The two patients were 35 and 39 years old, with a history of miscarriage.

Main results and the role of chance

The NGS technique was robust, with 82/82 samples yielding results. Aneuploidy diagnoses were concordant with those obtained using established cytogenetic techniques in all cases (100%). Detection of DNA sequence mutations was confirmed in 10/10 cells carrying a cystic fibrosis mutation. Application of NGS to cells with a heteroplasmic mtDNA mutation, succeeded in identifying the mutation and quantifying the proportion of affected mtDNA molecules. Clinical application of NGS revealed 3/5 euploid blastocysts from the first couple and 2/2 from the second. Single embryo transfers, based upon these results, led to healthy pregnancies in both cases. Simultaneous chromosome screening and mtDNA quantification, revealed an association between blastocyst aneuploidy and mtDNA content ($P<0.05$), an interesting biological finding with potential implications for the origin and fate of aneuploid cells.

Limitations, reason for caution

The NGS method developed provides an unprecedented insight into embryo genetics and has the potential to dramatically reduce the costs of preimplantation genetic diagnosis (PGD) and preimplantation genetic screening (PGS). However, before recommending widespread application, a randomized clinical trial, confirming efficacy, is advisable. Such a trial is now underway.

Wider implications of the findings

The NGS technique developed allows simultaneous testing for aneuploidy, gene mutations and mtDNA with exceptional accuracy. This strategy may revolutionize research and diagnosis in fields where the amount of tissue available is extremely limited (e.g. PGD). The cost of NGS was significantly lower than existing methods, suggesting that this approach may ultimately bring genetic analysis within the reach of a much larger number of patients. The feasibility of applying NGS in clinical cycles was confirmed.

Study funding/competing interest(s)

Institutional funding was used for this investigation . None of the authors have competing interests.

Trial registration number

Not applicable.