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Study results suggest that hypothalamic amenorrhea may have a genetic basis in some women

A new study suggests that hypothalamic amenorrhea could have a genetic basis in some women. The authors, from Massachusetts General Hospital (Boston, MA, USA), suggest that if this small study can be repeated in larger cohorts there may be a place for genetic screening of women to aid in the diagnosis of the common menstrual condition.

“...mutations are a predisposition factor rather than cause of the condition...”

Hypothalamic amenorrhea is a condition that presents as cessation of menstruation for several months, resulting in infertility. The condition is usually very treatable but evidence of a genetic basis could help in the diagnosis of the condition, as well as allowing for prediction of its occurrence. Although the condition is known to stem from a deficiency of gonadotropin-releasing hormone, the causes of this deficiency are probably multifactorial and could include excess exercise, stress and poor nutrition. The fact that the majority of women continue to produce gonadotropin-releasing hormone

even under these stressors points to a possible genetic-based susceptibility to the condition in some individuals.

In order to investigate a potential genetic basis for the condition, Lisa Caronia (MA, USA) and colleagues recruited 55 women with existing hypothalamic amenorrhea and 422 control-group women with no menstrual irregularities, 47 of whom exercised for a least 5 h a week, which is a stressor for the condition.

A group of seven genes known to be implicated in the gonadotropin-releasing hormone pathway were sequenced in all of the recruited women. No mutations were found in the majority of women but seven women with hypothalamic amenorrhea were found to have mutations in four of the seven target genes, these mutations were not present in any of the control group women. Each of the seven women with gene mutations had two mutations in both prokineticin receptor 2 genes and the FGF receptor 1 gene, as well as one mutation in each of the other two genes. Through a series of bench top experiments, the researchers were able to show that the mutations caused a loss in function of the FGF receptor protein and the prokineticin receptor 2 gene. Caronia notes that the

mutations lead to “abnormal patterns of endogenous GnRH-induced luteinizing hormone secretion.”

The authors observed that the seven women with mutations to their gonadotropin-releasing hormone pathway genes, all had risk factors for hypothalamic amenorrhea. The authors note that the mutations are a predisposition factor rather than a cause of the condition, adding that five of the women resumed normal menstruation after hormone replacement therapy.

The authors note that the mutations “could set a lower threshold for functional inhibition of the hypothalamic–pituitary–gonadal axis under adverse hormonal, nutritional or psychological conditions and thereby lead to hypothalamic amenorrhea.”

Although this study is a small one, Caronia suggests that the results do highlight “the role of rare [genetic] variants in common multifactorial disease,” and the findings could be used to inform larger studies of the genetic basis for hypothalamic amenorrhea, which may lead to widescale screening for the disorder.

Source: Caronia LM, Martin C, Welt CK *et al.*

A genetic basis for functional hypothalamic amenorrhea. *N. Engl. J. Med.* 364, 215–225 (2011).

Study suggests a novel function for vasopressin in the brain

New research carried out at the Graduate University for Advanced Studies (SOKENDAI; Okazaki, Japan) has highlighted a possible new function for the antidiuretic hormone vasopressin. The hormone, which is released in the brain, is known to suppress diuresis in the kidneys via a vasopressin receptor. By labeling vasopressin neurons in a rat brain, the researchers, led by Yasunobu Okada (SOKENDAI), were able to show that

vasopressin acts on the brain to maintain the size of vasopressin neurons. The group demonstrated that vasopressin was released into the brain when body fluid becomes more diluted. The vasopressin acts on neuronal cells to enable them to maintain their size as opposed to swelling, which is the usual reaction to diluted body fluid.

“It is a surprising result that the same type of the vasopressin receptor as the kidney exists in the brain and the vasopressin

works on it. It can be expected to clarify the condition of cerebral edema which swells along with the brain trauma or the cerebral infarction, and to develop its treatment method,” noted Okada.

Source: Sato K, Numata T, Saito T, Ueta Y, Okada Y. V2 receptor-mediated autocrine role of somatodendritic release of AVP in rat vasopressin neurons under hypo-osmotic conditions. *Sci. Signal.* 4(157), ra5 (2011).

