PAX3/FOXO1 fusion gene status reveals rhabdomyosarcoma risk stratification

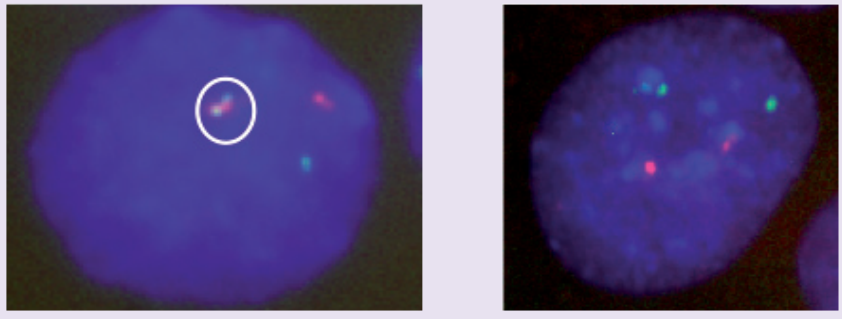
A simple genetic test for PAX3/FOXO1 *fusion gene status shows promise for improving risk stratification in childhood rhabdomyosarcoma.*

A recent study led by the Institute of Cancer Research (ICR; London, UK) has revealed that testing for *PAX3/FOXO1* fusion gene status as part of a combined clinical and molecular risk-stratification scheme could significantly improve prediction of patient prognosis and tumor aggressiveness in pediatric rhabdomyosarcoma (RMS) patients. The authors propose that clinical implementation of the simple genetic test for the abnormality has great potential for improving personalization of treatment regimens.

RMS, a relatively rare cancer that is more common in children, requires treatment with a combination of chemotherapy and surgery, and sometimes radiotherapy. Whilst such regimens have improved survival, patients often experience debilitating and long-term side effects, including an increased risk of cancer in later life.

The recent findings, published online in the *Journal of Clinical Oncology*, demonstrate that testing for *PAX3/FOXO1* in the clinic using a simple genetic test could significantly improve prediction of tumor aggressiveness, allowing therapy to be tailored more closely to the patient's risk. This would ensure that intense treatment is only given to those patients with the most aggressive disease, while those with milder forms could be spared some of the side effects. At present, the *PAX3/FOXO1* fusion gene is only used as a classification marker in tumor histology, which is used in the current means of determining patient risk in RMS.

To investigate the potential of gene expression patterns to improve patient risk



Treatment for children with tumors called rhabdomyosarcomas depends on whether they have an alveolar or embryonal histological appearance down the microscope. Just over half of alveolar rhabdomyosarcomas have a genetic rearrangement which fuses the *PAX3* gene (red) to the *FOXO1* gene (green), seen as red and green signals together (circled) in the nucleus (blue) of tumor cells in contrast to cells without this rearrangement where they are separate. The results of the study suggest that results of this genetic test could be used to improve risk management of patients with rhabdomyosarcoma.
Image courtesy of Janet Shipley.

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stratification, the ICR-led researchers first utilized two independent datasets of gene-expression profiling from 225 patients with RMS. However, obtaining sufficient samples for analysis was not without its challenges, as Dr Janet Shipley, leader of the Sarcoma Molecular Pathology Team at the ICR, explained to *Personalized Medicine*: "Generally, small biopsy samples are taken from children for diagnosis before treatment and only suitable material in excess of that required for diagnosis, and which has appropriate approval, can be used in our research. Having enough material that was of high quality for profiling thousands of genes from a large number of patients was a challenge that led us to the successful collaborative effort." The study also involved several institutions from throughout the UK, Switzerland and France.

Thousands of genes from a total of 225 RMS biopsy samples were analyzed and investigators discovered that altered activity levels of 15 genes could be predictors of therapy response in RMS. The majority of these changes were related to the *PAX3/FOXO1* fusion gene.

> "This would ensure that intense treatment is only given to those patients with the most aggressive disease..."

A novel clinicomolecular risk score, which considers fusion gene status (*PAX3/FOXO1* postive or *PAX3/FOXO1* negative), stage of tumor development and age at diagnosis, was then developed and found to be a highly effective prognostic test, which the study authors recommend incorporating into routine clinical practice: "The test for the fusion gene in samples is quite straightforward and already done in some centers," explained Shipley. "The next step is to introduce the risk-classification scheme that includes the fusion gene into clinical trials so that patients may benefit. We are talking to clinical colleagues in the UK and Europe about this." In addition, validation studies are proposed using a larger European and independent dataset.

– Written by Sarah Miller

Sources: Missiaglia E, Williamson D, Chisholm J et al. PAX3/FOXO1 *fusion gene status is the key prognostic molecular marker in rhabdomyosarcoma and significantly improves current risk stratification.* J. Clin. Oncol. *doi:10.1200/JCO.2011.38.5591 (2012) (Epub ahead of print); ICR News Release: www.icr.ac.uk/press/press_archive/press_releases_2012/22641.shtml*

Using genomic insights to guide adjuvant chemotherapy decisions may be feasible in the clinic

A recent first of its kind study suggests that evaluation of breast tumor genetic signatures could be a valuable and feasible clinical tool for deciding whether a patient should receive systemic adjuvant chemotherapy following surgery. The encouraging results were presented at the recent 8th European Breast Cancer Conference (EBCC-8): "Based on our data, the use of the genomic test could lead to a reduction of nearly 30% in the use of adjuvant chemotherapy without compromising patient outcomes," reported Dr Sabine Linn, Professor of Medical Oncology at The Netherlands Cancer Institute (Amsterdam, The Netherlands), where the study was performed. "These findings are important both for quality of life and for cutting down unnecessary healthcare costs," she continued.

