Preconception genetic carrier screening in an Australian fertility clinic, the first 1000 patients

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Virtus Diagnostic Genetics provides preconception genetic carrier screening for patients using a NATA accredited Illumina Inherited Disease screening panel. This panel contains 552 genes for a total of 959 rare diseases. ACMG guidelines are utilised to interpret and report pathogenic/likely pathogenic variants. For this study, 1095 patients were screened/reported.

In the 1095 patients (table 1), 576 pathogenic/likely pathogenic variants in 232 genes were reported. 55% were female patients and 44% were male patients. 61% of all patients had at least one variant to report. 101 genes had a single variant reported. 419 patients including 73 donors had no variant.

These 1095 patients present a reasonable overview of the variants present within an Australian population. Interpreting and reporting any variant without a disease phenotype is a challenge.

The Australian population is a diverse genetic population and the majority of patients screened in this test had no significant phenotype, other than fertility issues. The screening was conducted on a private fee for service basis (figure 1), with continued growth and uptake of testing. Reports were returned to the requesting clinician. Table 2 presents the top 20 genes reported. Each gene in this table had a carrier rate of at least 1 in 100. CFTR was reported the most often, with 35 different variants reported and a carrier rate of 1 in 15. Both non-syndromic hearing loss (GJB2) and phenylketonuria (PAH) are also common with 1 in 19 and 1 in 100.

The table shows calculated carrier rates from within the 1095 patients compared to the estimated incidence (sources include ClinGen (GJB2) and phenylketonuria (PAH) are also common with 1 in 19 and 1 in 100.

Table 1: Total patients screened, reports with and without pathology. A local variant database is available using Golden VariomeQ and VSPipeline are compared. Alamut by VSDiagnostics is the only tool available that integrates both ACMG guidelines and ClinVar for homocystinuria. The insertion creates a splice acceptor site, creating a new start to the exon and removing the pathogenic variant in the functional transcript. In this scenario, even though the variant is detected by the software and is classified as pathogenic, each instance needs to be checked for the insertion 11bp downstream of the variant, and thus be correctly reported as a benign variant.

200 cross referenced couples (identified by the clinician before testing) were screened with no joint carrier risk i.e. no shared variants in the same gene. 180 donors were screened in total, with 73 being reported with no variants. Five patients, including 1 donor, had a total of 5 different variants reported (table 4).

Interpreting and reporting any variant without a disease phenotype is a challenge. All data is analysed and stored in Australia. A comparison using Illumina’s Nextera Flex2 Library preparation was presented at the recent ASDG meeting in Adelaide. MiSeq and Sentieon alignment/variant calling are likewise being compared. Euromarkers’ omomicsQ and omomicsV2 are used to monitor the quality of FASTQ, BAM and VCF data at any one time and over each time point. Illumina Variant Studio and Golden Helix VarSeq with it’s VSPipeline are compared. Alamut, gnomAD, ClinVar, HGMD Professional, Google Scholar, PubMed and other available resources are used to streamline the interpretative process. A local variant database is available using Golden Helix’s VSWarehouse. CVN evaluation using VSCNV and reporting directly to the local laboratory information system using VSRreport are expected to follow soon.

Table 2: The top 20 most reported genes in the 1095 patient reports. Female, male and number of different variants within each gene is shown. Calculated carrier rate from within the 1095 patients compared to the estimated incidence (sources include ClinGen (GJB2) and phenylketonuria (PAH) are also common with 1 in 19 and 1 in 100.

Table 3: Thirteen carrier couples (table 3) were identified utilising this screening panel, each partner with a variant in the same gene (CBS, CFTR, DHC7, ERCC6, GALT, GJB2, PAH and TREX1).

These carrier couples are at risk of having an affected child with the associated autosomal recessive disorder. Genetic counselling with pre-implantation genetic testing was available.

Table 4: Multiple variants reported in a cross section of patients

References:
3. Virtus Diagnostics Genetics, Level 1 Boundary Court, 5 Little Edward Street, Brisbane QLD 4000 Australia.
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5. Virtus Diagnostics Genetics, Level 1 Boundary Court, 5 Little Edward Street, Brisbane QLD 4000 Australia.
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