ENDOCRINOLOGY UPDATE

FALL 2016

In This Issue

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From the Division of Endocrinology and Metabolism

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Message from the Chief

Welcome to the Division of Endocrinology and Metabolism at the University of Pittsburgh. Please join us on our journey as we relentlessly pursue our overall mission to promote health and combat disease in endocrinology and metabolism through high-quality, cutting-edge clinical care, education, and research.

Please allow me to introduce myself as the new chief of the Division of the Endocrinology and Metabolism as of July 1, 2016. I have dedicated my life to achieving the above mission, and my greatest dream is to see a cure for obesity and diabetes in my lifetime. To achieve this goal, I have developed expertise in the field of obesity and its complications. I am board certified in Endocrinology, Obesity Medicine, and Clinical Lipidology. I received my medical doctorate from Cornell University Medical College, my internal medicine training from New York Presbyterian Hospital–Cornell Campus, and my endocrinology fellowship training from Beth Israel Deaconess Medical Center–Harvard Medical School and the Joslin Diabetes Center. Since joining the University of Pittsburgh in 2008, I have run a clinical practice focused on obesity, diabetes, lipid disorders, and adipose tissue disorders (i.e., lipodystrophies). I also have developed a complementary translational research program focusing on obesity and its complications. There is a tremendous need to combat these diseases, which have reached epidemic proportions, and are leading causes of morbidity and mortality worldwide.

However, our mission extends far beyond obesity and diabetes. Indeed, endocrinology is the study of how all cells and tissues in our bodies communicate with each other to maintain health. Given its fundamental role in the physiology and pathophysiology of virtually every organ system, the endocrine system is clearly highly relevant to all subspecialties of medicine. We are committed to working with our medical colleagues and community partners to improve prevention and treatment of disease. Such collaborative approaches are critical, now more than ever. Indeed, the world is experiencing an unprecedented evolution of the health care and biomedical research landscape. This transformational change is driven, in part, by rapid advances in technology, as well as escalating health care costs. These changes have led to the emergence of more value-driven and personalized approaches to medical care. However, many challenges persist in translating these advances into practice. Overcoming these challenges will increasingly rely on more multidisciplinary, collaborative approaches that are integrated across all core academic areas: clinical care, education, and research.

In the current and subsequent issues of this newsletter, we hope to highlight how the Division of Endocrinology and Metabolism at the University of Pittsburgh is facing these challenges and creating opportunities for improvement across each of the above core academic areas. In this issue, our neuroendocrine unit presents a case of familial pituitary adenoma, highlighting how genetic testing can improve detection and treatment of these tumors. In addition, this issue describes two key programs we have implemented to enhance community outreach and education through innovative models of care: 1) using a collaborative model of diabetes care to empower patients and the whole care team to improve diabetes outcomes, and 2) using telemedicine to provide diabetes care to rural communities. Finally, this issue shares a new, exciting research discovery of a unique obesity-risk variant that paradoxically protects against diabetes that may reveal novel insights into the prevention and treatment of diabetes.

I look forward to working with you to rise to the challenge of providing the best of tomorrow's endocrine care today.

Erin E. Kershaw, MD
Chief, Division of Endocrinology and Metabolism

Building Capacity for the Diabetes Epidemic — Empowering the Care Team

Linda Siminerio, RN, PhD

A Survey of Current Trends

Despite our progress, the number of Americans with diabetes mellitus (DM) and prediabetes continues to rise. More than 29 million Americans — about 9% of the population — have DM, and another 86 million have prediabetes.[1] One study projected the lifetime risk of a diabetes diagnosis for American adults to be 40%, meaning 2 out of every 5 American adults may be diagnosed if current trends continue.[2]

DM is a lifestyle disease that requires the person at risk for, or living with the disease, to make numerous daily decisions regarding food, activity, and medications. It also necessitates that the person with DM be proficient in a number of self-care skills, such as blood glucose monitoring (BGM), foot exams, and administering medications. People living with diabetes need ongoing support throughout the course of their disease for effective self-management.[3]

Diabetes educators, who are most often nurses, dietitians, and pharmacists, are trained in the skills necessary to support behavior change and provide direct assistance in helping patients to self-manage their condition. It has repeatedly been demonstrated that diabetes educators can improve HbA1c levels by as much as 7.6%.[4] The effectiveness of diabetes self-management education on HbA1c levels has been directly correlated to the amount of contact time spent between an educator and the patient. In addition, patients who receive self-management education are reported to have better quality of life, self-care, coping skills, and adherence, and fewer complications.[5] The take-home message: the more access a patient has to diabetes support staff, such as educators, the better.

