CUSTOM demonstrates feasibility and challenges of genetics-guided clinical trials

US researchers have recently presented promising findings from their CUSTOM clinical trial, which, among other results, demonstrated that both patients and physicians are enthusiastic about genetics-guided cancer clinical trials; researchers reached their target number of participants 3 years earlier than anticipated. The findings were presented at the 2013 annual meeting of the American Society of Clinical Oncology and the researchers propose that CUSTOM could be a model for more efficient clinical trials.

CUSTOM is the first completed prospective clinical trial that employed next-generation sequencing to assign cancer patients to the most appropriate treatment option. Patients with non-small-cell lung cancer, small-cell lung cancer or thymic cancer were recruited, and the trial's reception exceeded the researchers' expectations: “We expected it would take 5 years to enroll 600 patients into CUSTOM. But in less than 2 years, 668 patients were recruited,” explained the study's lead investigator, Giuseppe Giaccone, who is the associate director for clinical research at Georgetown Lombardi Comprehensive Cancer Center (DC, USA). Giaccone led the CUSTOM trial while at the National Cancer Institute, who collaborated with Oregon Health and Science University (OR, USA) for the trial.

“This was a surprise to all of us, especially since patients with advanced cancer who already had biopsies needed to undergo an additional biopsy for the study. But we found patients and their doctors are quite interested in this type of personalized medicine. They know that the molecular profile of the tumor is important,” Giaccone added.

In the CUTSOM trial, tumor biopsies from eligible patients were screened for mutations in approximately 200 genes using next-generation sequencing. Turnaround time was 2 weeks and the trial also demonstrated that it is safe to obtain new biopsies for genetic analysis from patients with advanced cancer. CUSTOM demonstrated that patients with KRAS mutations did not benefit from selumetinib, a single-agent investigational drug being tested in non-small-cell lung cancers, in addition to other cancer. However, despite this and the unanticipated popularity of CUSTOM, which has reaffirmed patient and physician interest in such trials, one of the end points was not met – they were unable to produce an accurate statistical analysis of response to novel drugs.

Results for the small-cell lung cancer and thymic cancer groups were inconclusive owing to not enough patients having the specific mutations to assess therapy response, as Giaccone explained: “When we started the study, we didn’t know how frequently the mutations occurred. Now we know that many mutations represent only 1–2% of patients and to do this right, you need to screen thousands of patients. That is only possible with a global study that involves, potentially, hundreds of institutions.”

“The CUSTOM trial demonstrates both the feasibility of the approach for common mutations ... as well as the difficulty of studying treatment for rare mutations.”

Source: Georgetown Lombardi Comprehensive Cancer Center news release: http://explore.georgetown.edu/documents/70469/?PageTemplateID=141

– Written by Sarah Miller
Light shed on genetic causes of epileptic encephalopathies

Recent research from an international collaboration of epilepsy genetics investigators has identified \textit{de novo} mutations in \textit{CHD2} and \textit{SYNGAP1} as causes of epileptic encephalopathy. The study used the largest cohort of epileptic encephalopathy cases to date to undergo targeted resequencing. Researchers hope that implementation of this method could lead to improved diagnosis and outcomes in this severe childhood epilepsy. The study was published in \textit{Nature Genetics}.

Epileptic encephalopathies occur in infants and children, with the majority of cases being of unknown etiology and prognosis is often poor. “This is a very exciting breakthrough, which could lead to dramatic benefits in the lives of the children who suffer this condition,” explained Professor Ingrid Scheffer (University of Melbourne and the Florey Institute of Neuroscience and Mental Health, Melbourne, Australia), who was the clinical leader of the recent study.

The study included collaboration from University of Washington (DC, USA) and pediatric neurologists from Australia, New Zealand, Denmark and Israel.

Using targeted massively parallel resequencing of 19 known and 46 candidate genes for epileptic encephalopathy, pathogenic mutations were found in approximately 10% of the cohort (52 out of 500 patients). Amongst these, \textit{de novo} mutations in \textit{CHD2} and \textit{SYNGAP1} were identified as new causes of the epilepsy.