Study to be carried out into why some diabetics escape complications associated with the disease

A new study looking at why some diabetic individuals never develop severe complications associated with the disease is to be carried out in Sweden. The Protective Genes in Diabetes and Longevity (PROLONG) study will compare a cohort of individuals who have had diabetes for over 30 years without complications with a group who developed severe complications from diabetes after having the condition for less than 15 years. It is hoped that information gleaned from these 'diabetic veterans' will help to inform management

and prevention of severe complications associated with diabetes.

The PROLONG study, which will act as a pilot study, is to be carried out in Skåne, Sweden. As Valeriya Lyssenko and Peter Nilsson (Lund University Diabetes Centre, Sweden), leads in the study, state the long-term plan will be to roll out the study to all hospitals in Sweden. Severe complications associated with diabetes include nephropathy, retinopathy, heart attacks and stroke. It is estimated that 70% of diabetics will develop some form of nephropathy and/or

retinopathy in their lifetime, and the risk of dying from heart disease is two-to-three-times higher among the diabetic population as compared with the non-diabetic population. The mechanisms associated with the increased risks of these complications in diabetes are not completely understood and the damage to blood vessels associated with long-term diabetes, described by Nilsson as "blood vessels and other organs of the body becoming sugar coated and stiff", can currently neither be treated or prevented. Despite this, there are a significant proportion of diabetic individuals who do not develop any severe complications associated with their diabetes. These 'resistant' individuals are of great interest to Lyssenko and his team as he mentions "The majority of diabetics will over time develop severe or fatal complications, but 10–15% never do. They are the ones we are interested in in the PROLONG study."

"Severe complications associated with diabetes include nephropathy, retinopathy, heart attacks and stroke."

As Lyssenko notes "If we can identify factors protecting these veterans from devastating complications, then it might be possible to develop drugs that can do the same thing."

Source: Lund University, via AlphaGalileo:
www.alphagalileo.org

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Study calls for increased screening for hypothyroidism in older adults

A UK-based study has suggested that older people in the UK should be screened for thyroid dysfunction. The authors of the study suggested that as many as 100,000 older people in the UK who could benefit from treatment for thyroid problems are not currently being treated.

"...routine screening for thyroid dysfunction in older adults could improve the quality of life of as many as 1% of the population..."

Symptoms of hypothyroidism include depression, tiredness, forgetfulness and weight gain, treatment of the condition with thyroxine can significantly improve the quality of life of sufferers. The study carried out at the Wolfson Institute of Preventive Medicine (London, UK) assessed a group of 4365 women over 50 years of age and men over 65 years of age. The cohort consisted of people attending a general practitioner for a health assessment. Thyroid function was assessed through a thyroid-stimulating hormone measurement. Within the cohort, the authors found that 8% of the sample had an under-active thyroid, judged as thyroid-stimulating hormone levels above 4.0 mU/l. These

individuals were offered the opportunity to be entered into a randomized double-blind crossover trial of thyroxine and placebo. A total of 56 individuals were treated with thyroxine and approximately a quarter of these patients benefited from treatment, with the main symptoms relieved being tiredness and forgetfulness. If these results are extrapolated to the whole population, the authors suggest that 100,000 people within the age group studied would benefit from treatment.

Nicholas Ward, lead author of the study notes that: "It is rare to be able to find chronic diseases in adults that can be identified by screening, but this research shows that screening adults for hypothyroidism would be worthwhile."

The authors suggest that routine screening for thyroid dysfunction in older adults could improve the quality of life of as many as 1% of the population and call for pilot screening programs for hypothyroidism to be rolled out across the UK.

Source: Abu-Helalah M, Law MR, Bestwick JP, Monson JP, Wald NJ. A randomized double-blind crossover trial to investigate the efficacy of screening for adult hypothyroidism. *J. Med. Screen.* 17, 164–169 (2010).

Could spending too much time in warm conditions be associated with obesity?