Physicians report that they have limited time for patient visits, let alone providing diabetes education and ongoing self-management support.[6] Other health care providers can increase practice efficiency by taking on some of the duties (e.g., patient education, counseling, and follow-up) that require significant time investments.[7] Investigators and clinicians in the Division of Endocrinology and Metabolism have implemented and evaluated several health care delivery models, and have demonstrated the effectiveness of a team-based approach that relies on the specialty services of a diabetes educator.[7-9]

System-wide Initiatives at UPMC

UPMC has taken these messages seriously and has engaged diabetes educators in a variety of initiatives across the health system. Educators have been employed to serve as liaisons between community entities and to support patient self-management throughout the health system. Their roles have been expanded to serve as hub resources for hospital staff and patient education, provide health system staff diabetes training,[10] conduct therapeutic management with physician-approved protocols,[11] and facilitate long-term follow-up for complex, high-risk patients.

The following case studies illustrate the ongoing education and community-based support required for successfully operationalizing treatment plans for high-risk patients who require complex diabetes care.

Case Presentation

A 68-year-old female with type 2 diabetes, and a current HbA1c level of 15.2%, was referred for advanced treatment and a visit with a nurse educator. The patient was visibly upset and frustrated regarding her high HbA1c level, and admitted to having difficulty controlling her food intake. She also reported stress regarding limited finances and the cost of her insulin prescription. She recently started an antidepressant prescribed by her primary care provider (PCP). She reported taking Lantus (10 units) daily, and Humalog (8 units) insulin with her meals, but admitted that she had not been testing her blood glucose routinely for a variety of reasons. Recent BGs ranged from: AM 198-480 mg/dl; pre-lunch 246-374 mg/dl; pre-dinner 344-366 mg/dl. Based on these results, and according to the glycemic management protocol[11], the educator instructed the patient to continue to increase her Lantus dose for fasting BGs >130 mg/dl, up to a maximum dose of 40 units. If the dose reached 40 units, the educator would review records with the provider to consider prescribing an increase in the prandial Humalog doses.

The nurse educator reviewed DM basic information, including the importance of healthy eating, activity, monitoring, and adhering to her medication regimen. The patient was instructed on a 1,500 calorie consistent carbohydrate (CHO) meal plan (45 grams CHO/meal and 15 grams CHO for snack), and the basic principles of label reading and portion control. The patient complained of back and knee pain, thereby limiting exercise. A modified walking plan was discussed. The diabetes educator also was able to assist the patient in navigating options to cut prescription costs. The patient was encouraged to call with any questions and follow-up as needed. In collaboration with the patient, behavior goals were selected in which the patient agreed to work to limit CHOs to 45 grams per meal/15 grams per snack and continue to titrate Lantus insulin daily for fasting BG >130 mg/dl (up to max dose of 40 units). If her BG was <70 mg/dl, she was instructed to reduce Lantus by 4 units. She agreed to start walking 5 to 10 minutes, two times a week, and to call the educator in two weeks with her current readings (or with any questions).

At her next follow-up visit, the patient reported being more active and feels pleased that she has lost several pounds. The majority of her BG results were in the low 100 mg/dl range. Over three months, Lantus was increased to 32 units with prandial Humalog 8 units. From baseline to three months, her HbA1c was reduced from 15.2% to 8.1%.

