How Genomic Medicine helps in Proactive Detection and Treatment

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ABSTRACT

Great advances have been made in understanding the genetic profile of human beings. Such genetic information is opening up new and exciting branch of genetic medicine. This has great promise in predictive healthcare, pre-emptive treatment, effective and precision treatment for existing illnesses and more importantly for highly personalised healthcare.

This article explains the potential with a case study.

Introduction

Genomic medicine is an emerging medical discipline that involves the decoding and use of genetic information from an individual that will be an indication of his/her health and any prevailing medical condition. A decade ago it was a billion dollar project to sequence a human genome. However, in the last 5 years, with the advances in sequencing technologies, the sequencing costs have drastically reduced to $1000, thus facilitating its use in routine clinical practice. The USFDA had cleared the first next generation sequencing (NGS) platform in November 2013 for clinical laboratories. Ever since, genetic information is being extensively used to address diverse clinical questions, that include arriving at a more accurate diagnosis, developing effective and targeted treatment strategies, predisposition to any disease conditions, focused clinical evaluation and life style changes to address metabolic disorders, and assessment of drug sensitivity.

Genomics has had its greatest impact in being able to refine the diagnosis of cancer, and guiding therapeutic approaches to individuals based on their tumor genetic profile. Genome sequencing of circulating tumor DNA from patient's plasma is an emerging tool to monitor response to treatment, prediction of early relapse,thus, helping in clinical decision making and guide changes in treatment protocols. In addition to this, several clinical trials have been initiated based on genomics, wherein patients are stratified based on their tumor and normal genetic profile that could give a clear demarcation of responders versus non-responders. Beyond oncology, genomics based clinical decision making has been well established, in prenatal screening using non-invasive procedures (NIPS) and understanding of several other familial genetic disorders.

Case Study: Genomics and PeutzJeghers Syndrome

Background

Peutz-Jeghers Syndrome (PJS) is a rare inherited autosomal dominant disease in which polyps form in the intestines (gastrointestinal polyps), accompanied by pigmentation that affects skin and mucous membranes.[1] PJS has an incidence of 1 in 12-30,000 live births globally.[2]

Clinical features of PJS can be divided into two types, cutaneous and gastrointestinal –The most noticeable cutaneous feature of PJS is the appearance of pigmented spots, also known as melanocytic macules, in 95% of patients. These spots can appear near the mouth, lips, gums, inner lining of the mouth, eyes, hands and feet, fingers and toes, rectal and genital areas. Pigmentation usually appears before 5 years of age and may fade after puberty. Gastrointestinal polyps rarely occur in the early years of growth and are more common later in life. The polyps may cause bleeding and abdominal pain. They run the risk of turning malignant. Small intestine intussusception and intestinal obstruction are also fairly common complications of Peutz-Jeghers syndrome.[3,5]

PJS polyps are hamartomas i.e. benign tumours made up of a mixture of mature cells normally found in that tissue. They can turn either benign (non-cancerous) or ma-

Sl No.	Gene	CDS variant#	Amino acid variant	Impact on protein function	Function of the gene in cancer	Pathway in which the gene functions
2	*STK11*	c.836_837insC (ENST00000326873	p.Leu282Alafs Ter3	Yes	Tumor supressor	Adipocytokine signaling pathway/ mTOR signaling pathway

Alignment is performed against theGRCh37/hg 19 human genome assembly and annotation is done against the Ensembl release 75 gene model.
cDNA base is reverse compliment of genomic base in case on negative strand.

lignant (cancerous).[3]

Patients suffering from PJS run a risk of developing cancer that is 15 times greater than that of people who don't suffer from this. Approximately 50% of patients with PJS develop and die from cancer by 57 years of age. The overall risk of Peutz-Jeghers syndrome patients developing a cancer over adult life is 93%. Cancers are not only located on the gastrointestinal tract but can occur on many other sites including the breast, ovary, testicle, pancreas, uterus, oesophagus and lung. There is no specific treatment for PJS but the main goal is to manage and prevent associated problems of intestinal obstruction and intussusception, and cancer development.[3]

Role of STK11 in PJS

Peutz-Jeghers syndrome is found to be caused by germ line mutations in the Serine Threonine Kinase tumor-suppressor gene found on chromosome 19p13.3 (also called STK11/LKB1). These genetic mutations result in an altering of the structure or function of the STK11 protein, thereby disrupting its ability to restrain cell division. The resulting uncontrolled cell growth leads to the formation of noncancerous polyps and cancerous tumors in people with PJS.[6]

This gene abnormality may be inherited or arise sporadically – familial PJS may be due to autosomal dominant inheritance of the STK11 mutation, while sporadic PJS is not passed down through families and appears unrelated to an STK11 mutation. The key factor may be reduced apoptosis, or programmed cell death, in the affected cells.[4,5]

Experience in screening for tumor somatic mutations

We received a tumor biopsy for mutation analysis from a patient diagnosed with ovarian cancer. The goal of the assay was to screen for actionable driver mutations which could help in tailoring targeted therapy for this patient. In this regard, we had used an in-house developed tumor somatic mutation "HOTSPOT"screening panel that screens for mutations in more than 50 cancer related genes involved in cell signaling, tumor suppressors, serine threonine kinases and tyrosine kinases, epigenetic regulation.

Methods

The tumor DNA was isolated and NGS libraries were prepared and sequenced on HiSeq 2500 NGS platform (Illumina Inc.). The raw data was filtered with various QC parameters and the mutations were identified and annotated with in-house bioinformatics tools.

Results

We identified a deleterious mutation in Serine Threonine Kinase 11, which is known to be an inactivating mutation with regard to the function of this gene.

Discussion

Importance of the mutation identified in STK11: p.Leu282Alafs-Ter3 a protein truncating mutation

A single nucleotide insertion (chr19:1221313G>GC; c.836_837insC) that results in a frameshift and subsequent termination of the protein, 3 amino acids downstream to codon 282 (p.Leu282AlafsTer3) was detected in the STK11 gene of this subject. Codon 279-281 of STK11 is considered a mutational hotspot. This deletion results in the production of a truncated, functionally deficient protein. Homozygous deletions or somatic sequence mutations coupled with loss of heterozygosity in the STK11 gene, have been identified in sporadic pancreatic and biliary adenocarcinomas[7] and in ovarian carcinomas.[13] STK11 acts as a tumor suppressor bynegatively regulating the mTOR pathway. Hence, STK11 loss of function results in increased mTOR signalingsuggesting that therapies targeting mTOR (eg. mTOR inhibitors like FDA approved Everolimus and Temsirolimus) may be relevant for STK11 deficient tumors.[8,9,10] A patient with pancreatic cancer and an STK11 mutation experienced a partial response to the mTOR inhibitor Everolimus.[11] Loss of STK11 also leads to activation of the downstream kinase Src, suggesting that inhibitors such as Dasatinib or Bosutinib maybe relevant for the treatment of STK11-deficient tumors.[12]

In the above mentioned case study, somatic mutation analysis of tumor biopsy has helped in identifying other possible options of targeted therapy for this patient. Nevertheless, based on the guidelines of treatment, incorporating the mutation data, the treating physician can decide the optimal treatment plan.

Summary

The future of genomic medicine in clinical practice is moving towards cataloguing of individuals based on their genetic profiles and assessment of their health and wellness at the time of birth. This enables documentation of their sensitivity to drugs based on their genetic information and any predisposing medical illness.Genomics possesses the potential to change healthcare from retrospective, interventional care to prospective, preventative care that is highly personalized and pre-emptive.

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