High-Fidelity Embryo Genome Sequencing: Concordance with Live Born Children

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PURPOSE & OBJECTIVES

Evaluate the concordance between whole genome sequencing (WGS) results from amplified trophectoderm biopsies used in preimplantation genetic testing and those from the resulting children.

MATERIAL & METHODS

Ten (10) embryo-child pairs (including 2 full siblings), were included in the study (Figure 1). Nine parental saliva samples (3 couple, 3 paternal only) were obtained. Live-born children were assayed using either cord blood (1) or buccal swab (9). DNA from trophectoderm biopsies underwent whole- genome amplification. All samples were sequenced to a minimum depth of 30x on either NovaSeq X or DNBSEQ-T7 machines, and variant calling was performed across the genome. Sample-pair kinships were calculated using the KING algorithm, and per-sample genetic risk scores were calculated for 12 chronic conditions. To refine analyses, a panel comprising over 1200 curated genes associated with severe monogenic diseases was used to filter for clinically relevant variants, and parental samples when available, were used to control for genotyping noise in the child samples.

Whole genome screening offers the detection of genetic variants beyond the scope of traditional embryo screening, including monogenic disease that may cause significant phenotypes.

RESULTS

Figure 1:
Study Flow

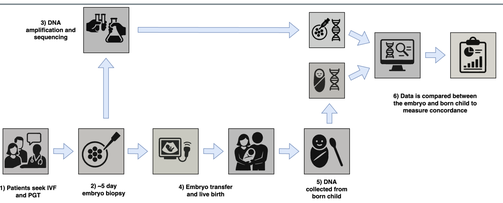

Table 1:

Sensitivity and Precision of PGT-WGS Variant Calls in Embryos Against WGS Variant Calls in Born Children.

Reportable Variants	Genome			Curated Panel		
Offspring	# Variant Calls in Born Child	Sensitivity	Precision	# Variant Calls in Born Child	Sensitivity	Precision
A-1	3900634	96.980%	97.880%	2562	98.730%	99.610%
A-2	3920906	97.510%	97.720%	2648	99.400%	99.400%
B-1	3833045	96.610%	97.550%	2682	98.490%	99.260%
C-1	3963448	96.090%	97.910%	2670	98.960%	99.180%
D-1	3840381	95.640%	98.040%	2610	98.860%	99.200%
E-1	3861296	96.150%	97.740%	2654	99.620%	99.210%
F-1	3859422	96.490%	98.410%	2655	99.400%	99.660%
G-1	3880927	97.970%	97.320%	2633	99.580%	99.320%
H-1	4024358	97.160%	97.740%	2763	99.390%	99.500%
I-1	3841963	97.350%	97.280%	2617	99.470%	99.430%
average	3892638	96.795%	97.759%	2649	99.190%	99.377%

Table 2:

PGT-WGS detection of de novo variants in embryos using in born child + parent trios

Pair	Candidate variants	Confirmed *de novo* variants	PGT-WGS Sensitivity
C-1	8	3 (SNP)	100% (3/3)
H-1	10	4 (SNP)	100% (4/4)
I-1	9	7 (2 Indel)	100% (7/7)
Total		SNP	**12/12 (100%)**
		Indel	**2/2 (100%)**

RESULTS

Kinship scores confirmed that 10/10 children matched the biopsies of embryos reported as transferred by the clinics. Genome-wide sensitivity was 96.80% (± 0.73) and precision 97.76% (± 0.33), against 3.89M (±0.06) monogenic variant calls in the child; restricting to the curated screening panel, sensitivity was 99.20% (± 0.40) and precision 99.38% (± 0.17) against 2.26K (± 0.4) child variant calls (Table 1). Genetic risk scores showed a correlation of 0.9997 between the sample pairs. Three children in which both parental samples were available was analyzed in concert with unimplanted sibling embryos to identify potential de-novo variants at sites with acceptable amplification performance. 14 de novo variants, confirmed by sanger sequencing to be present in the cord blood but absent in both parents, were also detected (100%) in the PGT-WGS data (Table 2a).

CONCLUSIONS

Whole genome sequencing of embryos shows high concordance compared to sequencing after birth. It reliably detects both inherited and likely de novo mutations and accurately predicts genetic risk scores. Sensitivity and precision were greater than 99% on genes associated with severe monogenic diseases. These results confirm that direct variant detection from amplified embryonic DNA is a reliable approach for embryo screening.

CONTACT INFORMATION

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