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MMT – Multiple Primary Malignant Tumours

NIHR BioResource – Rare Diseases study project

Lead Investigator: Professor Eamonn Maher

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Summary

Multiple primary malignant tumours (MPMT) describes the occurrence of two or more histologically distinct malignancies in the same individual that are not due to metastasis, recurrence or local spread. Patients with multiple malignant tumours make up around 6% of registered cancer cases. Inherited genetic predisposition to cancer can be suspected in the presence of clinical factors such as positive family history, early age of diagnosis and multiple tumours. Patients with *de novo* germline mutations in an inherited cancer syndrome gene do not have a family history but typically will have an earlier age at diagnosis and propensity to multiple tumours.

The identification of an underlying predisposition to cancer in individuals with MPT is important for the management and surveillance of both the affected individual and their relatives. However, in the absence of a clear family history fitting a known familial cancer syndrome, genetic testing is often not performed because of failure to refer and/or uncertainty about which genes to test. In addition some individuals with isolated MPT harbour mutations that cannot be readily detected by the conventional Sanger sequencing techniques that are employed in most Regional genetics Laboratories (e.g. mosaicism).

Though individuals with MPTs are not rare, the large range of combinations of different primary tumours means that individual MPT phenotypes are rare. Hence even in large cohort studies of patients with a specific cancer the frequency of different MPT cases will be too small to generate data useful to guide clinical management. By concentrating on cases that do not fit known inherited cancer syndromes we will preferentially ascertain rare cases and expect to identify individuals with novel inherited cancer genes and individuals who have a novel phenotype for known inherited cancer genes.

Comprehensive genetic analysis using high throughput massively parallel sequencing techniques of a cohort based on a variety of MPT phenotypes (and in which known familial cancer syndromes have been excluded) will generate important data for improving the clinical management of such cases.

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Recruitment Criteria

Inclusion

- Patients with a histological diagnosis of multiple primary tumours (either at least two primary tumours at age <60 years or three primary tumours at age <70 years) and a clinical diagnosis of likely inherited cancer syndrome

Exclusion

- Patients with a *known* underlying genetic cause of multiple primary tumour (e.g. BRCA1 mutation)
- Patients with a clinical phenotype that fits a known inherited cancer syndrome will be excluded until they have tested negative for a mutation in the relevant inherited cancer gene(s)
- Patients with MPT considered to have tumours related to exposure to environmental carcinogen