Uncovering the role of **genes in disease**

Professor Fahd Al-Mulla

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Professor Fahd Al-Mulla divides his time between his leading genomics research unit at Kuwait University and his private genomic medicine centre Genatak. Here, he discusses how gene sequencing technology improves patient outcomes.

To start with, could you please tell us what inspired you to get into genomic research?

Two events shaped my life and career direction. First, I suffered from poliomyelitis at seven-months-old, only to learn later in life that it was simply because of medical negligence.

The second event happened after gaining my medical degree from Glasgow University in 1993 and during my residency in Ayr Hospital in Scotland. I clearly remember attending to this nice middle-aged lady in her hospital bed. She told us about how she had repeatedly informed her general practitioner that many of her family members died of breast cancer.

Now, after many years, we have come to know that the family was a carrier of a genetic defect in the BRCA2 gene, which leads to hereditary breast, ovarian or other cancers. These events made me realise that many diseases are preventable, just by knowing the genetic code. In fact, this knowledge may be the key to changing one's future.

How did you come to start a private genomic medicine clinic and how do you balance your research and business responsibilities?

In late 2013, I approached Dr. Jamal Al Ghanim, an eminent entrepreneur in the medical field. He listened to my introduction about genomic medicine, and 10 minutes into the conversation, he immediately invited me into a joint venture with him.

As a visionary, he realised the potential of my proposal primarily in improving the health and wellness of our people. We have now performed thousands of genetic tests and have gained the trust of almost all the physicians and patients who have used our services.

There is no doubt that research is the engine that drives entrepreneurship. During the last 10 years, I have received more than $3 million in funding to perform research on identifying diagnostic and prognostic factors in cancer. Research has always been the backbone of my strength.

Is personalised medicine beginning to live up to its hype and offer practical benefits to patients?

The premise of personalised medicine is to tailor treatment to overcome abnormally activated or inhibited pathways specific to a patient due to their private genetic mutations or epigenetic events. This knowledge benefits even cancer treatments, as it contributes to extending the disease-free survival rate of patients tremendously.

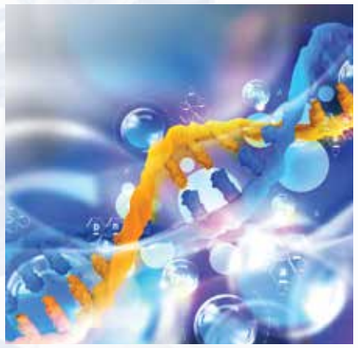
Today, we are sequencing whole genomes from cancers and informing clinicians of the disrupted pathways found in their patients. This would then allow them to tailor therapies accordingly. We have a long way to go in understanding many of the genetic changes in a particular cancer, but this is a good start.

You provide both exome and full-genome sequencing. Why is it important to have both approaches?

Exome sequencing looks at the tip of the iceberg—the 1% of variations in the genome that occur in exons or areas of the genome that are translated to mRNA and protein. The whole genome examines all three billion bases that constitute the human genome and thus represents a window through which you see almost the whole iceberg.

Exome sequencing is less expensive and may be useful in cases where you have a good idea of what is going on with the patient. Whole genome sequencing is perhaps the most effective technology we have in personalised therapy and prevention. We no longer have to rely on traditional techniques where we're guessing what could be wrong.

The lack of a well-documented Arab genome means you sometimes get variants of unknown significance. How do you explain these to patients?



The model we currently follow at Genatak is to report pathogenic or actionable mutations. Of course, our knowledge of pathogenicity varies perhaps daily, where new research changes a variant of unknown significance to pathogenic and *vice versa*.

Therefore, Genatak adopted a dynamic reporting mechanism, which is introduced into the clients' counselling process so they understand this complexity. The client is invited back every six months after their genome has been reanalysed with the updated information.

You established the office for Technology Transfer and Patenting at Kuwait University. How important do you think it is for researchers to develop their commercial skills?

