Copy number variants and their role in hereditary breast cancer and hereditary colorectal cancers

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Amy Louise Masson Date: 01/09/2015

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I dedicate this work to my daughter Ainslie Evelyn Masson
who reminds me every day what determination is.

List of publications included as part of this thesis

Published original research articles

Amy L. Masson, Bente A. Talseth-Palmer, Tiffany-Jane Evans, Desma M. Grice, Garry N. Hannan and Rodney J. Scott (2014) Expanding the genetic basis of copy number variation in familial breast cancer, *Hereditary Cancer in Clinical Practice*, 12:15.

Amy L. Masson, Bente A. Talseth-Palmer, Tiffany-Jane Evans, Desma M. Grice, Konsta Duesing, Garry N. Hannan and Rodney J. Scott (2013) Copy Number Variation in Hereditary Non-Polyposis Colorectal Cancer, *Genes*, *4*, 536-555.

Submitted manuscripts

Amy L. Masson, Bente A. Talseth-Palmer and Rodney J. Scott (2015) Interrogation of genes disrupted by copy number variants in familial breast cancer using a bioinformatics approach, *International Journal of Cancer Research and Diagnosis*.

Amy L. Masson, Bente A. Talseth-Palmer, Tiffany-Jane Evans, Patrick McElduff, Allan D. Spigelman, Garry N. Hannan and Rodney J. Scott (2015) Copy number variants associated with 18p11.32, *DCC* and the promoter 1B region of *APC* in familial adenomatous polyposis, *Gene*.

Amy L. Masson, Bente A. Talseth-Palmer, Tiffany-Jane Evans, Trish Collinson, Michelle Wong-Brown, Melissa A. Tooney, Garry N. Hannan and Rodney J. Scott (2015) Intronic variants resulting in aberrant mRNA species are rare in Hereditary Non-Polyposis Colorectal Cancer, *Hereditary Cancer in Clinical Practice.*

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List of additional material relevant to the thesis but not forming part of it

Publications

Bente A. Talseth-Palmer, Elizabeth G. Holliday, Tiffany-Jane Evans, Mark McEvoy, John Attia, Desma M. Grice, Amy L. Masson, Cliff Meldrum, Allan Spigelman and Rodney J. Scott (2013) Continuing difficulties in interpreting CNV data: lessons from a genome-wide CNV association study of Australian HNPCC/Lynch syndrome patients, *BMC Medical Genomics, 6*(*10*), 1-13.

Conference presentations

Amy L. Masson, Bente A. Talseth-Palmer, Tiffany-Jane Evans, Desma M. Grice, Konsta Duesing, Garry N. Hannan and Rodney J. Scott (2013) Expanding the genetic basis of hereditary non polyposis colorectal cancer. *InSight Meeting*, Cairns, Australia.

Amy L. Masson, Bente A. Talseth-Palmer, Desma M. Grice, Konsta Duesing, Garry N. Hannan and Rodney J. Scott (2012) A comprehensive catalogue of copy number variants in hereditary colorectal cancers. *Biomarker Discovery Conference*, Shoal Bay, Australia.**

Amy L. Masson, Bente A. Talseth-Palmer, Desma M. Grice, Garry N. Hannan and Rodney J. Scott (2012) Copy number variation in hereditary colorectal cancer. *American Society for Human Genetics*, San Francisco, United States of America.

Amy L. Masson, Bente A. Talseth-Palmer, Desma M. Grice, Garry N. Hannan and Rodney J. Scott (2012) Copy number variation and its role in hereditary non-polyposis colorectal cancer. *Australian Society for Medical Research NSW scientific meeting*, Sydney, Australia.

Amy L. Masson, Bente A. Talseth-Palmer, Desma M. Grice, Garry N. Hannan and Rodney J. Scott (2012) Elucidating the genetic predisposition to familial adenomatous polyposis. *Human Genome Meeting*, Sydney, Australia.

Amy L. Masson, Bente A. Talseth-Palmer, Desma M. Grice, Garry N. Hannan and Rodney J. Scott (2011) Elucidating the genetic predisposition to colorectal cancer. *Hunter Medical Research Institute Cancer Research Program Symposium*, Newcastle, Australia.*

Amy L. Masson, Bente A. Talseth-Palmer, Desma M. Grice, Garry N. Hannan and Rodney J. Scott (2011) Elucidating the genetic predisposition to colorectal cancer. *Australian Society for Medical Research NSW scientific meeting*, Sydney, Australia.

**invited presentation*

***oral presentation*

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ABSTRACT

Hereditary breast cancer and hereditary colorectal cancers are associated with an earlier age of diagnosis and a higher frequency of disease among family members. In recent decades cancer susceptibility genes have been associated with hereditary forms of breast cancer and colorectal cancers however these genes only account for a minority of families seeking diagnostic testing.

Genetic variation explains a significant proportion to susceptibility of disease. Copy number variants (CNVs) are a form of structural genetic variation yet to be fully explored for their contribution to hereditary breast cancer or hereditary colorectal cancers. CNV analysis can be used to identify new genes and loci which may be associated with disease risk.

The Affymetrix Cytogenetic Whole Genome 2.7M (Cyto2.7M) array was used to detect regions of genomic gain and loss in a cohort of 350 samples (encompassing 129 *BRCA1*/*BRCA2* mutation negative hereditary breast cancer patients, 56 Familial adenomatous polyposis (FAP) *APC* mutation negative and 125 Hereditary non-polyposis colorectal cancer (HNPCC) mismatch repair (MMR) mutation negative colorectal cancer patients and each were compared to 40 healthy control genomes).

CNV analysis revealed the presence of 614 genes unique to the combined patient cohort which represent candidates for involvement in hereditary breast cancer and hereditary colorectal cancers. Several CNVs were found that were associated with previously reported cancer susceptibility genes. These included CNVs associated with *APC*, *DCC*, *MLH1* and *CTNNB1* in four polyposis patients and *RPA3*, *NBN* (*NBS1*), *MRE11A* and *CYP19A1* in five breast cancer patients and suggests their role in disease development in the affected individuals. Of special interest was the identification of *WWOX* and *FHIT* rearrangements in three breast cancer patients, and a recurrent deletion that was observed on chromosome 18 at position 18p11.32 in 9% of the polyposis patients screened. These variants could further account for disease in the affected patients. Bioinformatic analysis of the uniquely identified gene sets provided further insight into the roles of these genes in disease.

This thesis provides evidence supporting the hypothesis that CNVs are likely contributors to disease development in a small but significant proportion of hereditary breast cancer and hereditary colorectal cancer patients.