Case Presentation

An 18-year-old female with type 2 diabetes, an HbA1c level of 9.7%, and a BMI of 32 was referred by the patient's PCP for evaluation. The patient had been prescribed Glipizide ER 5 mg daily and metformin 1000 mg BID. The patient has attention deficit disorder and mild autism. She participates in a community counseling behavioral health program. She attended the visit with her mother, who is concerned about her daughter's limitations in performing diabetes self-care. For example, the patient was unable to perform BG monitoring. Without BG results, determining appropriate therapy was a challenge. In addition, both the patient and her mother are overweight and have problems controlling their eating. They have never received any type of diabetes self-care instruction. While teaching the patient basic BG testing skills, the nurse educator also identified the mother's low literacy challenges. Over several visits, she was able to successfully instruct both the patient and her mother on basic healthy eating choices. The patient was trained to perform her own blood BG and now tests with minimal cues. The nurse educator communicated the plan to the patient's PCP, the practice-based care manager, the community behavioral health team, and the insurer-based health coach for reinforcement and long-term support. After the three-month follow-up visit with the patient's PCP, the practice-based care manager reported that the patient is walking daily, making healthier food choices, independently checking BG BID, and has lost 9 pounds. Her HbA1c was 7.9%.

Conclusion

One of the most promising concepts in diabetes management is team-based care.[12] Diabetes educators, nurses, dietitians, pharmacists, care managers, health coaches, and community health workers, among others, are poised to coordinate care, offload provider workloads, and support patients in behavior change. Our diabetes team continues to expand the roles of all disciplines to their highest level of practice, to better coordinate services, and to provide the evidence of these advancements through continuous quality improvement and research. Currently, through an award from the NIDDK, we are examining care delivery models that integrate diabetes education services into practice. As the diabetes epidemic continues, more strategies to help patients meet their targets and lower their risk of diabetes complications are needed. The provision of team care and self-management support are critical in overcoming the barriers associated with the complexities of diabetes care.

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Familial Isolated Pituitary Adenomas

Pooja Manroa, MD, and Sue Challinor, MD

Case Presentation

A 25-year-old man with a history of acromegaly due to a growth-hormone (GH) producing pituitary macroadenoma was referred for management of persistent disease after recent transphenoidal pituitary surgery at an outside hospital. Prior to the operation, he reported that over a span of two years, he grew taller than his identical twin brother and started experiencing gradually worsening occipital headaches. He noticed gradual loss of vision in the temporal aspect of the left eye, particularly when driving. He sought help when he experienced a more acute loss of vision in both eyes, with proptosis and periorbital swelling. He also recalled that he snored, had low libido, and erectile dysfunction. His shoe size had increased by three sizes. Family history revealed that his paternal grandfather had a history of a nonfunctioning pituitary adenoma, causing vision loss, and had undergone surgical resection in his 60s. He had a monozygotic twin without any medical conditions. On exam, he showed signs of GH excess, such as frontal bossing, prognathism, enlarged tongue, and acral hypertrophy of his hands and feet. A brain MRI revealed a large sellar mass with suprasellar extension (Figure 1), and lab work revealed elevated GH and IGF-1 levels.

> The majority of pituitary adenomas in adults are sporadic and occur in patients with no family history of pituitary disease. However, up to 5% of pituitary adenomas are caused by genetic mutations that are associated with familial syndromes.

After his first surgery, the symptoms of headache and snoring resolved, and soft tissue swelling and vision loss improved. However, his IGF-1 and GH levels remained persistently elevated. Postoperative MRI showed persistent adenoma in the left cavernous sinus (see Figure 2 on Page 5). He also failed to respond to octreotide and pegvisomant therapy. He was then referred to UPMC for consideration of either gamma knife stereotactic surgery or repeat pituitary surgery.

He underwent a second pituitary surgery by Paul Gardner, MD, using the Endoscopic Endonasal Approach (EEA). Final pathology revealed a pituitary adenoma with weakly positive staining for growth hormone and Ki67 index of 1% to 3%. His postoperative course was uneventful, with the exception of transient diabetes insipidus, which resolved quickly.

Prior to the second operation, the patient's GH levels were 13.5 (normal range 0.01-3.0 ng/mL). His IGF-1 was 917 (normal range 63 to 373 ng/mL). Initial postoperative levels were 0.6 and 359, respectively. He was referred to us because of slightly abnormal IGF-1 levels — 391 ng/mL during follow-up. On latest MRI imaging, no residual tumor was noted (Figure 3 on Page 5). An oral glucose tolerance test confirmed biochemical persistence of his disease. We recommended medical therapy. In view of his family history of pituitary adenoma and his young age of presentation, we also referred our patient for genetic testing.