Kuwait and the Gulf states generally rely heavily on oil as the sole source of income. Moreover, Kuwait dedicates only 0.1% of its GDP to research and development.

The ability to commercialise research is vital to any economy. Our attempt was intended to highlight the capability of local researchers to commercialise their research. The office managed to patent at least 42 inventions in record time and at least two of them address diabetic wound healing, an industry worth $2 billion dollars annually.

Tailoring medicine for the Arab world

Societal pressures have resulted in a unique public health landscape in the Middle East, which holds both opportunities and obstacles for personalised medicine. Professor Fahd Al-Mulla is working to overcome its hurdles while championing the benefits.

INDIVIDUALISING INTERVENTIONS

The last great revolution in healthcare came at the end of the previous century when the adoption of evidence-based medicine became widespread. Using knowledge gained from well-conducted, large-scale clinical trials to inform public health policy has helped to optimise patient outcomes and promote consistency of treatment.

Despite the success of the approach, however, the broad view it takes on the efficacy of various medical interventions can make it imprecise when dealing with individual patients. A treatment might be the best on average for a population as a whole, but biological variations between individuals can make it ineffective for certain patients.

Prevention is vital. Our vision stems from the fact that genomics may be able to pinpoint individuals who are prone to these chronic disorders and an early intervention could be useful in their prevention.

Professor Fahd Al-Mulla is the head of Molecular Pathology at Kuwait University where he investigates the impact of genetic variation on people's propensity for certain diseases and their reactions to different treatments. "Traditionally, all cancer patients are treated with the same effective therapy that has been validated and verified in randomised clinical trials. However, we know that some patients respond well – about 20% – while others do not do so well," he says.

THE NEXT MEDICAL REVOLUTION

The reasons for this mixed response can be environmental, but most of the time, it is the genetic variation between patients that determines the treatment's effectiveness. With the completion of the Human Genome Project in 2003 and the rapidly falling cost of

sequencing an individual's genome, predicting the variations' influence on a patient's medical outcomes is finally becoming feasible.

These advances mean that the prospect of personalised medicine is moving from science fiction to science fact. This promises to be the next great revolution in healthcare, and Al-Mulla has made it his mission to pioneer the approach in the Gulf States.

His first foray into the area came when he was urged by colleague Dr. Issam Francis, Director of the pathology laboratory at Kuwait Cancer Control Center, to introduce the fluorescent in situ hybridisation (FISH) test to Kuwait. This test ascertains whether breast cancer patients have amplified levels of the HER2 gene. High levels of the gene are an indicator of particularly aggressive cancer types, but they are responsive to Herceptin, a new monoclonal antibody therapy produced by drug maker Roche.

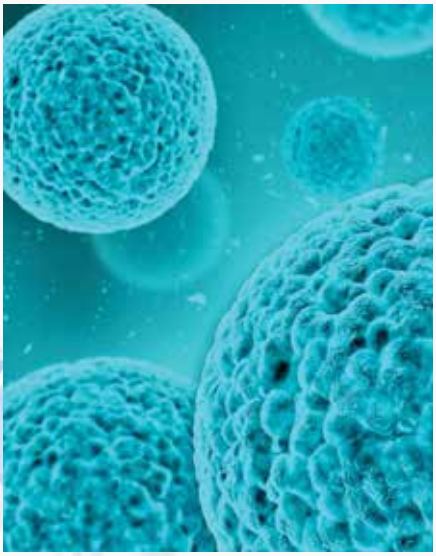
After establishing his lab's test locally in 2000, the drug was introduced to Kuwait in 2004. Since then, mortality rates for advanced breast cancer patients with amplified HER2 have dropped from 80 per cent to 20 per cent. "This reality reflects the success of personalised medicine and how its proper implementation can improve outcome," says Al-Mulla.

