http://bit.ly/2NVPd99

Pattern of hospital visits offers clue to spotting people at risk of myeloma

A condition that can progress to myeloma could be identified in patients by their unusually frequent hospital visits

Glasgow, UK: A condition that can progress to myeloma could be identified in patients by their unusually frequent hospital visits, according to research presented at the 2019 NCRI Cancer Conference.

The study found that people with a pre-cancerous blood condition called monoclonal gammopathy of undetermined significance (MGUS) made around twice as many visits to hospital as other people of the same age.

Although myeloma is almost always preceded by MGUS, MGUS is rarely spotted. So, the researchers say this finding could help ensure myeloma is diagnosed at the earliest possible opportunity when the likelihood of successful treatment is highest.

The study was led by Dr Maxine Lamb, a research fellow in the department of health sciences at the University of York, UK. She said: "MGUS is a benign condition that doesn't have obvious symptoms. It is usually only diagnosed incidentally when doctors are investigating other problems, so around 90% of cases remain undiagnosed.

"In the majority of people, this condition doesn't progress to cancer. However, virtually all people with myeloma, as well as a proportion of patients with some types of lymphoma, had MGUS before their cancer developed. That's why we're interested in spotting this condition."

Previous research suggests that people with MGUS are also at risk of being diagnosed with autoimmune disorders, fractures and infections. So, Dr Lamb and her team wanted to see if it would be possible to spot MGUS cases based on how often people visited clinics and hospitals for these seemingly unrelated issues.

The study included 2,219 cases (people who were known to have MGUS) as well as 22,190 matched controls (people who had not been diagnosed with MGUS but were similar in terms of their ages, sex and where they live).

Researchers looked at data on out-patient hospital visits both before and after MGUS diagnosis and compared this with hospital visits made by the control group. They calculated rates of hospital attendances per 100 people per month.

On average, they found that MGUS patients had 31 visits per hundred people per month in the three years prior to diagnosis. Among people not diagnosed with MGUS, this figure was 16, meaning that, on average, MGUS patients were 1.9 times as likely to have an outpatient appointment than people without MGUS.

There were even stronger patterns in certain medical specialties. For example, MGUS patients were 5.5 times more likely to visit a nephrology clinic, 3.7 times more likely to visit rheumatology and 2.4 times as likely to visit dermatology. These differences increased in the years after patients were diagnosed with MGUS.

Researchers also looked at a different blood condition, called monoclonal B-cell lymphocytosis, that can lead to other types of blood cancer and they did not see this distinctive pattern of hospital visits, suggesting it may be unique to MGUS.

Dr Lamb said: "Once someone is diagnosed with MGUS they are monitored for signs that that they are developing myeloma. Previous research suggests that myeloma patients whose MGUS had been diagnosed have better survival and we know that, in general, early diagnosis improves cancer survival chances.

"This study suggests a possible way to spot more cases of MGUS and this could give us the opportunity to try to diagnose more cases of myeloma, and some types of lymphoma, at an earlier stage."

Dr Lamb and her team continue to study MGUS, including how the condition progresses into myeloma and other cancers.

Gordon Cook, Professor of Haematology & Myeloma Studies and Honorary Consultant Haematologist at the University of Leeds, is Chair of the NCRI Myeloma sub-group and was not involved in the research. He said: "Although survival rates for myeloma are improving, we are still diagnosing too many patients late. Approximately one in three cases are diagnosed through an emergency admission. So, improving the diagnostic rate is an unmet need.

"We believe that all cases of myeloma are preceded by MGUS but very few MGUS patients develop myeloma. Spotting MGUS early and finding those at greatest risk of developing myeloma is essential if we are to improve outcomes.

"However, it's important to remember that MGUS itself does not require treatment and the majority of people found to have MGUS will not go on to develop myeloma."

http://bit.ly/33vmbUr

Some skin cancers may start in hair follicles

Some of the most deadly skin cancers may start in stem cells that lend color to hair, and originate in hair follicles rather than in skin layers, a new study finds.

Hair follicles are complex organs that reside within skin layers. It is there that immature pigment-making cells develop cancer-causing genetic changes - and in a second step - are exposed to normal hair growth signals, say the study authors.

Past models of the disease had argued that sunlight (e.g., ultraviolet radiation) was a major risk factor for melanoma - but current work argues that the triggers are always there in normal follicles.

The new study, published online November 4 in *Nature Communications*, found that unlike their normal counterparts, newly cancerous pigment stem cells then migrate up and out of the follicles to establish melanomas in nearby surface skin before spreading deeper. The study was conducted in genetically engineered mice, with the results confirmed in human tissue samples.

"By confirming that oncogenic pigment cells in hair follicles are a bona fide source of melanoma, we have a better understanding of this cancer's biology and new ideas about how to counter it," says corresponding study author Mayumi Ito Suzuki, PhD, associate professor in the Ronald O. Perelman Department of Dermatology at NYU School of Medicine and Perlmutter Cancer Center.

Invisible Trail Revealed

The study results reflect development, in which a human starts as a single stem cell, the embryo, and becomes a fetus made up of hundreds of cell types. Along the way, stem cells divide, multiply and specialize, until, finally, they become cells capable of playing a single role (e.g., nerves, skin, etc.).

Complicating matters, stem cells can become more than one cell type, and can shift between them. This flexibility is useful during development, but can be dangerous in adults, in whom cancer cells are thought to re-acquire aspects of early embryonic cells. Because of this malleability, researchers have theorized that melanomas might arise from several stem cell types, making them hard to treat and their origins difficult to track.

The new study addresses the stem cells that mature into melanocytes, cells that make the protein pigment melanin, which protects skin by absorbing some of the sun's ultraviolet, DNA-damaging rays. By absorbing some wavelengths of visible light, but reflecting others, pigments "create" hair color.

In a series of elegant steps, the research team established a new mouse model for the study of melanoma, one engineered such that the team could edit genes in follicular melanocyte stem cells only (the c-Kit-CreER mouse). This capability enabled researchers to

introduce genetic changes that made only melanoctye stem cells - and their descendants destined to form melanomas - glow no matter where they traveled.

Able to accurately track a key stem cell type for the first time, the authors confirmed that melanoma cells can arise from melanocyte stem cells, which abnormally migrate up and out of hair follicles to enter the epidermis, the outermost layer of skin. The team then tracked the same cells as they multiplied there, and then moved deeper into the skin layer called the dermis.

Once there, the cells shed the markers and pigment that went with their follicular origins, presumably in response to local signals. They also acquired signatures similar to nerve cells (neurons) and skin cells (mesenchymal), molecular characteristics "almost exactly like" those noted in examinations of human melanoma tissue.

Knowing where to look for the original, cancer-causing event, the researchers temporarily eliminated signals one by one in the follicular environment to see if cancer still formed in their absences. In this way, the team confirmed that follicular melanocyte stem cells, even though they had cancer-causing genetic mutations, did not multiply or migrate to cause melanomas unless also exposed to endothelin (EDN) and WNT. These signaling proteins normally cause hairs to become longer and pigment cells to multiply in follicles.

"Our mouse model is the first to demonstrate that follicular oncogenic melanocyte stem cells can establish melanomas, which promises to make it useful in identifying new diagnostics and treatments for melanoma," says first study author Qi Sun, PhD, a postdoctoral fellow in Ito's lab. "While our findings will require confirmation in further human testing, they argue that melanoma can arise in pigment stem cells originating both in follicles and in skin layers, such that some melanomas have multiple stem cells of origin."

Along with Ito Suzuki and Sun, study authors from the departments of Dermatology, Cell Biology, and Pathology at NYU School of Medicine were Wendy Lee, Makoto Takeo, Chae Ho Lim, Markus Schober, Iman Osman, and Rana Moubarak.

Also study authors were Yasuaki Mohri and Emi Nishimura in the Department of Stem Cell Biology at Tokyo Medical and Dental University; Xiaowei Xu in the Department of Pathology and Laboratory Medicine at the University of Pennsylvania; Peggy Myung in the Department of Dermatology at Yale Cancer Center; Radhika Atitin the Department of Biology at Case Western Reserve University in Cleveland; Mark Taketo of the Graduate School of Medicine at Kyoto University in Japan; Denise Gay of the Institut de biologie François Jacob in Fontenay-aux-Roses cedex, France; and Dieter Saur of the German Cancer Research Center (DKFZ), German Cancer Consortium (DKTK), and Technische Universität München.

The work was funded by National Institutes of Health grants P30CA016087, R01 AR059768, R01 AR066022, R21 ES023034, and P50CA016087; along with a NYSTEM institutional training grant (C026880). Additional funding for the study was provided by the Arnold and Mabel Beckman Foundation and the American Skin Association.

http://bit.ly/36NVkon

Rare gene link to Alzheimer's resistance

Scientists have linked a rare gene mutation with protecting a woman from developing symptoms associated with Alzheimer's disease.

Nina Massey, Press Association

Researchers say it could be the first known candidate for a gene that has the potential to be used in the development of interventions to halt the progression of the disease.

Some people who carry mutations in genes known to cause early onset Alzheimer's disease do not show signs of the condition until a very old age.

Researchers found one such person in a study of 1200 individuals in Colombia for whom Alzheimer's disease is extremely likely to develop owing to genetic predisposition.

The woman, from a large extended family with more than 6000 living members, did not develop mild cognitive impairment until her seventies - nearly three decades after the typical age of onset.

Like her relatives who showed signs of dementia in their forties, the patient carried the E280A mutation in a gene called Presenilin 1 (PSEN1).

This gene has been shown to cause early onset Alzheimer's disease, according to the research published in the Nature Medicine journal.

Analysis showed the woman had a high degree of brain amyloid pathology, a hallmark of the disease, but did not present with symptoms associated with the disease.

Researchers found she also had a rare variant of the APOE gene, called Christchurch. They suggest this may have counteracted the detrimental effects of the PSEN1 mutation, which could have protected her against the disease.

In several experiments, they suggested mechanisms by which this mutation may exert its protective effects by impairing binding of APOE to certain sugars - called heparan sulphate proteoglycans (HSPG) - implicated in Alzheimer's disease.

Co-author Dr Yakeel Quiroz, researcher at Massachusetts General Hospital, said: "This single case opens a new door for treatments of Alzheimer's disease, based more on the resistance to Alzheimer's pathology rather than on the cause of the disease.

"In other words, not necessarily focusing on reduction of pathology, as it has been done traditionally in the field, but instead promoting resistance even in the face of significant brain pathology."

Co-lead author Dr Joseph Arboleda-Velasquez, of the Schepens Eye Research Institute of Massachusetts Eye and Ear, said: "This finding suggests that artificially modulating the binding of APOE to HSPG could have potential benefits for the treatment of Alzheimer's disease, even in the context of high levels of amyloid pathology."

Further research with larger samples is required to establish a definitive causal relationship between the mutation and protection from disease.

https://wb.md/34FjhfS

FDA OKs First Rifabutin-Based *H pylori* Therapy *Talicia*

First rifabutin-based treatment for* H pylori *infection in adults

The US Food and Drug Administration (FDA) has approved *Talicia* (RedHill Biopharma Ltd), the first rifabutin-based treatment for *Helicobacter pylori* (*H pylori*) infection in adults, according to a company news release.

Each delayed-release capsule of Talicia contains omeprazole 10 mg (equivalent to 10.3 mg omeprazole magnesium), amoxicillin 250 mg, and rifabutin 12.5 mg.

Research has shown that resistance o*f H pylori* to clarithromycin more than doubled between 2009 and 2013, the company said.

"Talicia offers patients a much-needed new treatment option for *H pylori* with an excellent safety and efficacy profile that is not compromised by clarithromycin or metronidazole resistance," David Graham, MD, professor of medicine, molecular virology, and microbiology at Baylor College of Medicine in Houston, Texas, who led the Talicia phase 3 studies, said in a news release from RedHill.

"The clinical studies for Talicia demonstrated high efficacy in eradication of *H pylori*. Studies with Talicia found zero resistance to rifabutin and showed 17% resistance to clarithromycin, a current standard-of-care macrolide antibiotic, consistent with current data showing that clarithromycin-containing therapies fail in approximately 25% to 40% of cases," said Graham.

The two phase 3 studies involved *H pylori*-positive adults complaining of epigastric pain and/or discomfort.

In the confirmatory phase 3 trial, 4 of 305 patients (1%) treated with Talicia stopped the medication due to an adverse reaction, the company said. Adverse reactions leading to discontinuation were nausea and vomiting, nasal congestion, and nasopharyngitis.

"Treatment of *H pylori* infection has become increasingly difficult due to growing bacterial resistance and the lack of advances in treatment options over the past decade," Colin Howden, MD, chief of gastroenterology at University of Tennessee Health Science Center in Memphis, said in the news release.

"Talicia offers a new effective treatment option to overcome bacterial resistance and provide optimal efficacy and I believe it could become a recommended, first-line standard-of-care treatment for *H pylori* infection," added Howden.

