MCG Mainstreaming Cancer Genetics

Methodology for target selection for TruSight Cancer Panel

The TruSight Cancer Panel was designed to allow analysis of genes and genetic variants associated with predisposition to cancer. It targets germline variants detectable in lymphocyte DNA (rather than the somatic variants that are restricted to tumor tissue).

The panel focuses on genes for which there is already strong evidence of an association with cancer; it does not contain the many genes/variants for which a putative role in cancer has been proposed, but not proven.

The panel focuses on genes that predispose to malignant cancers, although many genes also predispose to non-malignant tumours. A minority of genes are associated predominantly/solely with non-malignant tumours.

We used the following methodology to select the Cancer Panel content:

1) Systematic, expert review of the scientific literature, to identify genes that predispose to cancer. One or more of the following were considered strong evidence of association of a gene with cancer :
   i) Linkage and positional cloning evidence demonstrating segregation of gene mutations in individuals with the cancer phenotype.
   ii) Statistically significant difference in the frequency of the relevant mutation class (e.g. protein truncating mutations or activating missense mutations) between individuals with the cancer phenotype and controls.
   iii) Evidence of *de novo* mutations in individuals with the cancer phenotype.

2) For certain cancer-associated conditions all causative genes were included on the panel, even if some have not been formally associated with cancer. This is because one often does gene testing before an individual has developed cancer, and it is therefore important to be able to analyse all genes associated with the condition.

3) Common variants, typically identified through genome-wide association studies were included if association at $P \leq 5 \times 10^{-8}$ was reported in the Catalog of Published Genome-Wide Association Studies on 06/08/2012 (Hindorff et al).

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We also included 24 polymorphic variants to facilitate sample identification as reported by Fisher et al, comprising 23 common SNPs and a Y-chromosome insertion-deletion (to inform on sample gender).

Our aim is for the panel to be fully comprehensive of all genes/genetic variants that predispose to cancer/cancer-associated conditions. This will require ongoing iteration. Content will be updated as new genes emerge and/or evaluation of existing genes allows their inclusion.

We welcome comments and suggestions about the content, which should be emailed to: mcg@icr.ac.uk

References

Fisher S et al. A scalable fully automated process for construction of sequence-ready human exome targeted capture libraries. *Genome Biol* 12(1), R1 (2011).PMID21205303

Hindorff LA, Junkins HA, Hall PN, Mehta JP and Manolio TA. A Catalog of Published Genome Wide Association Studies. www.genome.gov/gwastudies