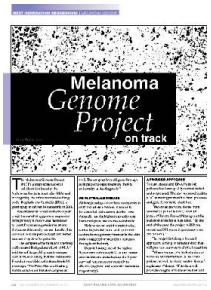

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Melanoma Genome Project on track

Susan Williamson

The Melanoma Genome Project (MGP), a large-scale national collaboration based at the Melanoma Institute Australia (MIA) and managed by the infrastructure-enabling body, Bioplatforms Australia (BPA), is gearing up to deliver its data early in 2014.

Researchers involved in the two-year project are analysing genome sequences from primary tumours and metastases to identify common genetic mutations that cause this deadly cancer. Ideally, this will lead to more personalised and better treatment options for patients.

"The samples come from an incredibly well-curated BioSpecimen Bank at MIA," said Anna Fitzgerald, project manager with BPA, explaining that the Melanoma Foundation established a tissue bank 14 years ago. "The Peter Mac and Ludwig Institutes have contributed samples as well. The samples have all gone through a single pathologist to ensure there is uniformity in the diagnosis."

AN AUSTRALIAN DISEASE

Although malignant melanoma represents only 15% of skin cancers, it accounts for almost all skin-cancer deaths – and Australia has the highest mortality rate from malignant melanoma worldwide.

Melanoma can rapidly metastasise, spreading via the blood and lymphatic system from a primary tumour in the skin to form aggressive secondary tumours throughout the body.

Despite having one of the highest 5-year survival rates (90%) of any cancer, once melanoma metastasises, the 5-year survival rate drops dramatically to 45–10% (regional and systemic metastasis, respectively).

A FOCUSED APPROACH

To date, tissue and DNA from 146 patients has been quality control tested and sequenced. The raw sequencing data of 87 somatic genomes has been processed and genetic variants identified.

"We are sequencing tissue from another 51 patients now," said Dr James Wilmott, Project Manager at the Melanoma Institute Australia. "By the end of the year the project will have sequenced 311 somatic genomes from 208 patients."

The project is taking a focused approach, aiming to generate data that will provide answers to clinical questions.

"Where we can, we look at primary tumours and metastases in the same patient, as well as blood control tissue," explained Wilmott. "This data will provide insights into the evolution and

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progression of melanoma. We are also looking at brain and bowel metastases, with the aim of identifying factors that favour metastases to these often deadly sites."

"The project has also prioritised a large cohort of tumours from patients with either primary or stage III metastatic melanoma with long and short survival times so we can compare their data."

TERABYTES TO ANALYSE

The researchers intend for data from the MGP to be made publically available, in the International Cancer Genome Consortium (ICGC) repository or equivalent database.

Whole genome sequencing (>60X coverage) and array comparative genomic hybridisation (aCGH) is being conducted at the Australian Genome Research Facilities (AGRF), the Ramaciotti Centre for Genomics at UNSW and John Curtin School of Medical Research at the Australian National University (ANU), while aCGH, whole genome (>40X coverage) and exome sequencing (75X coverage) is taking place at Axeq Technologies (Macrogen) in Korea.

This next generation sequencing of the genomes generates significant amounts of raw data, an estimated 400TB of data, the analysis of which Wilmott says is the most time consuming part of the work.

"We can sequence and generate the raw data pretty quickly," he said. "The time-consuming bit is taking these nucleotide sequences and comparing them to the normal genome, which can take weeks for one patient."

Fitzgerald and Wilmott admit it's too early to tell yet whether any patterns are emerging in the data. Although Wilmott said they are identifying the genetic mutations they expect to be seeing, it is too early to draw too many conclusions.

The aim is to finalise the data input by the end of this year and begin assessing patterns of activity and what the biology means at a meeting in early 2014.

"It is a large collaboration and analysing the data is an enormous task," Fitzgerald added. "It has been a massive education process and to date has cost about $5.5 million to sequence tissue and controls."

Developing a collaborative approach to support people in tackling these big problems is a key approach in BPA's work. The data generated is then made available to any number of researchers, which fosters national and international collaborations with the Australian researchers.

"When we select these projects, the money BPA invests goes directly into BPA's facilities, such as the AGRF, Ramaciotti Centre or ANU who generate the data," Fitzgerald explained. "It's not a grant, the grant is the data we generate that in turn enables collaborations between Australian researchers. And because we are doing this for a large pool of researchers it really is a true enabling resource." ALS