The company expects to launch Talicia in the US in the first quarter of 2020.

http://bit.ly/2Q0qR0E

Planning to avoid temptations helps in goal pursuit

People who make plans to avoid or handle temptations may be more likely to achieve goals

People who make plans to avoid or handle temptations may be more likely to achieve goals, such as academic and weight loss goals, according to new research by University of Wyoming psychologists.

Proactively planning to manage temptations may be more effective than simply responding to temptation when it arises, say UW Associate Professor Ben Wilkowski and recent UW psychology master's degree recipient Zach Williamson.

Their research appears in Personality and Social Psychology Bulletin, a journal of the Society of Personality and Social Psychology.

"People rely on several self-control strategies. The use of these strategies can be planned ahead of time, before a temptation is directly experienced," the researchers say. "And, planning self-control ahead of time may be critically involved in achieving long-term goals."

Wilkowski and Williamson conducted two studies of undergraduate college students to assess the effectiveness of five self-control strategies in their pursuit of long-term goals. Those are:

Situation selection

Avoiding situations where temptation is present. For example, if a dieter knows there are cookies in a kitchen, that person might stay in a different room.

Situation modification

Altering one's situation to minimize the influence of temptation. For example, if the dieter must remain in the kitchen to help cook, he may ask the host to move the cookies to the living room.

Distraction

Diverting one's attention away from a temptation. For example, the dieter might choose to not look at tempting cookies, even if they remain in front of him.

Reappraisal

Changing the way one thinks about a temptation to make it seem less appealing. For example, the dieter might tell himself that cookies are disgusting and might upset his stomach.

Response inhibition

Exerting effort to shun the temptation when confronted with it.

The researchers found that the first four strategies, which might be more easily planned in advance, are generally more effective than the latter.

"We found evidence suggesting that participants sometimes formed plans for how to manage temptations and that these plans were indeed related to the initiation of diverse self-control strategies," Wilkowski and Williamson say. "People can, indeed, proactively initiate self-control. And those who do so are better able to make progress toward their long-term goals."

http://bit.ly/34Kjwq1

Study calculates links between prescription medications and risk for suicide

New research from UChicago identifies 44 drugs with the potential to prevent suicide attempts, including the simple vitamin folic acid

A review of 922 prescription medications taken by almost 150 million people over an 11-year period shows that just 10 of these drugs were associated with an increased rate of suicide attempts. Forty-four drugs were linked to a decrease in suicide attempts, including many that carry a "black box" label from the Food and Drug Administration warning of their association with suicidal behavior.

The study, published in the Harvard Data Science Review, identifies several drugs with the potential to prevent suicide attempts that are not currently used for that purpose, including folic acid, a simple vitamin often prescribed to pregnant women.

"There's an anti-histamine that's associated with decreases in suicide. There's a Parkinson's drug associated with decreases," said Robert Gibbons, PhD, the Director of the Center for Health Statistics at the University of Chicago and lead author of the study. "If those test out in clinical trials to be real effects, we could be using more of these drugs to treat suicidal people."

The rate of suicide has been rising for 16 years and is now the tenth leading cause of death in the United States. Most suicides occur in patients with a psychiatric disorder, such as depression. However, common antidepressant medications like fluoxetine (Prozac) carry the FDA's black box warning, which has led to decreased use of these medications despite the benefits they might provide.

For the new study, Gibbons and his team developed a statistical tool to measure the links between drugs and suicide attempts. They analyzed data on 922 drugs with more than 3,000 prescriptions in a database of medical claims from 2003 to 2014.

The data contained records of 146 million unique patients from more than 100 health insurers in the United States. For each person taking each drug, they counted suicide attempts in the three months prior to filling the prescription and the three months after taking the drug. This approach allowed them to evaluate each drug individually within a single person and see its effect on suicide attempts.

"It's actually a very simple model that answers the question, 'Does a suicide attempt occur more frequently after taking the drug than before?'" Gibbons said.

That analysis found 10 drugs that showed a statistically significant increase in suicide attempts, including the opioid painkiller hydrocodone bitartrate and acetaminophen (Vicodin), anti-anxiety drugs alprazolam (Xanax) and diazepam (Valium), and prednisone, a corticosteroid. A total of 44 drugs showed a decrease in suicide risk, including a large group of antidepressants with black box warnings like fluoxetine and escitalopram (Lexapro), gabapentin (Neurontin), an anti-convulsant used to treat seizures, and, interestingly, the vitamin folic acid.

Gibbons said the statistical model can be used to calculate the risk of any adverse events that happen before and after taking a medication. The Veterans Administration has already expressed interest in using the tool, and Gibbons hopes other large hospital systems and local health agencies will adopt it to help decide which drugs to prescribe, especially for patients at risk of suicide.

"What we've done is come up with an alternative approach to drug safety surveillance that could be used by any agency, country or formulary," he said. "We simultaneously did this analysis on all 922 drugs, and from that model we can back out the risks for each one individually."

http://bit.ly/34N0KhV

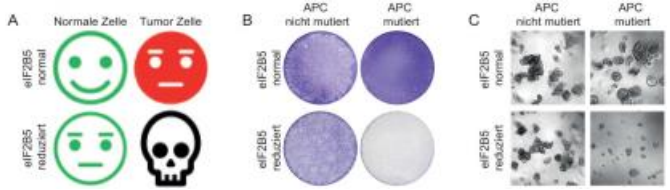
Achilles heel of tumor cells

If the gene called eIF2B5 is mutated, colon cancer cells die of programmed cell death

In 90 percent of all cases of colon cancer, the tumour cells have one thing in common: the APC gene is mutated.

Research groups at Julius-Maximilians-Universität (JMU) Würzburg in Bavaria, Germany, were looking for targets in these cells that could be used to destroy the cells.

"We wanted to find genes that are only important for the survival of cells with APC mutations, but not for healthy cells," explains Dr. Armin Wiegering, head of a junior research group at the JMU Biocentre and physician in surgery at Würzburg University Hospital.



If the eIF2B5 gene is inhibited, the colon cancer cells with an APC mutation do not do well: they die. On the left a schematic representation, in the middle cell cultures, on the right organoids **Armin Wiegering / University of Wuerzburg**

The search for a needle in a haystack was successful.

The research teams now report this in the journal Nature Cell Biology: If they inhibited the gene called eIF2B5, the mutated colon cancer cells died of programmed cell death - a self-destruction programme with which the organism normally disposes of damaged or aged cells. Healthy cells, on the other hand, were able to cope with the inhibition of the gene without any impairment.

Possible point of attack for treatment

"We have thus identified a very specific Achilles heel of APC-mutated tumours," says Professor Martin Eilers, cancer researcher at the Biocentre. We now know of a site where newly developed antitumour drugs might be able to have a very targeted effect.

The efficacy of an elF2B5 inhibition was shown in animal experiments.

If the gene is not fully active in mice, they do not develop colon cancer so quickly and survive much longer if they do.

The researchers also experimented with organoids. These are miniature tumours that are cultivated in the laboratory from the cancer tissue of patients.

If the amount of elF2B5 was reduced, the organoids died.

Further genes will be investigated

Next, the researchers want to investigate further genes in colon cancer cells - because elF2B5 is only one of five subunits of the larger eIF2B gene complex.

"We also want to characterize the other subunits and see if we can also find a specificity here," Wiegering announces.

We will then establish a method to degrade eIF2B5 in cancer cells.

If this is successful, it might lead to a new option for therapies.

Colon cancer

Colon cancer is one of the three most common tumour diseases.

About six percent of all people in Germany fall ill with it in the course of their lives; about half of those affected die from the consequences of the tumour.

Since more than 90 percent of all colon tumours show an APC mutation, research at JMU could lead to a very broad, new therapeutic approach.

Cooperation partners

The following institutions were significantly involved in the publication in Nature Cell Biology: the Department of General, Visceral, Transplantation, Vascular and Pediatric Surgery of the University Hospital Würzburg, the Chair of Biochemistry and Molecular Biology at the JMU Biocentre, the JMU Institute of Pathology and the Beatson Institute in Glasgow, Scotland.

https://bbc.in/2qAqmje

Cervical screening: DIY alternative to smear test 'promising'

A DIY home urine or swab test could potentially help more women discover whether they are at risk of cervical cancer, researchers say.

The new method could be used as an alternative to the smear test and would not require a visit to the doctor. Scientists at Queen Mary University of London asked 600 women to provide self-collected samples for screening. Although larger trials are needed, the work has been called "promising" and a potential "game-changer" by charities.

The findings, being presented at the NCRI cancer conference in Glasgow, suggest the method is feasible and popular. However, larger trials may still be needed before the NHS could decide whether to offer it to patients, say experts. Even then, it would only be one option for women - as the researchers believe smear tests would continue in their current form. But the researchers say that in the future, some women could order the test kits online, use them at home and then send their sample by post to be analysed.

The 25% who do not attend

Screening aims to pick up early warning signs of cancer - known as pre-cancers - that can be treated to prevent the disease.

All women and people with a cervix aged 25 to 64 in the UK are invited for NHS cervical screening, but the number of women attending cervical screening in the UK has been falling.

Around one in four UK women do not attend when invited, figures suggest. Experts have put the low uptake rates down to embarrassment, a lack of awareness or just putting it off.

Dr Belinda Nedjai and colleagues have developed an alternative screening method that does not rely on smear tests.

The S5 test measures chemical changes that are detectable in urine or self-collected vaginal fluid samples to gauge a woman's cancer risk. A high score suggests there is an increased risk of a pre-cancer lesion being present. In the study, the S5 test was good at distinguishing which women had pre-cancerous growths diagnosed following conventional screening.

'Potential to revolutionise'

Dr Nedjai said the self-sampling was "pretty accurate", but was not as quite as effective as the UK's current smear testing programme.

"It will be soon. With improvement we'll get there," she told BBC Radio 4's Today programme.

Dr Nedjai said the S5 test needed to be tried on more than 10,000 women before it could be offered on the NHS. She predicted the at-home tests could be available via the health service in five years.

Researchers say the test could also be used alongside conventional cervical screening to help improve detection and spare some women from unnecessary investigations.

The NHS is currently moving to primary human papillomavirus (HPV) screening of smears - testing for the presence of this virus in samples before looking for abnormal cell changes. Almost all cases of cervical cancer are linked to HPV.

Dr Manuel Rodriguez-Justo, from University College London, said: "This is exciting research that shows it's possible to detect cervical pre-cancer that is at high risk of developing into invasive cancer in urine and vaginal samples collected by women in the comfort and privacy of their own homes.

"This has the potential to revolutionise the way a positive HPV test is followed up, as well as making it easier for women in countries with no cervical cancer screening programme to be tested."

Sophia Lowes, Cancer Research UK's health information manager, said: "The results look promising for detecting women with advanced cell changes. But we need to know if this test picks up all

changes and if it's as successful when testing a wider group of people."

Robert Music, chief executive of Jo's Cervical Cancer Trust, said although more research was needed, DIY checks could be a "game-changer". "For women who find the current methods of cervical screening difficult, including those with a physical disability or who have experienced trauma, it could mean they can access screening in a far more acceptable and accessible way."

"It could mean those requiring treatment are identified faster and reduce the number of women having to go for potentially unnecessary investigations at colposcopy."

https://wb.md/2qArnYA

Pro Soccer Players at High Risk for Death From Alzheimer's, ALS, Parkinson's

Professional soccer players appear to be at considerably increased risk for death from neurodegenerative diseases, including Alzheimer disease (AD), amyotrophic lateral sclerosis (ALS), and Parkinson disease (PD), new research shows.

Deborah Brauser

A retrospective cohort study of more than 7000 former professional soccer players showed that overall, they had a threefold increased risk for death from neurodegenerative disease compared to a matched group of healthy control persons.

Former soccer players had a fivefold increased mortality risk from AD, a fourfold increased risk of dying from motor neuron disease/ALS, and a twofold increased mortality risk from PD.

On the other hand, soccer players had a significantly lower risk of dying from nonneurologic disorders, including heart disease and lung cancer.

"This is first, robust evidence of a considerable increase in neurodegenerative disease mortality in contact sports," principal investigator Willie Stewart, PhD, Institute of Neuroscience and Psychology, University of Glasgow, Scotland, told *Medscape Medical News.*

He added that although specific risk factors cannot be identified in the study, there is sufficient evidence from this study and previous research to support exposure to repetitive mild traumatic brain injury (TBI) and head trauma "as the number one" candidate risk factor.

"As such, across all sports, the aims should be to better recognize and manage TBI and to reduce exposure to head impacts where at all possible," said Stewart, who is also from the Department of Neuropathology at the Queen Elizabeth University Hospital in Glasgow. The study was published online November 7 in the *New England Journal of Medicine.*

Head Trauma and CTE

Stewart noted that there has been growing concern that exposure to repetitive mild TBI and head trauma in sport increases the risk for chronic traumatic encephalopathy (CTE).

"That used to be thought to be almost exclusive to boxers but has now been recognized in autopsy studies on former participants across numerous contact sports, including soccer," he said.

As reported by *Medscape Medical News,* CTE is also common among former hockey players and US football players.