Although effective, adjuvant chemotherapy can often cause distressing side effects and so targeting the treatment to patients most at risk of metastasis is a priority. "Many patients dread the idea of chemotherapy," explained Dr Linn, "and by avoiding it they can substantially reduce the stress involved in having cancer, as well as improve their overall quality of life."

This recent study aimed to evaluate the feasibility of incorporating genomic signatures into clinical decision-making regarding use of adjuvant chemotherapy in breast cancer patients, in addition to the impact of genetic insights into such decisions.

> "...the use of the genomic test could lead to a reduction of nearly 30% in the use of adjuvant chemotherapy..."

Follow-up data from 427 patients with node-negative early-stage breast cancer were analyzed and MammaPrint® – which is the only US FDA-cleared diagnostic tool currently available for predicting recurrence risk in early-stage breast cancer – was used to reveal the gene-expression signature of tumor samples by screening for a panel of 70 genes. Patients were stratified into low- (219 patients) and high-risk (208 patients) groups, and decisions regarding adjuvant chemotherapy use were based on the genomic signature, Dutch national guidelines and patient and clinician preferences.

Only 15% of patients identified as being at low risk of metastasis underwent adjuvant chemotherapy, compared with 81% of high-risk patients, demonstrating how many patients could be spared adjuvant therapy. Incorporation of the MammaPrint information into clinical decision-making did not compromise the 5-year distant disease-free survival rate.

Recent technical advances allow the use of standard formalin-fixed, paraffin-embedded tumor tissue as opposed to fresh-frozen samples, which should greatly improve the availability of the test and its associated advantages. "We will also assess further the cost–effectiveness of the 70-gene signature in comparison with the standard guidelines used to decide whether or not to give adjuvant chemotherapy," concluded Dr Linn. "We believe that our results already show that the use of genomic tests is feasible and effective in clinical practice, and can help in decision-making."

– Written by Sarah Miller

Source: EBCC-8 News Release: www.ecco-org.eu/Global/News/EBCC8-PR/2012/03/22_03-New-genomic-test-spares-patients-chemotherapy-with-no-adverse-effect-on-survival.aspx

UK-based competition to fund development of novel diagnostic tests

In a drive to spark the uptake of stratified medicine in the UK healthcare system, a recently launched competition will award development contracts for novel diagnostic tests that can predict treatment response. UK-based companies are invited to apply for funding to develop innovative diagnostic tests or assessments for use in the UK clinical care pathway. The competition, held by the Technology Strategy Board (Swindon, UK) in collaboration with the Department of Health (London, UK), hopes to allow the UK healthcare system to begin reaping the rewards of stratified approaches.

Identifying patients at risk of an adverse reaction or a lack of response to a therapeutic intervention has the potential to improve patient health and make savings in the healthcare budget. The upcoming contest will assess the potential value of stratified approaches in the UK health system, identifying the optimum ways for developing, commercializing and implementing such procedures in UK healthcare.

> "The organizers intend to invest a total of GB£7.5 million in development contracts."

The competition is exclusively open to UK-based companies, organizations and charities, from the public, private or third-party sectors. The organizers intend to invest a total of GB£7.5 million in development contracts. Budding developers must present industrially focused and business-driven proposals that promise clear economic benefits for the UK health service. Projects could involve diagnostic tests or analytical algorithms, which can predict whether a patient is at risk from an adverse reaction or no response, or to identify at an early stage if an individual is deriving no benefit from a treatment currently licensed for use in the UK.

Phase 1 of the competition opened on 26 March 2012. Successful applicants will receive funding to produce a full development plan, with the most beneficial and feasible entries going forward into phase 2; the fully funded development stage.

– Written by Sarah Miller

Technology Strategy Board News Release: www.innovateuk.org/content/news/stratified-medicine-diagnostics-for-adverse-or-non.ashx

Researchers may have found a new way to individualize pain therapy

Chronic pain is a major challenge to treat as understanding pain is very important in the development of new therapies. There is variability in the development of chronic pain between people with the same disorder, which raises the need for individualized treatments that can treat specific patient groups.

Research by Jeffrey Mogill (McGill University, Montreal, Canada) and colleagues published recently in *Nature* used genome-wide linkage analysis to identify a major gene that plays a part in pain sensitivity. They identified the *P2X7* gene, which affects chronic pain via both inflammation and nerve damage. They found an association between nerve injury-induced pain behavior and P451L mutation of the *P2X7* receptor. This mutation caused impaired pore formation of the receptor, the single amino acid change affected the formation of the pore, which allows large molecules to pass through.

The investigators found that administration of the peptide that affects the *P2X7* receptor C terminal domain by blocking the pore formation only and not any other function of the gene for example, cation channel activity, caused the reduction of pain-related behaviors.

The genetic differences between two independent human cohorts, one with chronic post mastectomy pain and the other with osteoarthritis, were assessed and it was found that the people with a genetic susceptibility to low pore formation in *P2X7* experience lower levels of pain.

These findings suggest that drugs could be developed that block pores at this crucial receptor leaving others intact to kill pain with a lower side effect profile as only one function of the gene will be impaired. This research could lead to a new strategy of individualizing the treatment of chronic pain.

– Written by Claire Attwood

Source: Sorge RE, Tang T, Dorfman R et al. *Genetically determined* P2X7 *receptor pore formation regulates variability in chronic pain sensitivity.* Nature *18(4), 595–599 (2012).*

About the News and Views

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