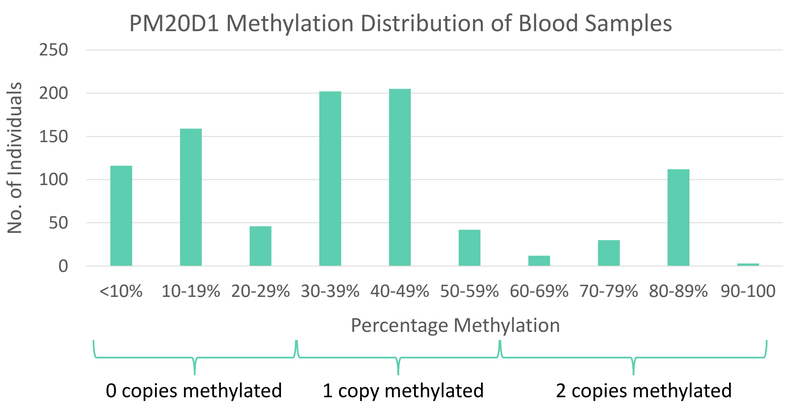
Potential Marker for Risk of Developing A Particular Cancer?

Investigation into the Effect of DNA Methylation of the PM20D1 Gene on Susceptibility to Solid Tumour Cancer

Introduction

- The purpose of this project was to assess the potential effect of DNA Methylation on the Peptidase M20 Domain containing 1 (*PM20D1*) gene in susceptibility to cancer
- DNA methylation is a change that occurs in DNA that can switch off genes
- PM20D1 is an unusual gene because it can be inherited in 2 forms: a common unmethylated form (gene switched on) and a rarer methylated form (gene switched off)
- As you inherit two copies of the gene (one from your father and one from your mother) a person can end up with 2 switched off versions of the gene, two switched on versions or one of each. This project is investigating whether inheriting two switched off copies of the PM20D1 gene makes you more likely to develop cancer



- Previous data (above) using blood samples taken from individuals from the general population showed 3 distinct groups of PM20D1 methylation which correspond to the inheritance pattern explained above
- When looking at solid tumours, the percentage of individuals with 2 methylated (i.e. switched off) versions of PM20D1 was higher than in the general population

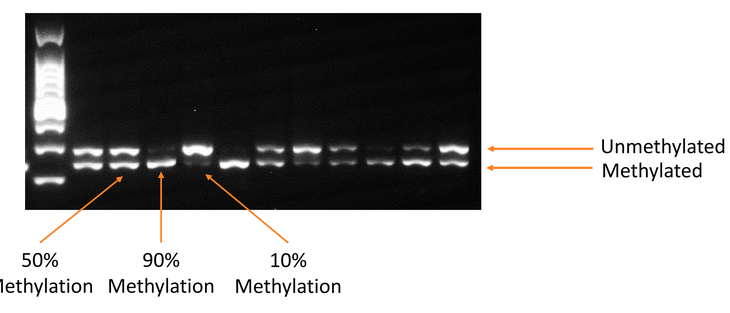
Category	0 Copies Methylated	1 Copy Methylated	2 Copies Methylated
General Population	298 (32%)	483 (52%)	146 (16%)
Solid Tumour	0	2 (29%)	5 (71%)

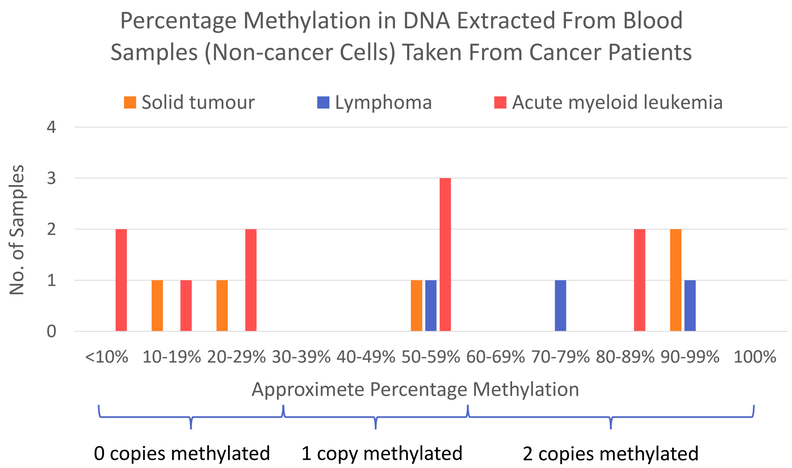
Project Aims

1. Analyse additional blood samples (non-cancer cells) from cancer patients to determine PM20D1 methylation
2. Assess whether DNA methylation switches off gene expression

Aim One Results

Method: Cobra Assay
What it does: separates methylated DNA from unmethylated DNA in order to estimate methylation percentage



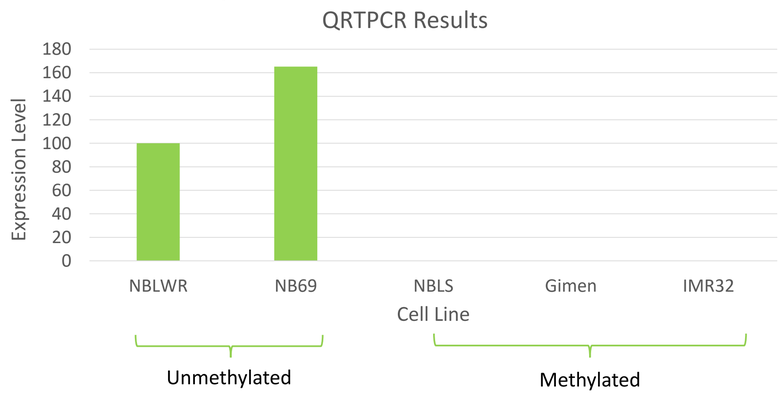


Type of Sample	0 Copies Methylated	1 Copy Methylated	2 Copies Methylated
Solid Tumour	2 (40%)	1 (20%)	2 (40%)
Lymphoma*	0	1 (33%)	2 (67%)
AML*	5 (50%)	3 (30%)	2 (20%)

*Remission blood samples, after treatment, were used so that the sample contained normal blood cells and not cancer cells

Aim Two Results

Method: Quantitative RTPCR in tumour cell lines
What it does: measures level of PM20D1 gene expression relative to methylation



Discussion & Conclusion

- PM20D1 has 3 distinct groups of low, intermediate and high methylation
- Methylation of PM20D1 switches off gene expression in cancer cell lines – confirming methylation of PM20D1 is associated with inactivation of the gene
- Blood samples from solid tumour and lymphoma patients' showed skewing towards higher methylation in comparison to the general population
- As the sample size was low these results need to be confirmed in a larger sample set

Future Work

- Increase the number of solid tumour and lymphoma samples to confirm link between high PM20D1 methylation and risk of cancer development
- Analyse the methylation distribution in blood samples from other cancers to assess the wider impact of PM20D1 methylation on cancer development
- Investigate whether switching off of PM20D1 directly causes cancer to develop

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