Despite recognition of CTE in past neuropathology studies, "only very limited data" exist on risk for neurodegenerative disease in contact sport participants. "And much of that is from studies with various methodological deficiencies," Stewart said.

The current study "represents the first investigation in any sport to address the multiple limitations of previous research," he added.

From the Football's Influence on Lifelong Outcomes and Dementia Risk (FIELD) study, the investigators evaluated mortality data from comprehensive electronic health records of 7676 male former professional soccer players from Scotland who were born between

1900 and 1976. Death records were used to identify 23,028 matched individuals from the general population, who served as the control group. "These death certification records provide the most complete picture of outcomes in the available datasets," Stewart noted. The national Prescribing Information System was mined for prescription information.

A Primary Cause of Death

Results showed that mortality of any type was actually lower for the former soccer players vs the control group — but only until age 70, when it increased. Mortality from the following nonneurodegenerative diseases was significantly lower for the full group of former soccer players vs the control group:

- Ischemic heart disease: hazard ratio (HR), 0.80; *P* = .02;
- Lung cancer: HR, 0.53; *P* < .001.

Neurodegenerative disease was listed at the primary cause of mortality in 1.7% of the soccer group vs 0.5% of the control group (HR, 4.10; 95% confidence interval [CI], 2.9 – 5.9; *P* < .001).

After adjusting the HR for risk for death from ischemic heart disease and/or cancer, the subhazard ratio for risk for death from neurodegenerative disease was still 3.5 in soccer players (95% CI, 2.1 – 5.6; *P* < .001).

In addition, "mortality with neurodegenerative disease listed as the primary or a contributory cause on the death certificate varied according to disease subtype," the investigators write.

For former players vs the control group, the HRs were 5.07 for mortality from AD (95% CI, 2.9 – 8.8; *P* < .001), 4.33 from ALS (95% CI, 2.1 – 9.2; *P* < .001), and 2.15 from PD (95% CI, 1.2 – 4.0; *P* = .01).

Former soccer players were prescribed dementia-related medications more frequently than control persons (odds ratio, 4.9; 95% CI, 3.8 – 6.3; *P* < .001).

Interestingly, goalkeepers were prescribed this type of medication less frequently than outfielders (*P* = .02), but mortality from neurodegenerative disease did not differ between the player subgroups. The researchers note that the findings now need "to be confirmed in prospective matched-cohort studies."

Higher Than Predicted

Stewart said that on the basis of available literature, as well as previous research from his team, they had anticipated that the current study would show "some evidence of lifelong health benefits" in former soccer players — but also a mild to moderate increase in neurodegenerative disease in this group.

"However, the extent of neurodegenerative diseases risk in former soccer players was perhaps at the upper end of our predictions," he said.

Asked how these rates might compare with those found in American football/National Football League (NFL) players, Stewart said this is not an easy question to answer.

"Although studies in former NFL players have been pursued, data were compared to US population mortality figures rather than appropriately matched controls. As such, these methodological limitations mean direct comparison with our data is not possible," he said.

"Nonetheless, the reported neurodegenerative mortality in former NFL American football players is similar to what we observed in former professional soccer players," he added. Stewart noted that the study did not evaluate young people, so relevance of the study's data to youth or amateur soccer players is unknown.

"I'd continue to recommend participation in physical activity, including soccer, whilst at the same time making every effort to better recognize and manage concussion and reduce exposure to unnecessary head impacts," he said.

"That way, if we can achieve this, we will have the potential to retain the health benefits of sport while reducing risk of neurodegenerative disease — a win-win."

Occupational Risk?

In an accompanying editorial, Robert A. Stern, PhD, Boston University Chronic Traumatic Encephalopathy Center, Massachusetts, noted that recent research has shown a link between some contact and collision sports and increased risk for later-life neuropsychiatric and cognitive impairment, as well as for CTE.

"It appears that it is not just the 'big hits' resulting in symptomatic concussions that increase the risk of neurologic disorders in later life. Rather, the total duration of exposure to repetitive head impacts...has been associated with neuropathology," Stern writes.

That said, these new study findings "should not engender undue fear and panic among soccer players, parents, and coaches," he notes. "As the authors of the current study indicate, it is not possible to generalize their findings...to participants in recreational, amateur, or collegiate-level soccer," he adds.

More research should be conducted on both short- and long-term consequences from heading a ball by amateur soccer players and female former professional soccer players "in order to confirm or refute" these new data.

"Perhaps, however, there is already adequate evidence that repeated blows to the brain from heading in professional soccer is an occupational risk that needs to be addressed," Stern writes.

Funder Response

The current study was funded by the Football Association (FA) and the Professional Footballers Association, as well by a National Health Service Research Scotland Career Researcher Fellowship.

The FA released a video of the organization's chairman in which he was asked whether rule changes are needed.

"Potentially, but not yet," answered Greg Clarke. He added that "the actual causes of these issues" still need to be identified in further research. "Globally, the game needs to evolve; we will evolve it. But today, all we need to do is to observe concussion management protocols and limit repetitive heading exercises. They're the only changes we're seeking to make," Clarke said.

Stewart reports no relevant financial relationships. However, he notes that he is an unpaid member of the Football Association's Head Injury and Concussion Expert Panel. Stern reports having received grants from the NINDS, the NIA, and the Concussion Legacy Foundation and personal fees from Biogen, Eli Lilly, and Psychological Assessment Resources, Inc.

N Engl J Med. Published online October 21, 2019. Abstract, Editorial

http://bit.ly/2Cqjc3C

NASA's TESS spacecraft is finding hundreds of exoplanets – and is poised to find thousands more

The all-sky search is on for possibly habitable planets close to our solar system

Daniel Apai *
Benjamin Rackham **

Within just 50 light-years from Earth, there are about 1,560 stars, likely orbited by several thousand planets. About a thousand of these extrasolar planets – known as exoplanets – may be rocky and have a composition similar to Earth's. Some may even harbor life. Over 99% of these alien worlds remain undiscovered — but this is about to change.

With NASA's new exoplanet-hunter space telescope TESS, the all-sky search is on for possibly habitable planets close to our solar system. TESS — orbiting Earth every 13.7 days — and ground-based telescopes are poised to find hundreds of planets over the next few years.

This could transform astronomers' understanding of alien worlds around us and provide targets to scan with next-generation telescopes for signatures of life. In just over a year, TESS has

identified more than 1,200 planetary candidates, 29 of which astronomers have already confirmed as planets. Given TESS's unique ability to simultaneously search tens of thousands of stars for planets, the mission is expected to yield over 10,000 new worlds.

These are exciting times for astronomers and, especially, for those of us exploring exoplanets. We are members of the planet-hunting Project EDEN, which also supports TESS's work. We use telescopes on the ground and in space to find exoplanets to understand their properties and potential for harboring life.

Undiscovered worlds all around us

Worlds around us await discovery. Take, for example, Proxima Centauri, an unassuming, faint red star, invisible without a telescope. It is one of over a hundred billion or so such stars within our galaxy, unremarkable except for its status as our next-door neighbor. Orbiting Proxima is a fascinating but mysterious world, called Proxmia b, discovered only in 2016.

Scientists know surprisingly little about Proxima b. Astronomers name the first planet discovered in a system "b". This planet has never been seen with human eyes or by a telescope. But we know it exists due to its gravitational pull on its host star, which makes the star wobble ever so slightly. This slight wobble was found in measurements collected by a large, international group of astronomers from data taken with multiple ground-based telescopes.

Proxima b very likely has a rocky composition similar to Earth's, but higher mass. It receives about the same amount of heat as Earth receives from the Sun.

And that is what makes this planet so exciting: It lies in the "habitable" zone and just might have properties similar to Earth's, like a surface, liquid water, and — who knows? — maybe even an atmosphere bearing the telltale chemical signs of life.

NASA's TESS mission launched in April 2018 to hunt for other broadly Earth-sized planets, but with a different method. TESS is looking for rare dimming events that happen when planets pass in front of their host stars, blocking some starlight. These transit events indicate not only the presence of the planets, but also their sizes and orbits.

Finding a new transiting exoplanet is a big deal for astronomers like us because, unlike those found through stellar wobbles, worlds seen transiting can be studied further to determine their densities and atmospheric compositions.

Red dwarf suns

For us, the most exciting exoplanets are the smallest ones, which TESS can detect when they orbit small stars called red dwarfs – stars with masses less than half the mass of our Sun.

Each of these systems is unique. For example, LP 791-18 is a red dwarf star 86 light-years from Earth around which TESS found two worlds. The first is a "super-Earth," a planet larger than Earth but probably still mostly rocky, and the second is a "mini-Neptune," a planet smaller than Neptune but gas- and ice-rich. Neither of these planets have counterparts in our solar system.

Among astronomers' current favorites of the new broadly Earth-sized planets is LHS 3884b, a scorching "hot Earth" that orbits its sun so quickly that on it you could celebrate your birthday every 11 hours.

No Earth-like worlds yet

But how Earth-like are Earth-sized planets? The promise of finding nearby worlds for detailed studies is already paying off. A team of astronomers observed the hot super-Earth LHS 3884b with the Hubble Space Telescope and found the planet to be a horrible vacation spot, without even an atmosphere. It is just a bare rock with temperatures ranging from over 700 C (1300 Fahrenheit) at noon to near absolute zero (-460 Fahrenheit) at midnight.

The TESS mission was initially funded for two years. But the spacecraft is in excellent shape and NASA recently extended the

mission through 2022, doubling the time TESS will have to scan nearby, bright stars for transits.

However, finding exoplanets around the coolest stars — those with temperatures less than about 2700 C (4900 F) — will still be a challenge due to their extreme faintness. Since ultracool dwarfs provide our best opportunity to find and study exoplanets with sizes and temperatures similar to Earth's, other focused planet searches are picking up where TESS leaves off.

The worlds TESS can't find

In May 2016, a Belgian-led group announced the discovery of a planetary system around the ultracool dwarf they christened TRAPPIST-1. The discovery of the seven transiting Earth-sized exoplanets in the TRAPPIST-1 system was groundbreaking.

It also demonstrated how small telescopes — relative to the powerful behemoths of our age — can still make transformational discoveries. With patience and persistence, the TRAPPIST telescope scanned nearby faint, red dwarf stars from its high-mountain perch in the Atacama desert for small, telltale dips in their brightnesses.

Eventually, it spotted transits in the data for the red dwarf TRAPPIST-1, which — although just 41 light-years away — is too faint for TESS's four 10-cm (4-inch) diameter lenses. Its Earth-sized worlds would have remained undiscovered had the TRAPPIST team's larger telescope not found them.

Two projects have upped up the game in the search for exo-Earth candidates around nearby red dwarfs. The SPECULOOS team installed four robotic telescopes – also in the Atacama desert – and one in the Northern Hemisphere. Our Exoearth Discovery and Exploration Network – Project EDEN – uses nine telescopes in Arizona, Italy, Spain and Taiwan to observe red dwarf stars continuously.

The SPECULOOS and EDEN telescopes are much larger than TESS's small lenses and can find planets around stars too faint for TESS to study, including some of the transiting Earth-sized planets closest to us.

The decade of new worlds

The next decade is likely to be remembered as the time when we opened our eyes to the incredible diversity of other worlds. TESS is likely to find between 10,000 and 15,000 exoplanet candidates by 2025. By 2030, the European Space Agency's GAIA and PLATO missions are expected to find another 20,000-35,000 planets. GAIA will look for stellar wobbles introduced by planets, while PLATO will search for planetary transits as TESS does.

However, even among the thousands of planets that will soon be found, the exoplanets closest to our solar system will remain special. Many of these worlds can be studied in great detail – including the search for signs of life.

Discoveries of the nearest worlds also represent major steps in humanity's progress in exploring the universe we live in. After mapping our own planet and then the solar system, we now turn to nearby planetary systems.

Perhaps one day Proxima b or another nearby world astronomers have yet to find will be the target for interstellar probes, like Project Starshot, or even crewed starships. But first we've got to put these worlds on the map.

*Associate Professor of Astronomy and Planetary Sciences, University of Arizona
**Postdoctoral Fellow, Massachusetts Institute of Technology

Disclosure statement

Daniel Apai receives research funding from NASA, NSF and the Gordon & Betty Moore Foundation. He is an Associate Professor of Astronomy and Planetary Sciences at The University of Arizona's Steward Observatory and Lunar and Planetary Laboratory. He pursues research in the field of extrasolar planets and related technology development.

Ben Rackham receives funding from the Heising-Simons Foundation, NASA, and the NSF.

University of Arizona provides funding as a member of The Conversation US.

http://bit.ly/36RlBlN

New Ancient Ape Species Rewrites the Story of Bipedalism

Danuvius guggenmosi, a "totally new and different" species of ape, would have moved through the trees using its forelimbs and hindlimbs equally

By Andrea Michelson

The picture is on T-shirts, coffee mugs and bumper stickers: the ubiquitous but misinformed image of the evolution of humankind. A knuckle-walking ape rouses himself to stand on two feet, and over a 25-million-year "March of Progress," he becomes a modern man.