“Overall, our findings have important implications for making a diagnosis in patients, optimizing therapy and genetic counseling for families,” explained Scheffer. The genes identified as having pathogenic mutations for epileptic encephalopathy could become a diagnostic test for the condition, which would also allow genetic counseling to be offered to affected families.

– Written by Sarah Miller


New genetic insights into pathway heterogeneity in schizophrenia

A recent study from Johns Hopkins University (MD, USA) has used a novel method of studying genetic variation in families to shed light on the possible genetic basis of pathway heterogeneity in schizophrenia. The findings suggest that multiple damaging mutations in different genes linked to a single signaling pathway could cause this complex genetic disease. Pathway heterogeneity has not previously been explored in schizophrenia and the researchers hope that one day their findings could contribute to a genetic test to predict which medications would be the most effective in patients.

Previous studies pursuing genetic insights into schizophrenia have only revealed weak associations to a few genes; according to the Johns Hopkins team, this is not enough to explain the prevalence of the disease, which affects 1% of the population. Their recent study, which was recently published in \textit{Translational Psychiatry}, examined mutations in genes coding for components of the neuregulin signaling pathway (NSP); for example, \textit{NRG1, NRG3, ERBB4, β-secretase} and the \textit{γ-secretase} complex. The NSP has previously been implicated in schizophrenia and researchers hypothesized that at least one damaging variant in the NSP genes are required in order for the individual to develop the disease. They proposed that while the body can usually compensate for a single damaging mutation affecting a certain pathway, carrying multiple mutations in that pathway could push towards developing the disease.

The recent study involved 123 European Caucasian multiplex families (those with >1 affected family member) for which genome-wide linkage data were available. Following
Metabolomics could provide a way to diagnose Alzheimer’s disease using blood tests

Researchers at the Mayo Clinic on Aging and Mayo Clinic Alzheimer’s Disease Center (MN, USA) have published findings that explore a potential diagnostic tool to detect Alzheimer’s disease, in the form of a blood test. It has been estimated that 5.2 million Americans suffer from this debilitating disease. Using blood as a means of diagnosis in an ever-aging population could provide hope of early diagnosis and better treatment.

“The team at Mayo Clinic also noted that the altered pathways found in plasma reflected those in the CSF. This suggests that blood could be used to diagnose a patient with Alzheimer’s disease by using biomarkers of perturbed metabolic pathways. Eugina Trushina, one of the authors of the article, explains: “We want to use these biomarkers to diagnose the Alzheimer’s disease before symptoms appear – which can be decades before people start exhibiting memory loss.”

Further larger studies are likely to be required before simple blood tests could be used in the clinic to diagnose an individual with Alzheimer’s disease.”

The study published in *PLoS ONE* involved 45 candidates split into three groups: candidates with no cognitive decline, mild cognitive decline and Alzheimer’s disease. The research team collected cerebrospinal fluid (CSF) and blood plasma from the candidates and analyzed the samples using metabolomics. The analysis process involved liquid chromatography and mass spectrometry to provide an insight into the activity of metabolic pathways within the cells. Previous research has found that the amyloid-β protein involved in Alzheimer’s disease could cause disruption of metabolic pathways; therefore metabolomics might be able to detect these changes in cells and could possibly provide an early indication of Alzheimer’s disease.

The team at the Mayo Clinic compared metabolic changes in the CSF and plasma of candidates with increasing severities of Alzheimer’s disease. The authors found that there were significant differences between the three samples. Using metabolomic techniques, there were more than 20 altered pathways in the plasma and CSF when comparing individuals with mild cognitive impairments and those who with no cognitive impairments, with a false discovery rate of <0.05. The authors also report a positive correlation between the severity of Alzheimer’s disease and the number of perturbed metabolic pathways in both plasma and CSF. The significant pathways that were affected included the Krebs cycle, amino acid metabolism and neurotransmitter function. This reinforces the idea that Alzheimer’s disease has its origins in malfunctioned mitochondrial pathways.

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Further larger studies are likely to be required before simple blood tests could be used in the clinic to diagnose an individual with Alzheimer’s disease. Trushina states that “the earlier we can detect the disease, the better treatment options we will be able to offer.” This could promise a better approach to treating patients and enabling a better quality of life.

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