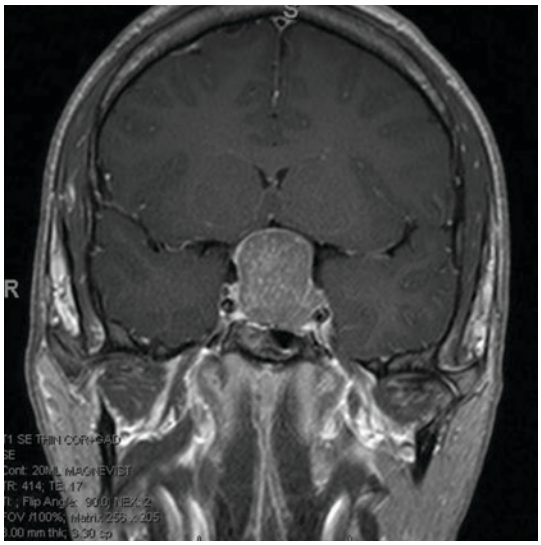

FIGURE 1. MRI at time of diagnosis.

Discussion

The majority of pituitary adenomas in adults are sporadic and occur in patients with no family history of pituitary disease. However, up to 5% of pituitary adenomas are caused by genetic mutations that are associated with familial syndromes. Some of the familial pituitary adenoma syndromes include multiple endocrine neoplasia type 1 (MEN type 1), Carney complex, McCune-Albright syndrome, and familial isolated pituitary adenoma (FIPA). The most frequent inherited conditions are FIPA and MEN type 1, each accounting for 2% of pituitary adenomas in general.[1]

FIPA is an autosomal dominant condition with incomplete penetrance resulting in the development of pituitary tumors, without any of the endocrine abnormalities that are seen in other familial pituitary adenoma syndromes.[2] FIPA is characterized by two or more members of a family with pituitary adenomas. Mutations in the aryl hydrocarbon receptor interacting protein (AIP) gene, a tumor suppressor gene located at 11q13, is implicated in 20% of FIPA cases.[3] The causative gene for the rest and, therefore, the majority of FIPA families, is currently unknown.

FIPA families are homogenous (i.e., all affected family members have the same type of tumor) in 60% of cases and the rest are heterogenous (i.e., family members have different types of tumor).[4] FIPA patients have a higher prevalence of GH-producing adenomas than the general population (35% versus 13% to 15%).[4] FIPA patients with positive AIP gene mutations are predominantly males (61%), have earlier disease onset by an average of four years, and have predominantly macroadenomas (88%) with extrasellar invasion at diagnosis. 78% of the patients with this mutation are diagnosed at an age younger than 30 years, and 36% present with gigantism.[4,5] Other characteristics associated with this mutation are rapid tumor growth, a higher frequency of apoplexy, poor response to somatostatin analogues, and pegvisomant, and therefore, greater use of radiotherapy.[4,5,6]

Current recommendations suggest referring individuals with the following characteristics for genetic testing for the AIP mutation:

- Those with a history of two or more members of a family with pituitary adenomas without any clinical features of other inherited pituitary adenoma syndromes
- Those with a pituitary macroadenoma diagnosed before the age of 30 years
- Those with any pituitary adenoma diagnosed before the age of 18 years[7]

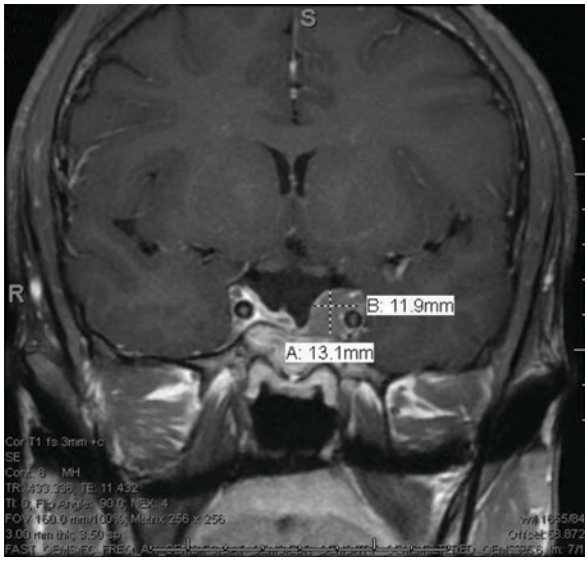

FIGURE 2. MRI after the first operation at the outside hospital, showing residual tumor encasing the left internal carotid artery by approximately 180 degrees.