The 21 bones of the most complete partial skeleton of a male Danuvius guggenmosi. **(Christoph Jäckle)**

Most paleoanthropologists will tell you that this version of evolution is oversimplified, misleading or just plain wrong. The theory that the last common ancestor of humans and apes walked on its knuckles like a chimpanzee is not supported by the fossil record, although it has seen popularity in scientific discourse. David Begun, a paleoanthropologist at the University of Toronto, used to be an outspoken proponent of the knuckle-walking hypothesis, until he was asked to consult on a newly discovered fossil that would challenge his assumptions about early hominid locomotion.

When Madelaine Böhme, a researcher at the University of Tübingen in Germany, unearthed the partial skeleton of an ancient ape at the Hammerschmiede clay pit in Bavaria, she knew she was looking at something special. Compared to fragments, an intact partial skeleton can tell paleoanthropologists about a creature's body proportions and how its anatomy might have functioned. A relative newcomer to the field and a paleoclimatologist by trade, Böhme enlisted Begun's expertise in analyzing the fossil ape.

Böhme and colleagues determined that the bones they found came from a dryopithecine ape, an extinct ancestor of humans and great apes that once lived in the Miocene epoch. The fossils are approximately 11.6 million years old and came from at least four individual apes, including one partial skeleton. The team described the newfound ancestor, named *Danuvius guggenmosi*, in a study published today in *Nature*.

D. guggenmosi was likely a small primate about the size of baboon, with long arms like a bonobo. The creature had flexible elbows and strong hands capable of grasping, which suggests that it could have swung from tree to tree like a modern great ape. But the similarities with known apes stop there. The animal's lower limbs have much more in common with human anatomy. With extended hips and knees, *D. guggenmosi* was capable of standing with a straighter posture than that of living African apes, and its knees and ankles were adapted to bear weight. The animal's locomotion would have therefore shared similarities with both human and ape movement, and *D. guggenmosi* may have been able to navigate the forest by swinging from tree limbs and walking on two legs.

"There is no reason to think it would not have used all four limbs when that made sense, for example, on smaller branches where balance was an issue," Begun says. "But it was also capable of both chimp-like suspension and unassisted bipedalism."

This hybrid form of locomotion, which Böhme and colleagues dubbed "extended limb clambering," was previously unheard of. Begun says before this discovery, scientists in the field used models of motion employed by living quadruped primates to inform how our early ancestors may have moved. "Here, we have something that doesn't exist today," he says. "It's totally new and different, and you couldn't imagine it. It would have been silly to even suggest it

unless you found fossils that told you that there was an animal like this."

Unlike suspensory great apes that favor their forelimbs and bipedal hominins which prefer their hindlimbs, the anatomy of *D. guggenmosi* indicates that the ancient primate used both sets of limbs equally. The curvature of the big toe suggests that this animal would have been able to walk flat-footed on branches, using its longest toe to grasp and balance.

Femoral head, ulna and tibia from a male Danuvius guggenmosi. **(Christoph Jäckle)**

"Our last common ancestor with great apes doesn't look like a chimp or any living great ape—he may have looked like *Danuvius*," Böhme says.

D. guggenmosi puts bipedality on the evolutionary timeline far earlier than scientists previously expected. Jeremy DeSilva, a paleoanthropologist who reviewed the study for *Nature*, says while this discovery sheds some light on how hominids began to walk on two feet, it also raises new questions about the evolution of locomotion. Rather than humans evolving to become bipedal after splitting from a quadruped ancestor, the great apes must have evolved from a creature with bipedal capabilities.

"Given what we know about the relationships between humans and the African great apes, then gorillas and chimpanzees would have had to have independently evolved knuckle-walking. That would have happened twice," DeSilva says. "That is unsettling. It's disruptive to what we once thought."

Böhme says it is also worth noting that *D. guggenmosi* was found in Europe, far from where most people imagine ancient apes lived. The narrative of human evolution is typically set on the African stage, but before early humans evolved, some of their primate relatives were living in forests that stretched across the Mediterranean. "We have to keep in mind that a big part of human history or human early evolution was not an African story," Böhme says.

Another mysterious part of the puzzle, DeSilva says, is that the European apes completely disappear a few million years after *D. guggenmosi*. And another couple million years after that, scientists start to see evidence of early human development in Africa. But there's a huge gap in the fossil record between *D. guggenmosi* and the next partial skeleton in the human family, *Ardipithecus ramidus*. "We've got these bookends with *Danuvius* and *Ardipithecus*, and then the in-betweens are now giant question marks," DeSilva says. "To a scientist, that's not discouraging. It's exciting."

http://bit.ly/33z0Aub

Women Missing Brain's Olfactory Bulbs Can Still Smell, Puzzling Scientists

Researchers have discovered a small group of people that seem to defy medical science.

By Yasemin Saplakoglu

The 29-year-old woman's brain scan was puzzling to say the least: It revealed she was missing brain structures she needed to be able to smell, yet she could sniff out odors even better than the average person.

It turns out, she's not the only one with this mysterious ability, according to a new study published today (Nov. 6) in the journal Neuron. Researchers have discovered a small group of people that seem to defy medical science: They can smell despite lacking "olfactory bulbs," the region in the front of the brain that processes information about smells from the nose. It's not clear how they are able to do this, but the findings suggest that the human brain may have a greater ability to adapt than previously thought.

A group of researchers in Israel made this discovery by chance: They were conducting a different study that involved imaging the brains of patients with a normal sense of smell using magnetic resonance imaging (MRI). But they noticed that one woman seemed to be missing her olfactory bulbs.

The scientists thought this was surprising because the ad for their study had noted participants should have a good sense of smell, and yet, based on her brain scan, the woman shouldn't be able to smell. The researchers thought "maybe she didn't notice" that part of the ad, said senior author Noam Sobel, a professor of neurobiology at the Weizmann Institute of Science in Israel. But when they asked her, she said she had a very good sense of smell.

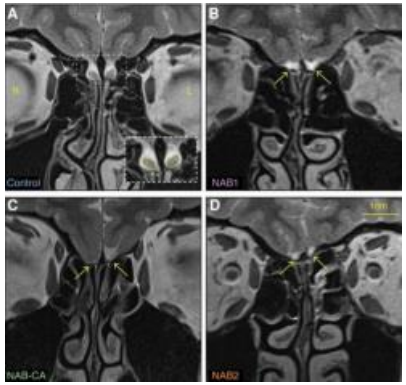
So Sobel and his team asked if they could conduct more scans and tests on her and found that indeed, she had a sense of smell slightly better than the average person. "Our understanding is that odors are essentially mapped on the surface of the bulbs," and the brain somehow reads this map, Sobel told Live Science. If you lack this map, you should also lack the ability to smell, he added.

Deciding to pursue this further, the researchers recruited more people as "controls" to compare with the unusual case. All of these controls were women and all left-handed like the original subject. "Lo and behold," in the ninth scan of a control "we discovered another woman without olfactory bulbs and a perfect sense of smell," Sobel said. At that point, "it started to look like no coincidence."

Fingerprint of the world's smells

The group then decided to search through a database called the Human Connectome Project that had published over 1,100 MRI scans, along with information about the participants' sense of smell. The researchers found that out of 606 women, three of them didn't have olfactory bulbs, yet they retained the ability to smell (and one of the three was left-handed).

They performed even more brain scans and smell tests on the two women, and one other woman who was also missing her olfactory bulb but could not smell. This third subject had what's called congenital anosmia, or a lifelong inability to smell. As expected, they found that the woman who had congenital anosmia couldn't smell most odors, while the other two women could smell as well as people with olfactory bulbs.



A brain scan of a person with olfactory bulbs (box A) looks very different than brain scans of people without olfactory bulbs (Boxes B, C and D). **Weiss et al.**

As a final step, the researchers wanted to create an "olfactory perceptual fingerprint" that documented what the world smells like to these participants. To do that, they asked the women and 140 other similarly aged women to rate how similar two smells were to each other, such as a lemon and an orange, or a lemon and a skunk. The fingerprints of the two women without olfactory bulbs were comparable to the fingerprints of the rest of the participants. What's more, the fingerprints of the two women were closer to each other than any other two participants.

There were slight differences, however. For example, neither of them could detect a rose-like odor, which is one of the most common odors in olfactory testing, said John McGann, an associate professor in the psychology department of Rutgers University who wasn't part of the study.

"It is surprising, it's not quite entirely shocking because there had been a previous report that sort of credibly showed one person who seemed to be able to have some sense of smell," without having an olfactory bulb, he told Live Science. (That study was published in

2009 in the American Journal of Rhinology). But that subject's sense of smell, in comparison to these new subjects, wasn't that great. So this study is a "stronger and compelling demonstration" that proves "it is possible somehow for some people to have a sense of smell despite not having olfactory bulbs," McGann said.

In the '80s and '90s, there were studies done on rodents that suggested if they had their olfactory bulbs removed they were still able to smell. But "those studies [were] pretty much ripped apart by our field; they were really hammered" for methodological problems, Sobel said. "Who knows, maybe now I'll be torn apart as well," he said. That's because their finding goes against dogma — the textbook definition of olfactory bulbs says they are "utterly essential" to the sensory system, he added. So what's going on?

The brain's nose

It's not clear why this ability was found only in women, specifically in left-handed women. Most brain-scan studies exclude participants who are left-handed to reduce variation among participants, which could be a reason why this wasn't found before, Sobel said. That's because people who are right-handed can have their brains wired differently than those who are left-handed.

It's also unclear how these women developed the sense of smell in their brains without having olfactory bulbs. But there are a couple of hypotheses that can explain what's happening, Sobel said. The first is that these women were born without olfactory bulbs and then somehow, as their brains developed in infancy, they found a way to make smell work, which would attest to how "plastic" the brain is, he said. In other words, another region of the brain might have taken on the task of transmitting scent information to the brain.

The sort of more exciting alternative might be that "you don't need olfactory bulbs" to detect, discriminate and identify smells, he said. That means that olfaction works very differently than we think and the olfactory bulb is doing something else, he added. For example, most mammals when they smell something have to make two decisions — what the smell is and where it's coming from. Maybe the olfactory bulb serves to figure out where the odor is coming from but not what the odor is, he said. But this is all speculative and needs to be tested, he added.

Thomas Cleland, the associate chair and professor in the department of psychology at Cornell University who was also not part of the study, says he thinks it's unlikely that the nerves that make up the olfactory bulbs are actually missing in these patients. "It's more likely that the relevant circuitry, or something resembling it, is somehow misplaced, internally anatomically disorganized, and/or differently shaped, as opposed to being genuinely absent," he told Live Science in an email. "And if this is true, it's not that strange that these women can smell somewhat normally."

But if there is some sort of displaced structure, "you'd expect that there would be some anomaly in their scan somewhere," said Joel Mainland, an associate member of the Monell Chemical Senses Center in Philadelphia, who was also not a part of the study. "The idea that maybe there's a different structure that's [taking] over the role of the olfactory bulb would be surprising and amazing."

The findings are "pretty counter to most of what the field thinks," Mainland told Live Science. "I think it's pretty critical that we figure out what's happening."

http://bit.ly/36UGhJZ

The genetic imprint of Palaeolithic has been detected in North African populations

They have identified a small genetic imprint of the inhabitants of the region in Palaeolithic times, thus ruling out the theory that recent migrations from other regions completely erased the genetic traces of ancient North Africans

An international team of scientists has for the first time performed an analysis of the complete genome of the population of North Africa. They have identified a small genetic imprint of the inhabitants of the region in Palaeolithic times, thus ruling out the theory that recent migrations from other regions completely erased the genetic traces of ancient North Africans. The study was led by David Comas, principal investigator at UPF and at the Institute of Evolutionary Biology (IBE: CSIC-UPF) and it has been published in the journal Current Biology.

The field of genomics has evolved greatly in recent years. DNA sequencing is increasingly affordable and there are major projects studying genomes at population level. However, some human populations like those of North Africa have been systematically ignored. This is the first genomic study to contextualize this region of the world.

The origin and history of the population of North Africa are different from the rest of the continent and are more similar to the demographic history of regions outside Africa: the Middle East, Europe or Asia. Palaeontological remains exist that prove the existence of humans in the region more than 300,000 years ago. In any case, previous genetic studies had shown that current populations of North Africa originated as a result of a Back to Africa process, that is, recent migrations from the Middle East that populated northern Africa.

Hence, the debate that arises is one of continuity versus replacement. On the one hand, the continuity hypothesis posits that current North African populations descend from Palaeolithic groups, i.e., that such ancient humans are the ancestors of present human populations. Meanwhile, other hypotheses argue that the populations that existed in Palaeolithic times were replaced, and that the humans that currently inhabit North Africa are the result of recent migrations that arrived there as of the Neolithic.

In this study, the researchers compared genetic data from current North African individuals with data recently published on the DNA of fossil remains found at different sites in Morocco. "We see that the current populations of North Africa are the result of this replacement but we detect small traces of this continuity from Palaeolithic times, i.e., total replacement did not take place in the populations of North Africa", reveals David Comas, full professor of Biological Anthropology at the Department of Experimental and Health Sciences (DCEXS) at UPF. "We do not know whether the first settlers 300,000 years ago are their ancestors, but we do detect imprints of this continuity at least since Palaeolithic times, since 15,000 years ago or more", he adds.

