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Title:

Clinical Utility of Virtual Progeny Analytics in Assessing Reproductive Disease Risk

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Objective:
To establish the clinical utility of a novel, high resolution reproductive genetic disease risk analysis.

Design:
Egg donors and male recipients were recruited and consented to provide de-identified carrier screening reports, demographic information, and saliva for DNA processing. Donor-recipient pairings were assessed for recessive disease risk with three methods: 1) ancestry-based proxy screening 2) expanded carrier screening panels and 3) Virtual Progeny Analytics (VPA). VPA simulates natural reproduction by generating haploid DNA sequences (virtual gametes) that are combined pairwise to create novel offspring genomes referred to as virtual progeny (VP). Each VP is examined at each gene of interest to assess the combined effect of alleles on total gene functionality. Final VPA output calculates the risk of conceiving a child with recessive disease.

Materials and Methods:
Carrier screen results and VPA results were evaluated independently. The automated VPA process was completed on over 600 recessive disease genes using an Illumina next-generation sequencing platform. Statistical evaluation was performed with McNemar's test.

Results:
Data from 242 male-female pairings reveal that VPA detects significantly more disease risk as compared to carrier screening ($p<0.01$). As expected, fewer than 1% of pairings were identified as at risk based on combined carrier screen results. VPA technology more than quadrupled disease risk visibility. For example, DHCR7-related disease risk was observed with one well known pathogenic variant (c.964-1G>C) and a second previously uncharacterized variant (p.R362H). At-risk pairings for Niemann-Pick disease (SMPD1), Charcot-Marie-Tooth

neuropathy type 4F (PRX), and a second Smith-Lemli-Opitz syndrome (DHCR7) case were all uniquely identified through VPA with two previously uncharacterized variants.

Conclusions:

Donors and recipients carry a wide range of known and novel variants that cause a spectrum of damage to the underlying gene. VPA is an effective methodology for expanding visibility into recessive disease risk for recipients of donor gametes. We suggest that consideration be given to augmenting or replacing existing carrier screening methods with joint comprehensive analysis of both donor and recipient variants.

Support:

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References:

None.