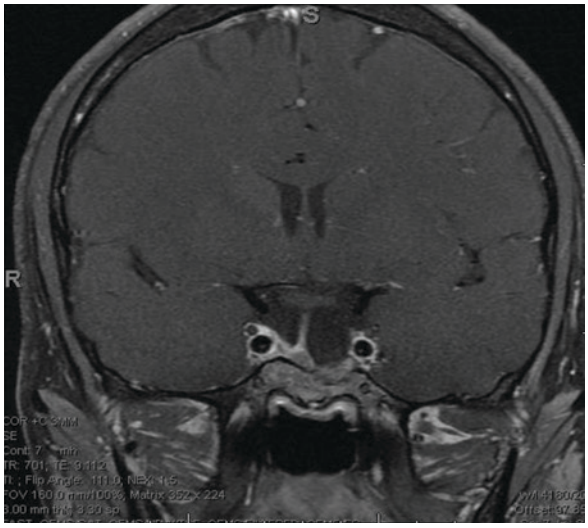

FIGURE 3. MRI after the second surgery by EEA.

Current data suggests that 11% to 20% of these patients will harbor an AIP mutation.[8] Our patient fulfilled two of these criteria and, therefore, was referred for genetic testing. He received genetic counseling but has not yet had the testing performed. Mutation testing includes sequencing (which detects 90% of known mutations) of the exons and exon–intron junctions, and testing for large deletions/duplications (which detects 10% of known mutations).[7] Recommendations for surveillance of family members of AIP mutation positive probands include referral for

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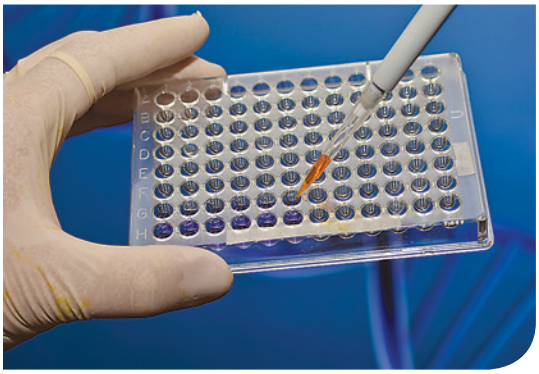
Familial Isolated Pituitary Adenomas (Continued from Page 5)

genetic testing for all members older than age 4. If found positive, patients should be referred to a pediatric or adult endocrinologist. Evaluation should include biochemical and radiological assessment of pituitary gland function, in addition to a detailed history and physical examination, which should be continued serially until age 30 and then at a decreased frequency until age 50.[7,9] Genetic screening allows early detection and treatment of those with adenomas, improving the prognosis of these tumors.

Conclusion

In summary, most pituitary adenomas in adults are sporadic. Providers should consider the possibility of FIPA in patients with a family history of pituitary adenomas and without clinical features of the other hereditary pituitary adenoma syndromes like MEN-1, Carney complex, or McCune-Albright syndrome. In addition, genetic testing should be considered for patients with any pituitary adenoma diagnosed ≤18 years old or a pituitary macroadenoma (>10 mm) diagnosed before the age of 30, even without a family history. The AIP gene mutation is positive in 20% of FIPA cases, and is associated with earlier onset of pituitary adenomas and increased tumor invasiveness. FIPA syndrome also is associated with a higher frequency of acromegaly than is found with sporadic pituitary adenomas. In addition, the GH-secreting pituitary adenomas in FIPA have a greater resistance to medical therapy. Earlier diagnosis as a consequence of serial screening in families with FIPA should improve surgical cure rates, which are generally more favorable for smaller adenomas. Therefore, knowledge of mutation status and recognition of a patient with characteristics of FIPA have important prognostic and therapeutic implications. These patients should be referred to institutions with access to genetic counselors and pediatric or adult endocrinologists who specialize in pituitary disorders.