"We have seen that the genetic imprint of Palaeolithic populations of North Africa is unique to the current North African populations and is decreasingly distributed from west to east in the region, inversely proportionally to the Neolithic component coming from the Middle East, which had a greater effect on the eastern region, which is geographically closer", says Gerard Serra-Vidal, first author of the article.

"Therefore, our results confirm that migrations from other regions such as Europe, the Middle East and sub-Saharan Africa to this area did not completely erase the genetic traces of the ancient North Africans", explains David Comas, head of the Human Genome Diversity research group of the IBE.

These results of the populations of North Africa are in contrast with what is known about the European continent, in whose current populations a strong Palaeolithic component is found, i.e., more continuity and less replacement than in North Africa.

Many genomic data are still missing, both of current populations and of fossil remains, to be able to establish the population history of the human species. "This is or particular concern in populations such as those of North Africa about which we have very little

information compared to other populations in the world. In order to have a complete picture of human genome diversity still have to do a considerable amount of research", David Comas concludes.

The study involved researchers from Taibah University (Saudi Arabia), Tunis El Manar University (Tunisia), the University of Oran (Algeria) and the Lebanese American University (Lebanon).

http://bit.ly/2pX0Ft6

Not so quiet, please

UC Riverside mouse study finds early exposure to sounds can address hypersensitivity to noise associated with Fragile X Syndrome

RIVERSIDE, Calif. -- A research team at the University of California, Riverside, has found exposure to sound -- not sound reduction -- during early development of mice engineered to have Fragile X Syndrome, or FXS, restores molecular, cellular, and functional properties in the auditory cortex, the area of the brain that processes sounds. The results suggest that facilitating exposure to sounds during early age can restore communication between brain cells that have been altered by the gene mutation that leads to FXS.

Caused by gene abnormalities, FXS, the most common inherited cause of intellectual disability and autism, affects approximately 1 in 4,000 males and 1 in 6,000 females. About 1 in 259 women carry FXS and could pass it to their children. Children, mostly boys, with FXS show neurodevelopmental and neuropsychiatric disabilities, including hyperactivity.

Humans with FXS and other autism spectrum disorders, or ASDs, are hypersensitive to sounds. Indeed, it is not uncommon to see persons living with FXS or ASDs frequently close their ears or wear sound-canceling headphones. Some loud sounds can even lead to seizures in these individuals.

"Our study has found that raising FXS mice in a sound-limiting environment leads to even more severe abnormalities than in FXS mice raised in a noisy vivarium," said Iryna Ethell, a professor of biomedical sciences in the School of Medicine, who led the research.

The researchers examined the structural changes in the auditory cortex of FXS mice at the cellular level and found that sound reduction -- or attenuation -- leads to a loss of inhibitory neurons in the brain. The loss of these neurons, which reduce brain activity, is most likely responsible for hypersensitivity in FXS. Sound exposure, on the other hand, restores levels of these neurons and brain responses to the normal range.

"Perhaps exposure to sounds, rather than isolation, in early development of individuals living with FXS is a better approach to treat hypersensitivity," Ethell said. The study, published in *Neurobiology of Disease*, is the first to show the beneficial effects of developmental exposure to pure tone in a mouse model of FXS.

"Our findings provide a scientific basis for future clinical work using exposure to sound as therapy, in addition to drugs," Ethell said. "Sensitivity in individuals with FXS and ASDs is not limited to sound. Other sensory modalities have similar avoidance effects -- such as light, touch, and smell. Our findings, therefore, may have broader implications for multisensory exposure."

In one experiment, the researchers placed FXS mice in a sound-limiting box five days after birth. They then examined their responses to reduced sound using electrophysiology. They also measured anatomical and biochemical changes in the brain when the mice were 21 days old. In another experiment, the researchers placed different FXS mice in a similar box five days after birth but exposed them to loud sound. They then performed a similar analysis on these mice when they were 21 days old.

The researchers found, unexpectedly, that exposure of FXS mice to repeated presentations of a 14 kilohertz tone at a 5 hertz repetition rate for 24 hours a day from when the mice were nine days old to

when they were 21 days old normalized their responses to sound and corrected deficits seen in the FXS mice.

"These beneficial effects of sound exposure were a surprise because we expected a sound reduction would prevent hyperresponsiveness and reduce the FXS mice's sensitivity to sound," Ethell said.

The study by Ethell's lab, done in collaboration with the labs of Khaleel Razak, a professor of psychology; and Devin Binder, a professor of biomedical sciences, was supported by a three-year grant from the Department of Defense. Next, the labs will identify specific beneficial properties of sound and examine if combining sound exposure with a pharmacological approach is helpful.

Ethell, Razak, and Binder were joined in the study by UC Riverside's Anna O. Kulinich, Sarah M. Reinhard, Maham Rais, Jonathan W. Lovelace, and Veronica Scott. Kulinich and Reinhard are the study's co-first authors.

http://bit.ly/2NVxWqi

Oh, oh, oh! The clitoris certainly gives pleasure. But does it also help women conceive?

New research reported in the media says the clitoris plays an important role in fertility and reproduction, making it more than an organ that exists purely for sexual pleasure.

Michelle Moscova *

But some media headlines were misleading, including:

The truth about the clitoris: why it's not just built for pleasure

and

New clue reveals how a woman can conceive, and it all comes down to the clitoris

The reports were based on a controversial review by retired UK scientist Dr Roy Levin published this week in the journal Clinical Anatomy. He brings together evidence to support a new theory that the clitoris is equally important for reproduction as it is for sexual pleasure, which he first proposed in 2018.

This is controversial as the clitoris has not previously been given a direct role in reproduction. Levin says this is because other researchers have been so fixated on its role in sexual pleasure they have completely overlooked its other role.

How the clitoris has courted controversy

Levin's review is the latest development in a long history of controversy about the clitoris. Over the centuries, anatomists have debated its function, a discussion often dominated by men.

As early as 1559, Matteo Realdo Colombo, an anatomist at the University of Padua in Italy, termed the clitoris:

the seat of a woman's delight.

However, his contemporary Andreas Vesalius, known as the "father of modern anatomy", dismissed the proposition. He said the clitoris was an anomaly and simply does not exist in normal healthy women.

Others saw the clitoris as a liability.

In the 1820s, English surgeon and president of the Society of British Medicine Isaac Baker Brown thought the clitoris was a source of "hysteria" and epilepsy. And he said it should be removed to cure hysteria and other forms of "female madness".

And as late as 1905, Sigmund Freud considered clitoral orgasm to be a sign of a woman's psychological immaturity.

Where are we today?

Today, most scientists agree the main function of the clitoris is for sexual pleasure. But how did we come to have such an organ and why would we need one?

Researchers just last month proposed the clitoral orgasm is a remnant of our evolutionary past that once served to induce ovulation during intercourse. Another view of the clitoris argues it allows women to discriminate between sexual partners based on who can help them reach orgasm with the right type of stimulation.

A third common view is clitoral orgasms lead to stronger bonding between sexual partners preparing them for childbearing and parenting.

So how does this fit with the latest claim?

This latest paper argues stimulation of the clitoris activates parts of the brain, leading to multiple physiological changes in the vaginal tract. These changes lead to vaginal lubrication, an increase in vaginal oxygen, an increase in temperature and decrease in acidity, so facilitating reproduction by creating the right environment for the sperm. While it's not unusual for organs to have two functions, Levin's view needs further investigation.

Some of the physiological changes he describes occur when a woman is sexually aroused, before her clitoris is stimulated.

For example, women can experience vaginal lubrication and engorgement of erectile tissues while watching erotic movies, without clitoris stimulation. He also discusses how female genital mutilation reduces a woman's fertility, implying this is a result of circumcision of the clitoris. However, he does not cite any evidence for this.

While there is some evidence for a decline in fertility after female genital mutilation it varies between studies. The link seems to be strongest where not only the clitoris, but parts of the labia are also removed and stitched together during the procedure, narrowing the opening into the vagina. In these cases, infertility may also be caused by the difficulty in sexual intercourse due to the narrowing of the vaginal opening, infections or other complications of the procedure.

With this equivocal evidence, Levin's conclusion that "the reappraisal of the functions of the clitoris as both reproductive as well as recreative are of equal importance is clearly now unavoidable", could be disputed. The conclusion is not quite that definite. However, this does not mean Levin's theory is incorrect; it just requires further investigation and discussion.

His review highlights that often the science around the clitoris has been heavily influenced by the cultural context — from feminism, through to religion and simply the morals of the time. While cultural context is important, this has diverted attention away from objectively examining scientific evidence. Perhaps the most important aspect of this review is it may trigger a discussion on the functions of the clitoris and bring that discussion back to science.

As Levin highlights, the two proposed functions of the clitoris as an organ of both "procreation" and "recreation" are not mutually exclusive and can be of equal importance, a proposition worth examining.

[*]***Senior Lecturer in Anatomy, UNSW***

Disclosure statement

Michelle Moscova does not work for, consult, own shares in or receive funding from any company or organisation that would benefit from this article, and has disclosed no relevant affiliations beyond their academic appointment.

UNSW provides funding as a member of The Conversation AU.

http://bit.ly/2X4109E

5-Inch-Long Tapeworm Lived in Man's Brain for More Than a Decade

The Spirometra tapeworm can live in humans for up to 20 years.

By Rachael Rettner - Senior Writer

A man in China experienced seizures and other mysterious symptoms for years before doctors finally found the cause: He had a rare parasite living in his brain, which had likely been there for more than a decade, according to news reports.

The man, who lives in Guangzhou, China, said that he began to feel numbness on the left side of his body starting in 2007, according to Fox News. In the following years, he developed more worrying symptoms, including blackouts and seizures, although doctors failed to find the true cause of his illness.

Then, in 2018, doctors discovered a nearly 5-inch-long (12 centimeters) tapeworm in his brain. He was diagnosed with sparganosis, an infection caused by a type of tapeworm larvae known as *Spirometra*.

Humans are rarely infected with *Spirometra* are rare — the parasite typically lives in the intestines of dogs and cats, according to the Centers for Disease Control and Prevention (CDC). Other hosts in the parasite's life cycle include fish, reptiles, amphibians and freshwater crustaceans.

But humans can become infected if they drink water contaminated with the parasite, or if they eat undercooked meat from animals, such as frogs or snakes, that are hosts to the parasite. The parasite can live for up to 20 years in humans, the CDC says.

Although *Spirometra* tapeworms occur worldwide, most human cases have been reported in Southeast Asian countries, according to the CDC. Humans are accidental hosts and can't transmit the disease.

The *Spirometra* larvae can migrate anywhere in the body, including the eyes, urinary tract, lungs, abdomen and, as in this case, the central nervous system. Brain infections with the larvae can cause a variety of symptoms, including weakness, headache, seizures and numbness or tingling, the CDC says.

Doctors removed the tapeworm from the man's brain during a 2-hour surgery. "The surgery was risky," Dr. Gu Youming, the man's surgeon, told AsiaWire, according to Fox News. "The live tapeworm was moving in his brain, and we had to remove all of it, otherwise the leftover part could grow again."

In 2014, a similar case of a brain infection with *Spirometra* was reported in a man of Chinese descent living in England, according to The Guardian.

At that time, doctors involved in the case said that this type of tapeworm can survive in the brain by scavenging for fatty acids, which it absorbs through its body. "This worm is quite mysterious, and we don't know everything about what species it can infect or how," Dr. Hayley Bennett, who was involved in the 2014 case, told The Guardian.

http://bit.ly/2qD9Z5v

Study: Ransomware, Data Breaches at Hospitals tied to Uptick in Fatal Heart Attacks

Findings should prompt a larger review of how security — or the lack thereof — may be impacting patient outcomes

Hospitals that have been hit by a data breach or ransomware attack can expect to see an increase in the death rate among heart patients in the following months or years because of cybersecurity remediation efforts, a new study posits. Health industry experts say the findings should prompt a larger review of how security — or the lack thereof — may be impacting patient outcomes.

Researchers at **Vanderbilt University**'s Owen Graduate School of Management took the **Department of Health and Human Services** (HHS) list of healthcare data breaches and used it to drill down on data about patient mortality rates at more than 3,000 Medicare-certified hospitals, about 10 percent of which had experienced a data breach.

As **PBS** noted in its coverage of the Vanderbilt study, after data breaches as many as 36 additional deaths per 10,000 heart attacks occurred annually at the hundreds of hospitals examined.

The researchers found that for care centers that experienced a breach, it took an additional 2.7 minutes for suspected heart attack patients to receive an electrocardiogram.

"Breach remediation efforts were associated with deterioration in timeliness of care and patient outcomes," the authors found. "Remediation activity may introduce changes that delay, complicate or disrupt health IT and patient care processes."

Leo Scanlon, former deputy chief information security officer at the HHS, said the findings in this report practically beg for a similar study to be done in the United Kingdom, whose healthcare system was particularly disrupted by the Wannacry virus, a global

contagion in May 2017 that spread through a Microsoft Windows vulnerability prevalent in older healthcare systems.