A new review paper written by researchers at University College London (UCL, UK) has suggested that increasing indoor temperatures during winter in the UK and USA, among other countries, may play a role in increasing obesity rates in developed countries. The paper calls for further research to verify this theory.

The authors observed that in the last two decades the expectations for thermal comfort at all times of the year have increased, resulting in people being less exposed to colder temperatures.

As Fiona Johnson (UCL) notes, “increased time spent indoors, widespread access to central heating and air conditioning, and increased expectations of thermal comfort all contribute to restricting the range of temperatures we experience in daily life and reduce the time our bodies spend under mild thermal stress – meaning we’re burning less energy. This could have an impact on energy balance and ultimately have an impact on bodyweight and obesity.”

The authors discuss two possible mechanisms by which the trend of reduced exposure to cold temperatures could impact weight management. First, there is less need for the body to expend energy staying warm and, second, the body’s ability to produce heat could be reduced due to loss of brown adipose tissue. In this new paper, the authors discuss recent research into brown adipose tissue that suggests that prolonged exposure to warm temperatures may result in the loss of brown adipose tissue. As the tissue is capable of burning energy to create heat, loss of the tissue has been linked to obesity. The authors add that “pathways linking cold exposure and adiposity have not been directly tested in humans. Research in naturalistic and experimental settings is needed to establish effects of changes in thermal exposures on weight, which may raise possibilities for novel public health strategies to address obesity.”

The authors of the paper hope that their article will spark interest into novel

ways to manage obesity, which is becoming a worldwide problem. As Johnson states, “research into the environmental drivers behind obesity, rather than the genetic ones, has tended to focus on diet and exercise – which are undoubtedly the major contributors. However, it is possible that other environmental factors, such as winter indoor temperatures, may also have a contributing role. This research

therefore raises the possibility for new public health strategies to address the obesity epidemic”.

Source: Johnson F, Mavroggiani A, Ucci M, Vidal-Puig A, Wardle J. Could increased time spent in a thermal comfort zone contribute to population increases in obesity? *Obesity Reviews* DOI: 10.1111/j.1467-789X.2010.00851.x (2010) (Epub ahead of print).

Study suggests that menopausal symptoms could be associated with a reduced risk of breast cancer

A group from the Fred Hutchinson Cancer Research Center (Seattle, WA, USA) has investigated a possible link between menopausal symptoms and risk of breast cancer in women. This is the first time a study into the potential link has been conducted.

It has previously been shown that women who experience menopausal symptoms such as hot flushes, insomnia and depression have lower estrogen levels than those who do not, as the authors of this study describe this observation could link to lower incidences of breast cancer among these women due to the role that hormones play in breast cancer. “Since menopausal symptoms occur as hormone levels fluctuate and drop, we hypothesized that women who experienced symptoms such as hot flushes and night sweats – particularly frequent and severe symptoms – might have a lower risk of breast cancer due to decreased estrogen levels,” commented Christopher Li.

In order to assess a possible link, the group led by Li used data from a population-based case-control study of 1437 post-menopausal women in the Seattle area, 988 of whom had been diagnosed with breast cancer, to look at associations between menopausal symptoms and

risks of different types of breast cancer. As the authors note, they then “calculated multivariate adjusted odds ratios using polytomous logistic regression and evaluated several potential effect modifiers.”

The results strikingly suggest that women who experience menopausal symptoms may have a 50% reduced risk of developing invasive ductal and invasive lobular carcinoma, the two most common forms of breast cancer. As Li notes, “in particular we found that women who experienced more intense hot flushes – the kind that woke them up at night – had a particularly low risk of breast cancer.” The authors also note that the reduced risk is independent of other risk factors of breast cancer such as obesity and use of hormone replacement therapy.

Li suggests that “if these findings are confirmed, they have the potential to improve our understanding of the causes of breast cancer and improve approaches to preventing this disease.”

Source: Huang Y, Malone KE, Cushing-Haugen KL, Daling JR, Li CI. Relationship between menopausal symptoms and risk of postmenopausal breast cancer. *Cancer Epidemiol. Biomarkers Prev.* 20(2), 379–388 (2011).