CHAMPIONING ARAB GENOMIC MEDICINE

The success spurred Al-Mulla to open his own genomic medicine clinic in Genatak last year,

under the umbrella of Dr. Jamal Al Ghanim's Global Med Clinic Services group. Through the company's partnerships, it has access to 21 next-generation DNA sequencing machines, including 10 HiSeq X-TEN, six Illumina HiSeq 2500 systems, two Illumina MiSeq instruments and three of Life Technologies Ion Torrent Personal Genome Machines.

The clinic provides genome and exome sequencing services for a variety of patients, such as patients with cancers or undiagnosed disorders, who may be looking for appropriate treatments specific to their genetic make-up. The clinic's service may even be beneficial to individuals who want to know the risks, prevention, and management of chronic diseases.



Al-Mulla believes there is high demand for these kinds of services in his part of the world. "With 30% of the population of the Gulf States suffering from obesity and diabetes, the local economies will struggle in treating these diseases and their chronic complications," he says. "Therefore, prevention is vital. Our vision stems from the fact that genomics may be able to pinpoint individuals who are prone to these chronic disorders and an early intervention could be useful in their prevention."

Another factor driving demand for genomic medicine in the Gulf States is the prevalence of consanguineous marriage – marriage within the extend family – which results in higher frequencies of Mendelian genetic disorders. "A simple approach we are taking at Genatak is called pre-marital compatibility testing. This tests for about 600 to 1,500 genetic diseases in the future bride and groom, who may carry a single gene defect that will not be expressed in them. It also involves counselling on how to avoid having a child affected with a particular genetic disease," says Al-Mulla.

LOCAL CHALLENGES

But there are both technical and cultural challenges to making personalised genomic medicine widespread in the Gulf States. One issue that has preoccupied Al-Mulla is the fact that the majority of genome-wide-association studies on detection of disease-causing genetic variations and the Human Genome Project have been carried out on DNA from individuals in the West. While many of the lessons learned from these projects can be applied to Middle Eastern societies, Al-Mulla's work on Arab genomes has revealed that the population exhibits major differences in polymorphisms and background mutation rates.

This has prompted him to take a leading role in the Genome Arabia project A better picture of the Arab genome could help improve the targeting of treatments in a population with significantly different genetics to those in the West.

As an example, genomic screening for breast cancer in the West typically looks for mutated pathogenic BRCA1 and BRCA2 genes, which are a strong indicator that the patient will develop breast or ovarian cancer. While there is a strong genetic component to breast cancer cases in the Gulf States, mutations in these two genes are uncommon within families with a strong history of breast or ovarian cancer. "Sequencing only BRCA1 and BRCA2 in affected members with a strong family history of cancer is a common mistake made by doctors not specialised in genetics," says Al-Mulla. "We really need to sequence and examine small structural gene changes in at least 65 cancer causing genes in women with a family history of cancer, not only two."

On top of the technical challenges there are also significant cultural hurdles that need to be overcome before the deeply conservative societies of the Gulf States fully embrace personalised genomic medicine. According to Al-Mulla many physicians and patients remain sceptical about genetic testing, equating it with playing God. "This is why Genatak is focused on educating policymakers, the public and doctors about the strength and caveats of genomic medicine. Education is key," says Al-Mulla.

Researcher Profile

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Professor Fahd Al-Mulla is the head of the Molecular Pathology Unit in the Faculty of Medicine at Kuwait University and also founder and director of genomic medicine center Genatak. He attended Glasgow University, where he received his medical degree in 1993 and a PhD in molecular genetics of cancer metastasis in 1999. A fellow of the Royal College of physicians of Edinburgh, his research focuses on cancer and metabolism. His work led to the identification of two novel metastasis suppressors, namely carbonyl reductase and Raf kinase inhibitory protein. He holds patents on a method for prediction of metastasis by determining RKIP expression levels and another on a method of treating diabetes-related vascular complications by administering patients with a therapeutic dose of alpha-lipoic acid. As a professor at Kuwait University, he is responsible for teaching molecular pathology to medical students and MSc and PhD Pathology student

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