"The exploitation of cybersecurity vulnerabilities is killing people," Scanlon told KrebsOnSecurity. "There is a lot of possible research that might be unleashed by this study. I believe that nothing less than a congressional investigation will give the subject the attention it deserves."

A post-mortem on the impact of WannaCry found the outbreak cost U.K. hospitals almost $100 million pounds and caused significant disruption to patient care, such as the cancellation of some 19,000 appointments — including operations — and the disruption of IT systems for at least a third of all **U.K. National Health Service** (NHS) hospitals and eight percent of general practitioners. In several cases, hospitals in the U.K. were forced to divert emergency room visitors to other hospitals.

But what isn't yet known is how Wannacry affected mortality rates among heart attack and stroke patients whose ambulances were diverted to other hospitals because of IT system outages related to the malware. Or how many hospitals and practices experienced delays in getting test results back needed to make critical healthcare decisions.

Scanlon said although he's asked around quite a bit over the years to see if any researchers have taken up the challenge of finding out, and that so far he hasn't found anyone doing that analysis.

"A colleague who is familiar with large scale healthcare data sets told me that unless you are associated with a research institution, it would be almost impossible to pry that kind of data out of the institutions that have it," Scanlon said. "The problem is this data is hard to come by — nobody likes to admit that death can be attributable to a non-natural cause like this — and is otherwise considered sensitive at a very high and proprietary level by the institutions that have the facts."

A study published in the April 2017 edition of *The New England Journal of Medicine* would seem to suggest applying the approach used by the Vanderbilt researchers to measuring patient outcomes at U.K. hospitals in the wake of Wannacry might be worth carrying out.

In the NEJM study, morbidity and mortality data was used to show that there is a measurable impact when ambulances and emergency response teams are removed from normal service and redirected to standby during public events like marathons and other potential targets of terrorism.

The study found that "medicare beneficiaries who were admitted to marathon-affected hospitals with acute myocardial infarction or cardiac arrest on marathon dates had longer ambulance transport times before noon (4.4 minutes longer) and higher 30-day mortality than beneficiaries who were hospitalized on nonmarathon dates."

"Several colleagues and I are convinced that the same can be shown about WannaCry, on the large scale, and also at the small scale when ransomware attacks impact a regional hospital," Scanlon said.

In November 2018, I was honored to give the keynote at a conference held by the Health Information Sharing and Analysis Center (H-ISAC), a non-profit that promotes the sharing of cyber threat information and best practices in the healthcare sector.

In the weeks leading up to that speech, I interviewed more than a dozen experts in healthcare security to find out what was top of mind for these folks. Incredibly, one response I heard from multiple healthcare industry experts was that there is currently no data available to support the finding of a negative patient outcome as a result of a cybersecurity vulnerability or attack.

As I kept talking to experts, it occurred to me that if smart people in this industry could say something like that with a straight face, it was probably because not a lot of people were looking too hard for evidence to the contrary.

With this Vanderbilt study, that's demonstrably no longer true.

A copy of the new study is available here (PDF).

http://bit.ly/2NxCA4X

Bad dog? Think twice before yelling, experts say

Punishing your dog to discourage bad behavior could make them more stressed and "pessimistic," a new study finds.

By Eva Frederick

Few things are more adorable—or destructive—than a new puppy. When they pee on rugs, chew furniture, and get aggressive with other pups, their stressed-out owners usually turn to dog training. Now, a novel study suggests programs that use even relatively mild punishments like yelling and leash-jerking can stress dogs out, making them more "pessimistic" than dogs that experience reward-based training.

"[Punishment] training may seem to work in the short run … but these methods can have future negative consequences," says Marc Bekoff, an evolutionary biologist at the University of Colorado in Boulder who was not involved in the new study. "[These dogs are] living in perpetual stress."

Previous studies have suggested that although both reward-based and punishment-based training methods are effective, punishment-based training can have negative effects. But those studies tend to focus on police and laboratory dogs instead of family pets, and most used shock collars, which have been banned in several countries, as punishment.

To find out how companion dogs react to more routine punishments, scientists led by Ana Catarina Vieira de Castro at the University of Porto in Portugal recruited 42 dogs from reward-based training schools, which use food or play to encourage good behaviors. The team also enlisted 50 dogs from aversive-based programs, which use negative reinforcement like yelling and leash jerking to train dogs, or even pressuring their rumps to get them to sit.

The researchers videotaped the dogs during training and tested their saliva before and after for the stress hormone cortisol. Dogs in the negative reinforcement programs showed more stress-related behaviors during training, such as lip licking and yawning, and they had higher levels of cortisol in their saliva than when at home, the team reports on the preprint server bioRxiv. Dogs in the reward-based training group showed no changes in cortisol levels during training or at home.

To find out whether these effects lingered, the researchers measured how 79 of the dogs responded to a potential food reward. First, they trained the dogs to associate one side of a room with a delicious sausage. If a dog found a bowl in that part of the room, it would contain sausage. But bowls on the other side of the room would be empty.

Then, the researchers placed an empty bowl at various positions between the two extremes and measured how quickly the dogs approached it. An "optimistic" dog would run excitedly to a bowl in the middle, whereas a "pessimistic" dog would move more slowly. (In humans, an equivalent might be a glass half empty versus glass half full mindset.) Such "pessimistic" mindsets have been associated with separation anxiety and other problem behaviors in dogs. In the test, the more punishment a dog had received, the more "pessimistic" it was, and the more pronounced the results.

"This was a careful study," Bekoff says. And although the paper does not address which method is more effective at training dogs, Bekoff says this and other findings provide more than enough evidence that dog owners should avoid aversive-based training.

That's often easier said than done, because many dog training schools don't advertise their methods, and such training is not regulated—at least in the United States, says Zazie Todd, a dog trainer and animal psychology blogger. She adds that dog owners should look explicitly for keywords like "reward-based," and avoid

schools that use language like “balance training” or “dominance methods.”

Bekoff agrees and says owners should take the time to talk to the trainer and to other owners who have worked with them. “[Reward-based training] may take time, but so what? At least the dog isn’t living in fear or constant stress.”

http://bit.ly/2K4xFGQ

Cattle eyeball worms found in second human, raising worry of wriggly uprising

Cattle eyeball parasites, part deux: The wrath of flies that will drink your tears.

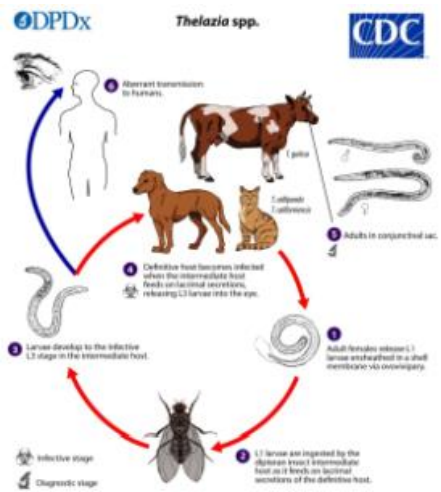
Beth Mole

A 68-year-old Nebraska woman has become the second human in history to discover parasitic cattle worms wriggling around her eyeballs.

The cringy case—which surfaced just two years after the first case in Oregon—raises concern that the worms may be angling for an uprising in the United States.

In a recent report in the journal Clinical Infectious Diseases, parasitologists at the Centers for Disease Control and Prevention noted that the worm—*Thelazia gulosa*, aka the cattle eye worm—has been in the US since the 1940s. "The reasons for this species only now infecting humans remain obscure," they write. But "[t]hat a second human infection with *T. gulosa* has occurred within two years of the first suggest that this may represent an emerging zoonotic disease in the United States."

T. gulosa is a parasitic nematode known to infest the eyes of cattle in the United States and Southern Canada, as well as Europe, Asia, and Australia. The worms move from eye to eye via face flies, aka *Musca autumnalis*, which feast on tears. Both the flies and the hitchhiking worms were introduced to the US immediately after World War II, and the infectious cycle began.



Generally, the worms' journey goes like this: worm larvae floating around an eyeball gets picked up by a fly while they're sucking down the tears of their victim. Those larvae grow and molt in the fly's tissues before reaching an infective stage. At that point, they migrate to the fly's mouth parts and wait to be delivered to a new eyeball. Once in a peeper, they prefer to hang out between the eyeball and the eyelid but can move around, causing scarring and other issues.

In the latest human case, the Nebraska woman said her right eye became irritated and started bothering her in early March 2018. When she tried flushing it out with tap water, a squirming, transparent roundworm approximately 13mm long came out. She took a closer look at her eye and noticed a second one, which she then pulled out on her own.

Adult Thelazia gulosa removed from the eye of a human, now on a person’s finger. **CDC**

The next day, she went to an eye doctor, who took out a third worm and sent it off to the CDC for identification. The doctor told her to continue pulling out worms she could see and gave the woman an antibiotic solution to prevent secondary bacterial infections. The woman's eye irritation continued, and later that month she saw another eye doctor and had an infectious disease consultation. Neither of the exams turned up additional worms.

But not long after the appointments, the woman flushed a fourth worm from her eye. After that, her symptoms resolved, and no more worms slithered out.

Infectious disease experts at the CDC suspect the woman picked up the infection while she was trail running in a regional park in Carmel Valley, California, which is where she spends her winters. She told the researchers that on one run, she remembered rounding a corner and colliding head-on with a swarm of small flies.

"She recalls swatting the flies from her face and spitting them out of her mouth," the CDC researchers reported. They also noted that the park is surrounded by cattle ranches.

In the first human case of *T. gulosa*—which occurred in a 26-year-old Oregon woman in August 2016—infectious disease experts think the victim may have just been too slow in swatting away a fly while she was fishing or horse riding earlier in the summer. In that case, the woman had a total of 14 worms extracted from her eye.

The CDC researchers call for monitoring of *T. gulosa* infections in animals as well as humans. Currently, there is no such monitoring, so there's no way of knowing if the worms are on the rise and will continue to show up in human eyeballs.

http://bit.ly/36RB1qc

Doctors Are Trying to Use CRISPR to Fight Cancer. The 1st Trial Suggests It's Safe.

Preliminary data from an innovative clinical trial suggests CRISPR could be safe for use in cancer therapy.

By Nicoletta Lanese - Staff Writer

In the first clinical trial of its kind, researchers used the gene-editing tool CRISPR to fine-tune the DNA of people's immune cells, in hopes of fighting cancer.

Now, preliminary data from the trial suggest that this technique is safe for use in cancer patients.

"This is proof that we can safely do gene editing of these cells," study co-author Dr. Edward Stadtmauer, a professor of oncology at the University of Pennsylvania, told the Associated Press.

Still, "this treatment is not ready for prime time," Stadtmauer added in an interview with NPR. "But it is definitely very promising."

So far, only three patients have received the pioneering therapy — two with a blood cancer called multiple myeloma and one with sarcoma, a connective-tissue cancer, according to a statement from the University of Pennsylvania. Researchers were able to safely remove, edit and return the cells to patients' bodies. Safety was measured in terms of side effects, and the authors found that there were no serious side effects from the treatment.

A Phase I clinical trial, like this one, usually only includes a handful of patients, according to the American Cancer Society. The small trial aims to determine how the body reacts to a new drug and whether patients experience any adverse reactions. Phase I trials don't address whether a drug actually works to treat a condition — that question crops up in later trials. As it stands, the CRISPR study suggests that the new cancer therapy is at least safe for three people, barring more data to come.

"I'm just so excited about this," Jennifer Doudna, a biochemist at the University of California, Berkeley, whose team first discovered and developed the CRISPR technique, told NPR. (Doudna was not involved in the current study.)

CRISPR allows scientists to cut specific snippets of DNA from a cell's genetic code and paste in new ones if desired. Stadtmauer and his colleagues applied this technique to T cells, a type of white blood cell that attacks diseased and cancerous cells in the body. Cancer uses several tricks to slip under the T-cell radar, but using CRISPR, researchers aim to help the immune cells spot elusive tumors and take them down.

The technique resembles another cancer therapy, known as "CAR T", which also equips immune cells with new tools to latch onto tumors but doesn't use CRISPR, according to the National Cancer Institute.

In the new study, scientistsfirst used CRISPR to snip three genes from the immune cells' DNA. Two of the genes contain instructions to build structures on the cell surface that had prevented the T cells from binding to tumors properly, according to the university statement. The third gene provided instructions for a protein called PD-1, a kind of "off switch" that cancer cells flip to stop immune cell attacks.

"Our use of CRISPR editing is geared toward improving the effectiveness of gene therapies, not editing a patient's DNA," co-author Dr. Carl June, a professor of immunotherapy at the University of Pennsylvania, said in the statement.

With these adjustments made, the researchers used a modified virus to place a new receptor on the T cells before injecting them back into patients. The new receptor should help the cells locate and attack tumors more efficiently. So far, the edited cells have survived inside patients' bodies and have been multiplying as intended, Stadtmauer told the AP. However, it's unclear if and when the cells will launch a lethal attack on the patients' cancer, he added.