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Telemedicine: Serving Rural Communities With State-of-the-Art Diabetes Care

Michelle Griffith, MD

Endocrinologists remain in relatively short supply nationwide, with a current workforce of approximately 1,500 fewer adult endocrinologists than is needed across the United States.[1] The gap between needed and available endocrine specialists is expected to continue to grow[1] even as diabetes remains highly prevalent, affecting 9.3% of the population[2] and driving 46% of endocrinology practice nationwide.[1]

In addition to the overall shortage, access to endocrinologists varies significantly, with access in rural areas lagging behind more urban areas.[3] The University of Pittsburgh Division of Endocrinology and Metabolism has been expanding the reach of expert diabetes care into rural areas with telemedicine since 2013. In these service locations, access to an endocrinologist would otherwise require patients to travel a significant distance. Working with diabetes educators based at two rural hospital sites in our health care system, patients have video visits with an endocrinologist. When the patient arrives for their visit, the patient's blood glucose (BG) meter and/or insulin pump is downloaded, and the report is scanned into the electronic medical record for immediate review by the endocrinologist. The patient meets and talks with the endocrinologist via a secure video visit with audio and video real-time connection. The diabetes educator remains at the patient's side during the interview. After interviewing the patient and reviewing the medical record and BG data, the endocrinologist gives the patient recommendations for care and issues any necessary prescriptions. Follow-up diabetes self-management education is provided by the partner educator, and a consult report is prepared to send to the patient's local primary care doctor.

Investigators at the University of Pittsburgh have previously demonstrated improvement in diabetes clinical outcomes, including improvement in hemoglobin A1c (HbA1c), using this team-based approach delivered via telemedicine. Our clinical service follows this evidence-based care model: the Telemedicine for Reach, Education, Access, and Treatment (TREAT) intervention.[4-6] Along with improvement in HbA1c, this care model led to improvements in patient self-care, empowerment, reduced diabetes distress, and high provider/patient satisfaction. The physician and nurse educator are both integral parts of the TREAT care team, and previous studies have shown that patients perceived the importance of both.[6] The TREAT model also provides unique opportunities for the patient, educator, and endocrinologist to share information and collaborate to set goals.

Importantly, though the endocrinologist and patient are meeting via telemedicine, we are able to establish relationships that are beneficial to the patient and rewarding for the endocrinologist and educator. When indicated, we have transitioned patients to more complex therapies and tools, such as U-500 insulin, insulin pumps, and continuous glucose monitors. By expanding the geographic reach of expert diabetes care using the TREAT model, we are able to provide advanced diabetes care to a rural population that would otherwise lack access to this care. Several insurers now support telemedicine services in our region, making this a billable service. Nationally, advocacy efforts to remove barriers to telemedicine expansion continue.

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Discovery of a "Thrifty" Genetic Variant in Samoans That Promotes Obesity but Protects Against Diabetes

Erin E. Kershaw, MD

Introduction

Obesity is a global public health problem, and yet the causes remain poorly understood. The severity and rates of obesity in Pacific Islanders are among the highest in the world. Thus, this unique population may hold critical clues to understanding the complex puzzle of obesity. Erin E. Kershaw, MD, chief of the Division of Endocrinology and Metabolism at the University of Pittsburgh, recently joined forces with an outstanding multi-institutional, interdisciplinary team from the University of Pittsburgh (RL Minster, DE Weeks, Z Urban, CT Su, J Lin, OD Buhule, EE Kershaw), Yale University (N Hawley), University of Cincinnati (G Sun, H Cheng, R Deka), Brown University (ST McGarvey), and the Government of Samoa and American Samoa Government (MS Reupena, S Viali, J Tuitele, T Naseri) to understand this mystery. In doing so, they discovered a novel "thrifty" genetic variant in Samoans that promotes obesity but paradoxically protects against diabetes. Their results were recently published in the September issue of the high-impact journal *Nature Genetics*.[1]

