Identifying breast-to-brain metastasis-associated gene mutations by whole exome sequencing

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Background

Over recent years breast cancer survival rates have improved. However, even after many years of apparent disease-free health, cancer can recur. Many of these tumours occur specifically in the brain and metastatic brain tumours have very poor prognoses. Identifying genomic alterations that occur in breast primary tumours that eventually metastesise to the brain will provide new opportunities for treatment and prognosis.

Method

Whole-exome sequencing (WES) was carried out in 18 brain metastasis samples that originated from breast tumours. Each sample was sequenced to a depth >100X. Bioinformatic analysis was carried out to identify common recurrent mutations. We are in the process of validating the candidate mutations by Sanger sequencing and screening a larger cohort of Breast to Brain Metastasis (BBMs) and non-metastatic primary breast tumours to confirm metastasis-associated alterations.

Results

Each of the 18 BBMs analysed by WES contain >7000 non-synonymous variants. All variants were screened for their consequence on the protein product (via Polyphen and the Exome Aggregation Consortium (ExAc)). Those variants with high scores relating to pathogenicity were retained. Following this filtering, potential germline polymorphisms were excluded by removing those variants with a minor allele frequency (MAF) of >0.1%. This screening has generated a long list of 300 variants found across all 18 tumours analysed. A final screen identified genes that contained pathogenic variant in more than 2/18 tumours and had been described in any other cancer type (via the catalogue of somatic mutations (COSMIC)).

Via this stringent screen, we have identified 22 candidate metastasis-associated genes. we are currently screening non-metastatic primary breast tumours and BBM tumours to determine how frequently these occur. The genes identified have varied cellular roles, including cell surface proteins, migration and gene regulation.

Conclusion

We expect that this analysis will identify genes that are frequently mutated in BBMs, but infrequently in non-metastatic breast tumours.