Two to three months after treatment, one patient's cancer continued to worsen, as it had before the treatment, and another patient remained stable, the AP reported. The third patient received treatment too recently for her reaction to be assessed. Meanwhile, the researchers aim to recruit 15 more patients to the trial to assess both the technique's safety and its efficacy in taking down cancer. The early safety results will be presented next month at a meeting of the American Society of Hematology in Orlando, Florida, according to the university statement.

"We'll want more patients and a longer follow-up to really make a call that the use of CRISPR is safe. But the data are certainly encouraging," Dr. Michel Sadelain, an immunologist at the Memorial Sloan Kettering Cancer Center in New York, told NPR. "So far, so good — but [it's] still early."

The study was funded in part by the biotech company Tmunity Therapeutics. Some of the study authors and the University of Pennsylvania have a financial stake in this company, the AP reported.

http://bit.ly/2K3T9mT

Ancient roman DNA reveals genetic crossroads of Europe and Mediterranean

All roads may lead to Rome, and in ancient times, a great many European genetic lineages did too, according to a new study.

日本のニュース

Its results, perhaps the most detailed analysis of changing genetic variation patterns in the region to date, reveal a dynamic population history from the Mesolithic (~10,000 BCE) into modern times, and spanning the rise and fall of the Roman Empire.

At its height, the ancient Roman Empire sprawled across three continents, encompassing the entirety of the Mediterranean and the lives of tens of millions across Europe, the Near East and North Africa. The size of the city at its center, Rome - the first to reach more than one million residents in the ancient world - would remain unrivaled in Europe until the dawn of the industrial revolution nearly 1,500 years later.

Even long before the rise of Imperial Rome, the region was an important cultural crossroads between Europe and the Mediterranean. However, while Rome and central Italy's antiquity is well-documented in a rich archaeological and historical record, little is known about the region's genetic history.

Margaret Antonio and colleagues present a new genetic record, built from genome data of 127 ancient individuals from 29 archaeological sites in and around Rome, spanning nearly 12,000 years of Roman prehistory and history.

Antonio et al. revealed two major prehistoric ancestry shifts - one occurring as Neolithic farmers replaced Mesolithic hunter-gathers

roughly 7,000 years ago, and another during the Bronze age likely coinciding with increased trade and interaction with populations from across the Mediterranean. The results suggest that by Rome's founding, the genetics of ancient central Italy were much the same as that seen in modern populations.

However, throughout the historic period (the past 3,000 years), genetic ancestry was greatly diverse, with genetic contributions from individuals from across the Near East, Europe and North Africa, and changes largely reflected major Roman historical events, the authors say.

http://bit.ly/34EyON4

Stem cell transplants used to grow fully functional lungs in mice

Findings suggest that it may be ultimately possible to use the technique to grow human lungs in animals for patients who need transplants

Researchers at Columbia University were able to grow fully functional lungs in mouse embryos using transplanted stem cells. The findings suggest that it may be ultimately possible to use the technique to grow human lungs in animals for patients who need transplants and to study new lung treatments.

The paper was published online in the journal Nature Medicine.

"Millions of people worldwide who suffer from incurable lung diseases die without treatment due to the limited supply of donor lungs for transplantation," said co-senior author Wellington V. Cardoso, MD, PhD, professor of medicine and of genetics & development at Columbia University Vagelos College of Physicians and Surgeons. "Our study shows that it may eventually be possible to develop new strategies for generating human lungs in animals for transplantation as an alternative to waiting for donor lungs."

Researchers have dedicated major efforts to bioengineer lungs by growing stem cells on synthetic scaffolds or in lungs that have been stripped of their original cells. Though substantial progress has been made, researchers have been unable to generate a fully functional lung capable of maintaining survival in animal models??? Or capable of keeping an animal alive?.

"We thought it might be simpler to grow new lungs in a developing animal, so that we could take advantage of the animal's natural signals for lung development," says first author Munemasa Mori, MD, PhD, instructor of medicine at Columbia University Vagelos College of Physicians and Surgeons.

The researchers' first challenge was to create tissue culture conditions that would allow the donor stem cells to expand proliferate and maintain their ability to transform into many different cell types.

Next, the researchers implanted these stem cells in two types of engineered mouse embryos. One type lacked the stem cells that develop into mature lung cells and another could not produce enough of the cells to make a lung. This procedure created a "chimeric" embryo that was a mix of donor and host cells.

The implanted stem cells outcompeted the host cells for growth-promoting molecules present in the embryo, leading to the formation of functional lungs that allowed the mice to live well into adulthood. A variety of lung function tests confirmed that the "chimeric" lungs worked as well as normal mouse lungs, with no signs of rejection.

"The stem cells were implanted before the embryos' immunological system was turned on, which may explain why the organs were not rejected," says Mori, who will later test his approach in larger animals and in interspecies organ transplants.

"Many of the signals for lung development are conserved across species, from frogs to mice to humans, so the idea of using animals to grow human lungs is not out of the question," Cardoso says.

The research was performed in collaboration with Hiromitsu Nakauchi, PhD, a professor at Stanford University School of Medicine and the University of Tokyo, a co-senior author of the paper.

The study is titled "Generation of functional lungs via conditional blastocyst complementation using pluripotent stem cells." The other contributors are Kazuhiro Furuhashi, Jennifer Danielsson, Yuichi Hirata, Miwako Kakiuchi, Chyuan-Sheng Lin, Mayu Ohta, Paul Riccio, Xinjing Xu, Charles Emala, and Chao Lu, all at Columbia University Vagelos College of Physicians and Surgeons, and Yusuke Takahashi at Stanford University School of Medicine (Stanford, CA).

The study was funded by grants from the Department of Defense, National Institutes of Health (R35-NHLBI), California Institute for Regenerative Medicine Research Leadership Award, Giannandrea Family Dale F. Frey Breakthrough Scientist (Damon Runyon Foundation), and Pew-Stewart Scholars Program for Cancer Research.

The authors declare no competing financial interest.

http://bit.ly/2O0RRKV

Oxygen-starved tumor cells have survival advantage that promotes cancer spread

Significant new evidence that tumor cells exposed to low-oxygen conditions have an advantage when it comes to invading and surviving in the bloodstream.

Using cells from human breast cancers and mouse breast cancer models, researchers at the Johns Hopkins Kimmel Cancer Center say they have significant new evidence that tumor cells exposed to low-oxygen conditions have an advantage when it comes to invading and surviving in the bloodstream.

The experiments mapping the "fate" of the cells in two- and three-dimensional lab-created tissue systems and in live animals specifically showed that cells from a primary cancer exposed to low oxygen levels, or hypoxia, have a four times greater probability of becoming viable circulating tumor cells--and likely spreading to distant tissues--than those under normal oxygen conditions.

The results were described Oct. 24 in the journal *Nature Communications*.

"Our findings also show that these post-hypoxic cells have six times the probability of forming lung metastases, suggesting that oxygen starvation enhances their metastatic capabilities," says study leader Daniele Gilkes, Ph.D., assistant professor of oncology and researcher in the breast and ovarian cancer program of the Johns Hopkins Kimmel Cancer Center.

Gilkes and her team also identified a pattern of genetic expression in post-hypoxic cells that appears to help the cells survive oxidative stress when they enter the bloodstream. Some tumor cells retain parts of this genetic signature as a "hypoxic memory" even after they have been reoxygenated, the researchers found.

"Cancer cells tend to become more aggressive as they adapt to low oxygen levels," says Gilkes, "but we were surprised to find that cells that were exposed to hypoxia in the primary tumor maintained their aggressive features even when they were reoxygenated in the blood."

In the future, the unique features of the hypoxic cells might be used as biomarkers to identify patients at risk for metastasis, or might be targeted directly by therapies to prevent or limit metastasis, the research team suggested.

Hypoxia occurs in 90% of solid tumors and is known to have an adverse impact on a patient's prognosis. However, little is known about how tumor cells change in response to low oxygen. Gilkes says most research teams--including her own--grow and experiment with tumor cells using the same oxygen concentrations as normal air.

"This is actually a much higher level of oxygen than what is found in our bodies," Gilkes says. "For example, the average concentration of oxygen in breast tissue is on the order of 6% to 8%, whereas solid breast tumors have a gradient of oxygen

concentrations that reach much less than 1% oxygen in some regions."

For their new experiments, designed to capture the changes that occur as normal breast cells become malignant, Gilkes and colleagues developed an experimental system that uses oxygen as a switch to make tumor cells "light up" with a fluorescent marker after they are exposed to low oxygen conditions of 0.5% or less, comparable to the levels measured in human tumors.

The study's first author and member of Gilkes' lab, Inês Godet, used this marker to follow the fate of these cells as they multiplied and moved around within 2D and 3D tissue "spheres " and "mini-organs" created in the laboratory, as well as in live mouse models of breast cancer.

Using fluorescence activated cell sorting to capture red or green (oxygen deprived) breast cancer cells, followed by RNA sequencing, the team found that the expression of many gene products, including integrin alpha 10 (ITGA10) and ceruloplasmin (CP) are induced in cells that experienced hypoxia within tumors, but not in cells exposed to hypoxia in the lab. The tumor-based hypoxia pattern was also better at predicting the survival of patients free of distant metastases, they concluded after studying similar genetic expression data from primary tumors from more than 1000 patients with breast cancer.

Among the next questions to answer, say the researchers, are whether post-hypoxic tumor cells at metastatic sites are more resistant to chemotherapy than other cells and whether targeting these post-hypoxic cells will be beneficial for treating patients with metastatic cancers.

Other Johns Hopkins researchers involved in the study were Yu Jung Shin, Julia Ju, Chae Ye, and Guannan Wang.

The research was supported by the National Institutes of Health under the awards U54-CA210173 R00-CA181352; The V Scholar Foundation, Susan G. Komen Foundation; The Jayne Koskinas Ted Giovanis Foundation for Health and Policy; Cindy Rosencrans Fund for Metastatic Triple-Negative Breast Cancer; The Emerson Collective; and the SKCCC Core Grant award P50CA006973.

http://bit.ly/2WWNRPA

Mapping the end of incest and dawn of individualism

If you're from a Western society, chances are you value individuality, independence, analytical thinking, and an openness to strangers and new ideas.

by Caitlin McDermott-Murphy, Harvard University

And the surprising reason for all that may very well have to do with the early Roman Catholic Church and its campaign against marriage within families, according to new research published in *Science* by Joseph Henrich, chair of the Department of Human Evolutionary Biology, and a team of collaborators.

"If you're going to ask the rise-of-the-West question," said Henrich, an author of the paper, "there's this big unmentioned thing called psychology that's got to be part of the story."

About a decade ago Henrich coined the acronym WEIRD (Western, educated, industrialized, rich and democratic) to describe the characteristics of cultures that embrace individualism. And those groups were weird, which is to say unusual within the rest of the modern world's substantial psychological variation. Most of the prior studies attempting to explain the discrepancies focused solely on geographic or ecological factors.

Henrich and his collaborators decided to look at how social groups mold the psychology and values of members, the most important and fundamental being the family.

"There's good evidence that Europe's kinship structure was not much different from the rest of the world," said Jonathan Schulz, an assistant professor of economics at George Mason University and another author of the paper. But then, from the Middle Ages to 1500 A.D., the Western Church (later known as the Roman Catholic Church) started banning marriages to cousins, step-

relatives, in-laws, and even spiritual-kin, better known as godparents.

Why the church grew obsessed with incest is still unknown. Co-author Jonathan Beauchamp, assistant professor of economics at George Mason University, suggests that one possible reason may have been material gain. Religious leaders could benefit financially from shrinking family ties—without a tight extended network those without heirs often left their wealth to the church. Whatever the reasons, one thing seems clear: The Western Church's crusade coincides with a significant loosening in Europe's kin-based institutions.

Comparing exposure to the Western Church with their "kinship intensity index," which includes data on cousin marriage rates, polygyny (where a man takes multiple wives), co-residence of extended families, and other historical anthropological measures, the team identified a direct connection between the religious ban and the growth of independent, monogamous marriages among nonrelatives. According to the study, each additional 500 years under the Western Church is associated with a 91 percent further reduction in marriage rates between cousins.

"Meanwhile in Iran, in Persia, Zoroastrianism was not only promoting cousin marriage but promoting marriage between siblings," Henrich said. Although Islam outlawed polygyny extending beyond four wives, and the Eastern Orthodox Church adopted policies against incest, no institution came close to the strict, widespread policies of the Western Church.

Those policies first altered family structures and then the psychologies of members. Henrich and his colleagues think that individuals adapt cognition, emotions, perceptions, thinking styles, and motivations to fit their social networks. Kin-based institutions reward conformity, tradition, nepotism, and obedience to authority, traits that help protect assets—such as farms—from outsiders. But once familial barriers crumble, the team predicted that individualistic traits like independence, creativity, cooperation, and fairness with strangers would increase.

