The most potent genetic risk factor for Alzheimer’s disease (AD) identified in the past 20 years—a gene so powerful it nearly triples the risk of AD—has been discovered by a team of researchers from 44 institutions around the world. The findings appear in the online edition of the New England Journal of Medicine.

The researchers used new sequencing techniques to home in on the TREM2 gene. These studies led to identification of a set of rare variants in TREM2 that occurred more often in 1,092 AD patients than in a control group of 1,107 healthy people.

The most common variant, R47H, was then evaluated in follow-up genotyping and analysis of R47H in DNA samples from 1,994 AD patients and 4,062 control participants. These follow-up studies showed unequivocally that the R47H variant of TREM2 substantially increases the risk of AD.

The TREM2 variant—rare but potent—was present in 1.9% of the AD patients and in only 0.37% of the control group. This strong effect rivals that of the well-established genetic variant APOE-4. Not all people who have the R47H variant will develop AD, and in those who do, other genes and environmental factors will also play a role.

R47H is described as the first “goldilocks” variant to show strong association with AD. Now being identified using the new sequencing technologies, goldilocks variants are an important type of rare variant, so named because they are just right, not too rare and strong enough to show highly significant association in well-powered follow-up genotypic studies.

Algorithm Shows Accuracy in Predicting Heart Attack Risk

A peer-reviewed study published in Current Medical Research and Opinion demonstrated that Aviir Inc.’s MIRISK VP (formerly Tru-Risk™) Assessment is an improved method of determining who is likely to experience a heart attack within 5 years, allowing preventive measures to be implemented. Aviir is a biotechnology company dedicated to the prevention of cardiovascular disease through innovative laboratory tests. The study investigators analyzed more than 5,000 individuals, culminating in a study that sampled blood from 1,084 individuals who
had no evidence of heart disease and were followed over 8 years. The MIRISK VP algorithm was shown to correctly identify significantly more individuals who experienced a heart attack as being at high risk versus the Framingham Risk Score, the current gold standard of measuring risk. The MIRISK VP assessment was then shown to perform more accurately than the current gold-standard method in a separate multiethnic study population, identifying correctly a net 43% more individuals as higher or lower risk for heart disease in the intermediate-risk group.

The MIRISK VP test measures the blood levels of seven coronary artery disease-related proteins associated with plaque formation and inflammation, along with other clinical risk factors, such as family history, in an algorithm to determine an individual’s personal risk of a cardiac event.

The Aviir MIRISK VP Assessment was developed out of basic research at the Stanford University School of Medicine. Researchers identified proteins associated with the biological processes underlying vulnerable plaque development and showed they could be measured in a patient’s blood up to 5 years prior to a plaque rupture and the ensuing heart attack. Aviir’s scientists developed sensitive multiplexed assays to measure proteins in a person’s serum and an algorithm that combines the levels of those proteins with other clinical risk factors into the MIRISK VP Assessment to provide an absolute risk score for coronary heart disease risk. That algorithm has been shown in an independent study population to significantly reclassify intermediate risk individuals into their true risk category. By objectively classifying those patients at high risk, the Aviir MIRISK VP Assessment supports physicians to more effectively manage and treat this group, aiding in the reduction and prevention of cardiac events.

Used in conjunction with other clinical information, the MIRISK VP Assessment’s risk score for the imminent 5-year horizon may motivate adherence and behavioral changes by patients previously misidentified as intermediate risk.


Best Practices Guideline Developed for Older Adults Undergoing Surgery

The American College of Surgeons (ACS) and the American Geriatrics Society (AGS) have collaborated to issue its first best practices guideline on improving care for surgical patients 65 and older. The statement about the 13-point checklist for optimal preoperative assessment appears in the Journal of the American College of Surgeons.

Aside from a complete history and physical examination of the patient, the evidence-based recommendations call for only three laboratory tests to be done universally in geriatric patients: hemoglobin, renal function, and serum albumin. Any other tests are indicated only when specific risk factors are present. Other assessment items on the checklist include:

- Cognitive ability and capacity to understand the surgery, including the Mini-Cog 3-Item Recall and Clock Draw test.
- Depression (i.e., Patient Health Questionnaire-2).
- Risk for postoperative delirium, including 18 risk factors stratified as cognitive and behavioral,

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illness-related, metabolic, functional, and other. Patients at risk should not be started on benzodiazepines, and existing benzodiazepine use should be reduced when possible. The guidelines also recommend against using meperidine (Demerol®) for pain in these patients, and using caution with anticholinergic medications.

- Substance abuse/dependence (i.e., modified CAGE [Cut down, Annoyed, Guilty, Eye-Opener] Questionnaire to identify patients who need perioperative prophylaxis against withdrawal syndromes.
- Cardiac evaluation should follow the American College of Cardiology/American Heart Association algorithm for patients undergoing noncardiac surgery.
- Documentation of functional status and history of falls and determination of a baseline frailty score.
- Nutritional status and possible preoperative interventions.
- Medication history, with perioperative adjustments as appropriate, and monitoring for polypharmacy.

- Patient counseling, treatment goals, and expectations.

The guideline can be viewed at http://www.surgicalpatientsafety.facs.org/surgical/geriatric.pdf.


Researchers Find Value in “Junk DNA” from Brain

Short snippets of DNA found in human brain tissue provide new insight into human cognitive function and risk for developing certain neurological diseases, according to study findings published in PLoS Biology.

The researchers found hundreds of regions throughout the human genome that showed a markedly different chromatin structure in neurons in the prefrontal cortex, the brain region that controls complex emotional and cognitive behavior, compared with non-human primates. The findings of the study provide important insights for diseases that are unique to human beings such as Alzheimer’s disease and autism.

The research team isolated small snippets of chromatin fibers from the prefrontal cortex. Next, they analyzed these snippets to determine what genetic signals they were expressing. Many of the sequences with human-specific epigenetic characteristics were, until recently, considered to be “junk DNA” with no particular function.

Now, they present new leads on how the human brain has evolved, and a starting point for studying neurological diseases. For example, the sequence of DPP10—a gene critically important for normal human brain development—not only showed distinct human-specific chromatin structures different from other primate brains such as the chimpanzee or the macaque, but the underlying DNA sequence showed some interesting differences from two extinct primates—the Neanderthal and Denisovan, most closely related to our own species and also referred to as “archaic hominins.”

The research team also discovered that several of these chromatin regions appear to physically interact with each other inside the cell nucleus, despite being separated by hundreds of thousands of DNA strands on the genome. This phenomenon of “chromatin looping” appears to control the expression of neighboring genes, including several with a critical role for human brain development.