Discovering a New Genetic Variant Linked to Obesity

To identify this new genetic factor's contribution to obesity risk, the team conducted a genome-wide association study (GWAS) of obesity-associated traits in Pacific Islanders from Samoa. The GWAS identified a genetic marker that was strongly associated with body mass index (BMI), the most commonly used anthropometric measure of obesity. Further analysis narrowed this signal down to a single missense mutation (that changed an arginine to a glutamine at position 457) in a hitherto poorly characterized gene known as *CREBRF* (CREB regulatory factor) on human chromosome 5 (see Figure 1 on Page 9). Although this missense variant *(CREBRF* pArg457Gln) is relatively rare in most populations, it is extremely common in Samoans (affecting ~45% of the population). Furthermore, it has an effect size larger than any other known common obesity-risk variant (increasing BMI by 1.36-1.45 kg/m^2 per copy of the risk-associated allele). This translates to an approximately 4 kg to 8 kg

increase in body weight (Figure 2a) or a 1.3 to 1.7-fold increase in risk of obesity (Figure 2b) for Samoans carrying one or two copies of the missense variant, respectively. In the field of obesity risk, this is a very large effect that has huge potential for influencing disease risk.

This New Genetic Variant Paradoxically Protects Against Diabetes

Obesity is well-known to be associated with increased risk of multiple additional metabolic abnormalities, including type 2 diabetes. Surprisingly, even though this missense variant increases the risk of obesity by 1.3-fold per copy, it is associated with 1.65 mg/dl lower blood glucose and a 1.6-fold lower risk of diabetes per copy. Similarly, the missense variant was not associated with other well-known complications of obesity, such as dyslipidemia. Together, these data suggest that the missense variant does not promote, and may even protect against, obesity-associated comorbidities. Additional studies will be required to confirm these findings and directly test this hypothesis, but these results nonetheless suggest that this missense variant has the potential for revealing new insights into the pathogenesis of both obesity and diabetes.

What Does This Gene Do and How Does the Variant Influence Obesity and Diabetes Risk?

Virtually nothing is known about this gene. A recent report examining the fruit fly homolog of this gene suggests that it may be involved in translating environmental and/or cellular cues into cellular responses that make the cell better able to adapt to nutritional stress. The team tested this hypothesis in a fat cell model and discovered that the missense variant was able to: 1) increase the development of fat precursor cells in fat cells, 2) increase the ability of fat cells to store more fat, and 3) decrease the ability of fat cells to burn fat. These data suggest that the missense variant may influence obesity and diabetes risk, in part, by influencing fat metabolism and storage. Additional studies are required to assess other potential mechanisms.

Is This a "Thrifty" Genetic Variant?

The "thrifty genotype hypothesis" for obesity has been around for many years.[2] This hypothesis states that one or more genes that favor energy conservation (or "thriftiness") in times of energy scarcity may have been selected over time through the process of natural selection. In the context of modern energy abundance, however, these same gene or genes may instead lead to adverse medical consequences, such as obesity, diabetes, and cardiovascular disease. Many other possible explanations for disparities in metabolic health across populations over time have been proposed[3], including genetic drift ("drifty hypothesis"), early environmental insults "thrifty phenotype hypothesis") and epigenetic inheritance of environmental influences ("epigenetic hypothesis"). Thus, the "thrifty gene hypothesis" remains controversial and has yet to be proven. To test the ("thrifty gene hypothesis"), the

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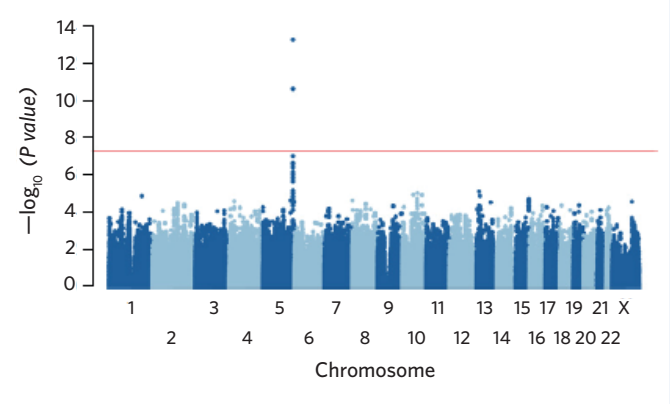

FIGURE 1. "Manhattan plot" of the genome-wide association scan for association with body mass index (BMI). The red line corresponds to a P value of 5 x 10-8. The graph demonstrates a strong signal on chromosome 5 corresponding to the location of *CREBRF* gene.