Using 24 psychological variables collected in surveys, experiments, and observations, they measured the global prevalence of traits that correspond or conflict with individualism. To test for willingness to help strangers, for example, they collected data on blood-donation rates across Italy, finding a correlation between high donation rates and low cousin-marriage rates. With their kinship intensity index, Schutz said, they can also predict which diplomats in New York City will or will not pay parking tickets: Those from countries with higher rates of cousin marriages are more likely to get a ticket and less likely to pay one.

And, although willingness to trust strangers, as opposed to family or neighbors, is associated with higher levels of innovation, greater national wealth, and faster economic growth, which factor causes which is not yet known.

"We're not saying that less-intensive kin-based institutions are better," said Beauchamp. "Far from it. There are trade-offs." Tight families, for example, come with inborn financial safety nets.

More information: *Jonathan F. Schulz et al. The Church, intensive kinship, and global psychological variation, Science (2019).* *DOI: 10.1126/science.aau5141*

http://bit.ly/2rq4wPG

Study vaccine protects monkeys against four types of hemorrhagic fever viruses

Investigational vaccine that protected cynomolgus macaques against four types of hemorrhagic fever viruses

Scientists funded by the National Institutes of Health have developed an investigational vaccine that protected cynomolgus macaques against four types of hemorrhagic fever viruses endemic to overlapping regions in Africa. The University of Texas Medical Branch in Galveston and Profectus BioSciences of New York are

developing and testing the candidate quadrivalent VesiculoVax vaccine, with support from NIH's National Institute of Allergy and Infectious Diseases (NIAID) and Redeemer's University in Nigeria.

The newly published study in the *Journal of Clinical Investigation* describes how the vaccine was created using a live-attenuated (weakened) vesicular stomatitis virus to deliver proteins that elicit protective immune responses. The proteins are from Ebola virus (Kikwit strain), Sudan virus (Boniface strain, which also causes Ebola virus disease), Marburg virus (Angola strain) and Lassa virus (Josiah strain). There are no licensed vaccines to provide protection from any of those viruses--all of which can cause severe disease and death--although the European Medicines Agency has recommended licensing a VSV-Ebola vaccine.

Importantly, the monkeys infected in the study were exposed to different strains of Sudan virus (Gulu) and Lassa virus (0043/LV/14) than those in the candidate vaccine to help the researchers determine whether the vaccine would be cross-protective. Lassa 0043/LV/14 is circulating in an outbreak in Nigeria that began in 2018. Previous studies indicate that the investigational Ebola virus (Kikwit) vaccine will protect against other strains of Ebola virus.

The scientists inoculated 20 macaques with a primary and booster dose of quadrivalent VesiculoVax. The animals had five blood draws to check for an immune response, including on the day of initial vaccination and on days 10 and 28, then on day 56 when they received a booster inoculation, and again on day 66. On day 84 scientists infected the macaques with the four different hemorrhagic fever viruses and monitored them to day 112.

Twelve additional macaques in the study who were infected with the four viruses but not vaccinated all became sick, but none of the vaccinated animals did. Only one of the 20 vaccinated animals had any of the four hemorrhagic fever viruses detectible (Lassa) following the study.

The scientists state that the addition of the Lassa virus component to their multivalent vaccine is an exciting research advance as they already had developed an investigational trivalent vaccine that provided protection against Ebola, Sudan and Marburg viruses. The researchers now plan further vaccine tests against other strains of Lassa virus, and they want to further evaluate whether a single-dose quadrivalent vaccine appears safe and effective.

This research was supported by NIH/NIAID intramural funding, contract HHSN272201700077C, and grants UC7AI094660 and U19AI142785; and by NIH/NHGRI grants U01HG007480 and U54HG007480.

ARTICLE: *R Cross et al. Quadrivalent VesiculoVax vaccine protects nonhuman primates from viral-induced hemorrhagic fever and death. Journal of Clinical Investigation. DOI: 10.1172/JCI131958 (2019).*

WHO: *Heinz Feldmann, M.D., Ph.D., chief of NIAID's Laboratory of Virology, is available to comment on this study.*

http://bit.ly/33z0Ucr

Copper hospital beds kill bacteria, save lives

Copper hospital beds in the Intensive Care Unit (ICU) harbored an average of 95 percent fewer bacteria than conventional hospital beds

Washington, DC - A new study has found that copper hospital beds in the Intensive Care Unit (ICU) harbored an average of 95 percent fewer bacteria than conventional hospital beds, and maintained these low-risk levels throughout patients' stay in hospital. The research is published this week in Applied and Environmental Microbiology, a journal of the American Society for Microbiology.

"Hospital-acquired infections sicken approximately 2 million Americans annually, and kill nearly 100,000, numbers roughly equivalent to the number of deaths if a wide-bodied jet crashed every day," said coauthor Michael G. Schmidt, PhD, Professor of Microbiology and Immunology, Medical University of South

Carolina, Charleston. They are the eighth leading cause of death in the US.

Hospital beds are among the most contaminated surfaces in patient care settings. "Despite the best efforts by environmental services workers, they are neither cleaned often enough, nor well enough," said Dr. Schmidt. Nonetheless, until recently, patient beds incorporating copper surfaces--long known to repel and kill bacteria--have not been commercially available.

Knowledge of copper's antimicrobial properties dates back to ancient Ayurveda, when drinking water was often stored in copper vessels to prevent illness. In the modern medical era, numerous studies have noted copper's antimicrobial properties.

However, until recently, no-one had designed acute-care hospital beds that enabled all high risk surfaces to be encapsulated in copper. "Based on the positive results of previous trials, we worked to get a fully encapsulated copper bed produced," said Dr. Schmidt. "We needed to convince manufacturers that the risk to undertake this effort was worthwhile."

This in situ study compared the relative contamination of intensive care unit (ICU) beds outfitted with copper rails, footboards, and bed controls to traditional hospital beds with plastic surfaces. Nearly 90 percent of the bacterial samples taken from the tops of the plastic rails had concentrations of bacteria that exceed levels considered safe.

"The findings indicate that antimicrobial copper beds can assist infection control practitioners in their quest to keep healthcare surfaces hygienic between regular cleanings, thereby reducing the potential risk of transmitting bacteria associated with healthcare associated infections," said Dr. Schmidt.

With the advent of copper encapsulated hospital beds, dividends will likely be paid in improved patient outcomes, lives saved, and healthcare dollars saved.

https://wb.md/32xiWKI

Even A Little Running Lowers Risk for Death

A little running has big health benefits, and lots of running may not do much more, researchers say.

Laird Harrison

Compared with no running at all, fewer than 50 minutes of running per week reduced the risk for death from all causes by 27%, report Zeljko Pedisic, PhD, associate professor of public health at Victoria University in Melbourne, Australia, and colleagues.

"We could not find an increased or decreased benefit with frequency, pace, or duration," he told *Medscape Medical News*.

The finding suggests that people can obtain substantial benefits with less than the amount of exercise typically recommended by public health authorities.

The study by Pedisic and colleagues was published online November 4 in the *British Journal of Sports Medicine*.

Running has long been associated with better health and longevity, but researchers have debated just how fast, how long, and how often individuals need to run in order to experience these benefits. Some studies have even suggested a U-shaped effect, with the longest distance runners suffering increased risk from their sport. Research is scant regarding the effects of running on heart disease and cancer.

To see whether they could answer some of these questions, Pedisic and colleagues conducted a meta-analysis of 14 studies that had a total of 232,149 participants.

Data from the 14 studies were self-reported, with runners making up about 10% of all study participants. Follow-up in individual studies ranged from 5.5 to 35 years. The mortality data, which were collected from national death registries, showed that 25,951 study participants across all studies died during the follow-up period.

Pooling these data and controlling for other types of physical exercise, the researchers found that running reduced the risk for mortality by 27%, the risk for cardiovascular mortality by 30%, and cancer mortality risk by 23% for all participants.

The finding that such significant benefits can be obtained by running only 50 minutes a week stands in contrast to many official recommendations.

For example, the World Health Organization recommends that adults get at least 150 minutes per week of moderate exercise or 75 minutes per week of vigorous exercise. Pedisic and colleagues found that even the smallest amounts of running in the studies (less than once a week, less than 50 minutes a week, less than 6 miles per hour, and less than 500 metabolic equivalent of task minutes per week) conferred similar all-cause mortality benefits.

The researchers were not able to determine what benefits might accrue with less running because 50 minutes per week was the minimum amount in the studies they found.

The studies investigated larger increments of running time, up to 4.5 hours per week, but the reductions in risks remained constant in this meta-analysis, Pedisic explained.

That doesn't prove that more running doesn't provide more benefit, Pedisic said. "We can't really say it's not better. We can only say from our results, it's not clear if it's better or not."

Likewise, Pedisic and colleagues could not find evidence that excessive running damages the runner's health. They noted that such strenuous running is rare enough that it is difficult to obtain a sample size large enough to derive statistically significant data.

The study could not be used to show the superiority of running over other forms of physical activity, Pedisic said. The differences in benefits among sports are generally not statistically significant, he explained.

"Making comparisons between different sports and their health outcomes I don't think is very useful," he said. "If you prefer swimming, you'll probably go ahead and choose swimming regardless of whether it has slightly less benefit."

Still, he said, the finding that a small amount of running has great benefits can make it an attractive choice for individuals who want to be physically active but are short on time.

Pedisic has disclosed no relevant financial relationships.

Dashiell Harrison contributed to this story. Br J Sports Med. 2019;0:1–9. Full text

http://bit.ly/33B2pXx

Common muscle relaxant causes severe confusion in patients with kidney disease

One in 25 patients with very low kidney function were admitted to hospital with severe confusion and other cognitive-related symptoms a few days after being prescribed a common muscle relaxant.

A new study from ICES Western, Western University and Lawson Health Research Institute has shown that patients with kidney dysfunction who were prescribed a high dose of the drug baclofen, were more likely to be admitted to hospital for disorientation and confusion, than those who weren't prescribed the drug. Their results are being published on November 9 in the high impact journal, JAMA and are being presented at the same time at the American Society of Nephrology meeting in Washington, D.C.

"When we looked at people with low kidney function (30 per cent or less) who received a high dose of baclofen from their prescriber, approximately one in 25 were being admitted to hospital with severe confusion, typically over the next few days, " said Dr. Amit Garg, Professor at Western's Schulich School of Medicine & Dentistry and Scientist at ICES and Lawson. "If you compare that to a group of people who had low kidney function who didn't get baclofen, that risk is less than one in 500, so it's quite a dramatic

difference between the two groups." Video of the researchers explaining the study findings: http://bit.ly/2ruUiO8 The research was initiated because of observations that nephrologists were noting in clinic at London Health Sciences Centre.

Dr. Peter Blake, Professor at Schulich Medicine & Dentistry, Lawson scientist and coauthor on the study says this drug is commonly prescribed for muscle spasms and muscle pain, and is also prescribed off-label for alcoholism, gastro-esophageal reflex disease, and trigeminal neuralgia. He says it is widely prescribed because it has not previously been associated with serious side-effects.

More than eight million prescriptions for the drug were handed out in the United States in 2016, and despite numerous case reports linking baclofen with cognitive symptoms in patients with kidney disease, this is the first population-based clinical study to look at the association between the two.

"It came to my clinical attention dealing with patients with advanced kidney failure, that this drug that is generally thought to be relatively harmless, appeared to be the precipitant of severe confusion," said Dr. Blake. "These are patients who had previously been very oriented, and they were suddenly extremely confused and when you took a history, we understood that they had recently started this drug, baclofen."

Using ICES data, the research team looked at a group of approximately 16,000 people in Ontario with kidney disease who started a new dose of baclofen between 2007 and 2018. They divided the patients into two groups, a group that received a high dose, and a group that received a low dose of the drug and compared both to a group of almost 300,000 kidney disease patients who were not prescribed the drug at all.

About 20 per cent of older adults live with kidney function of less than 60 per cent. The research team found that 1.11 per cent of such patients (108/9707) who started a high dose of the drug baclofen were admitted to hospital with cognitive-related symptoms, versus 0.42 per cent (26/6235) with the low dose. They found that the group most at risk had the lowest kidney function, 3.78 per cent of patients with kidney function less than 30 per cent were hospitalized with these symptoms after starting a high dose of baclofen (26/687).

"We found that in current practice most patients are getting a similar dose of baclofen no matter what the level their kidney function is," said Dr. Garg who is concerned about this discrepancy in dosing because prescribing guidelines already suggest a lower dose for patients with kidney dysfunction that isn't being followed. "We also found that the risk for hospitalization for severe confusion was higher amongst patients who received doses that were higher versus doses that were lower."

The authors hope this study will better inform physicians and pharmacists about the use of baclofen for patients with kidney disease. "This study shows quite clearly the potential harm of this drug.

When a patient with low kidney function presents to the hospital with confusion, when their medication list is reviewed baclofen should be considered as a potential culprit. We're hoping regulatory agencies will now take a look at this and perhaps add a new black box warning for baclofen. With this new information prescribers should reconsider risk-benefit, and should be quite cautious before they prescribe this drug. When they believe the drug is indicated, a low dose should be considered, and patients and their families should be warned about what to look out for in terms of side effects."

The authors also say patients should not stop their prescription medications without talking to their doctor.