CRUK Cambridge Centre MRes rotation project

Rotation Project Title	Combined effects of rare alleles in breast cancer susceptibility genes
Head of Laboratory (PI) Name	Douglas Easton
Second supervisor if applicable	
Programme	Breast/Gynae Quantitative
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Laboratory Location	Strangeways Research Laboratory

Project Outline	**Aims and objectives** Rare variants in ~10 genes are known to predispose to breast cancer. Little is known, however, about the combined effect of these variants on risk. The specific aim of this project is to evaluate the effect on risk of carrying variants in multiple predisposition genes, using data from a very large targeted sequencing project. A particular objective is to determine whether the combined effect of variants is consistent with simple genetic heterogeneity or whether there is evidence of non-additive interactions ("gene-gene interactions"). The results of these analyses could have implications both for genetic counselling and for understanding biological mechanisms.
Experimental plan	The project will be based on the analysis of targeted sequencing data of up to 35 genes on ~70,000 breast cancer cases and 50,000, generated as part of the Breast Cancer Association Consortium Bridges project. These data will be used to determine carriers of known or likely deleterious germline mutations in susceptibility genes. The case-control data will be used to fit different statistical models to estimate the risks associated with specific categories of variant, and specifically the risks associated with carriers of multiple mutations and the consistency of these risks with different models of interaction. These results will then be used to predict absolute risks associated with different variant combinations.
Main Techniques	The project will principally involve statistical analysis of case-control data, principally in R, combined with mutation classification algorithms. Therefore, prior familiarity with standard statistical methods and facilities with statistical analysis packages would be a strong advantage (but training in more advanced techniques will be provided). Depending on progress, the project may also involve some analysis of pedigree data.
Key References	Easton DF, Pharoah PDP, Antoniou AC et al. Gene-panel sequencing and the prediction of breast-cancer risk. NEJM 2015 Jun 4;372(23):2243-57 Turnbull C et al. Gene-gene interactions in breast cancer susceptibility. Hum Mol Genet 2012 Feb 15;21(4):958-62.