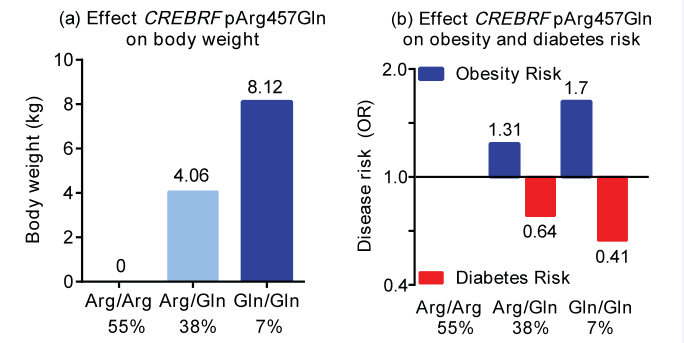

FIGURE 2. Effect of the *CREBRF* pArg457Gln variant on body weight (a) and disease risk (b). Graph (a) shows the effect of the zero (Arg/Arg, 55% of the population), one (Arg/Gln, 38% of the population), and two (Gln/Gln, 7% of the population) copies of the missense variant on body weight in kg. Graph (b) shows the effect of zero, one, and two copies of the missense variant on overall obesity and diabetes risk (expressed as an odds ratio, OR).

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team looked for "genetic signatures" of selection surrounding the *CREBRF* pArg457Gln variant. In doing so, they found evidence for selection in the genetic area surrounding this missense variant. These data support the "thrifty gene hypothesis" and suggest that the *CREBRF* pArg457Gln variant may be the first "thrifty variant" to be identified.

Summary

Clearly, this discovery has the potential to have a profound impact on the prevention and treatment of obesity and its complications, including type 2 diabetes. Not surprisingly then, this report received broad Internet and media coverage (see "In the News" below). However, it is important to note that many questions remain unanswered. For instance, how precisely does this missense variant influence energy homeostasis at the cellular and whole body level, and what tissues are most important for mediating its effects? Does this missense variant interact with other genes and/or environmental factors to influence disease phenotypes? Does this missense variant influence disease phenotypes other than obesity and diabetes? Can this missense variant be used to predict or diagnose disease, or perhaps more importantly, can it be targeted for pharmacological intervention? The answers to these questions are urgently needed to translate this important discovery into prevention and treatment for the millions of people worldwide who suffer from obesity and diabetes.

Take-home Points

- A novel genetic missense mutation has been discovered in Samoans that increases the risk of obesity more than any other known common obesity-risk variant.
- This genetic missense variant paradoxically reduces the risk of diabetes.
- There is genetic evidence of natural selection of this variant, thereby supporting the "thrifty gene hypothesis."

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Commentaries

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New Arrivals

The Division of Endocrinology and Metabolism welcomes five new clinical endocrinologists.

Esra Karslioglu French, MD

Clinical Assistant Professor

Dr. Karslioglu French received her medical degree from Hacettepe University, Turkey. She completed her residency in internal medicine and her fellowship in endocrinology at UPMC.

Pooja Manroa, MD

Clinical Assistant Professor

Dr. Manroa received her medical degree from Topiwala National Medical College, India. She then completed her residency in internal medicine at the Cleveland Clinic and her fellowship in endocrinology at UPMC.

Elena Morariu, MD

Clinical Assistant Professor

Dr. Morariu received her medical degree from the University of Pittsburgh School of Medicine. She then completed her residency in internal medicine and her fellowship in endocrinology at UPMC.

Alexandria Atuahene Opata, MD

Clinical Assistant Professor

Dr. Opata received her medical degree from the University of Medicine and Dentistry of New Jersey-New Jersey Medical School. She then completed her residency in internal medicine at North Shore–Long Island Jewish Health System followed by her fellowship in endocrinology, diabetes, and bone disease at the Icahn School of Medicine at Mount Sinai Hospital, New York.

Yunjiao (Joy) Wang, MD

Clinical Assistant Professor

Dr. Wang received her medical degree from the University of Virginia School of Medicine. She completed her residency in internal medicine, and her fellowship in Endocrinology at the University of Colorado.

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