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Opening Remarks

Atul Butte, MD, PhD
Inaugural Director, UCSF Institute for Computational Health Sciences

Thanks to an incredible planning team!

- **Ariel Deardorff**, Data Services Librarian, UCSF Library
- **Sharat Israni**, Executive Director, UCSF Institute for Computational Health Sciences
- **Rick Larsen**, Director Academic Research Systems
- **Dana Ludwig**, Research Database Architect, Enterprise Information and Analytics
- **Angela Rizk-Jackson**, Director of Operations, UCSF Institute for Computational Health Sciences
- **Rhona Snyman**, Chief Strategy Officer, UCSF CDHI
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- **Leslie Yuan**, Chief Information Officer, UCSF Clinical and Translational Science Institute

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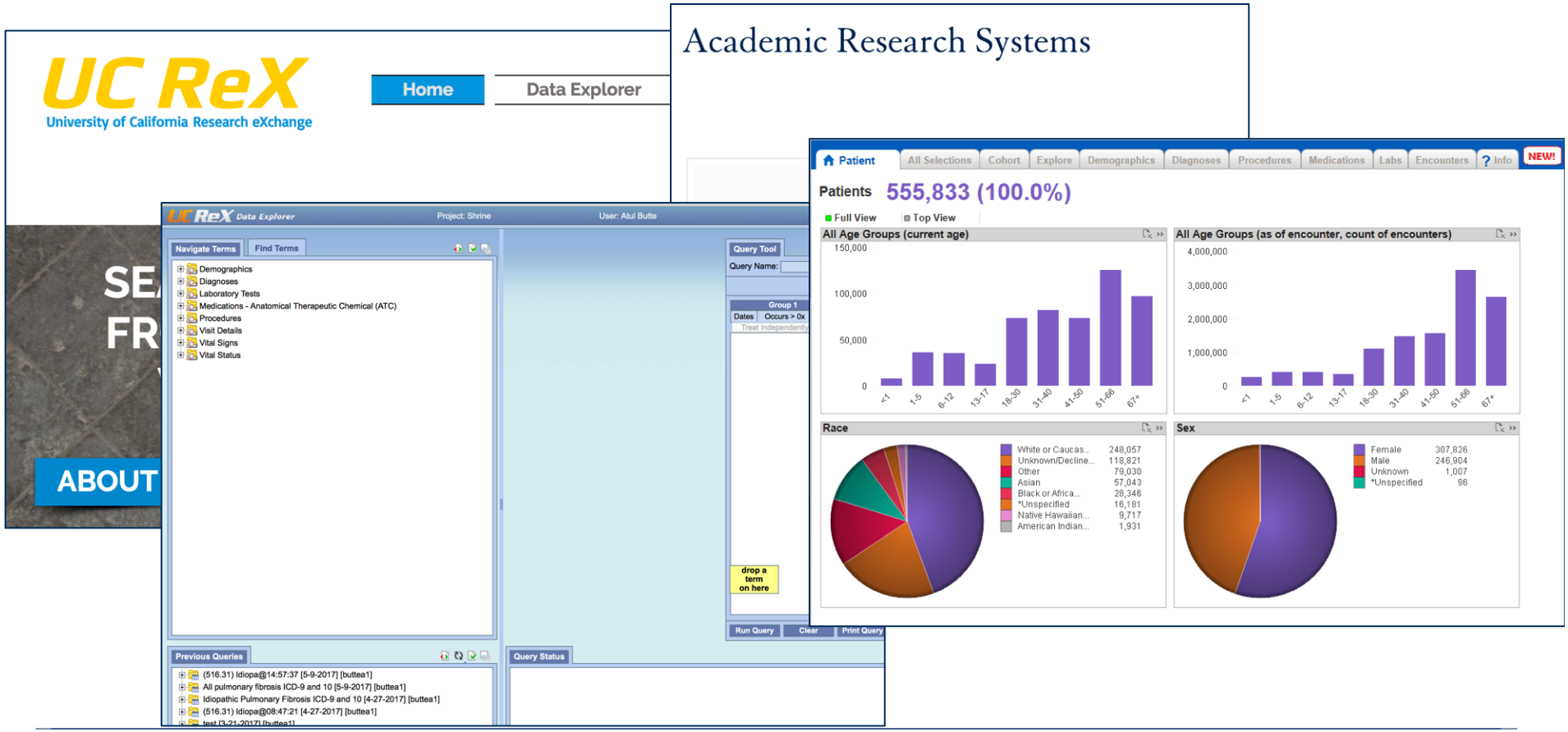
We are incredibly lucky to have what we have!



UCSF

The clinician of the future will use EHR data…

Evidence-Based Medicine in the EMR Era

Jennifer Frankovich, M.D., Christopher A. Longhurst, M.D., and Scott M. Sutherland, M.D.

culture of U.S. health care, but only if the federal government, as the nation's largest health care payer, demonstrates that it is serious about improving patient safety.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

From the Department of Health Policy and Management, Harvard School of Public

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Evidence-Based Medicine in the EMR Era

Jennifer Frankovich, M.D., Christopher A. Longhurst, M.D., and Scott M. Sutherland, M.D.

Many physicians take great pride in the practice of evidence-based medicine. Modern medical education emphasizes the value of the randomized, controlled trial, and we learn early on not to rely on anecdotal evidence. But the application of such superior evidence, however admirable the ambition, can be constrained by trials' strict inclusion and exclusion criteria — or the complete absence of a relevant trial. For those of us practicing pediatric medicine, this reality is all too familiar. In such situations, we are used to relying on evidence at Levels III through V — expert opinion — or resorting to anecdotal evidence. What should we do, though, when there aren't even meager data available and we don't have a single anecdote on which to draw?

We recently found ourselves in such a situation as we admitted to our service a 13-year-old girl with systemic lupus erythematosus (SLE). Our patient's presentation was complicated by nephrotic-range proteinuria, antiphospholipid antibodies, and pancreatitis. Although anticoagulation is not standard practice for children with SLE even when they're critically ill, these additional factors put our patient at potential risk for thrombosis, and we considered anticoagulation. However, we were unable to find studies pertaining to anticoagulation in our patient's situation and were therefore reluctant to pursue that course, given the risk of bleeding. A survey of our pediatric rheumatology colleagues — a review of our collective Level V evidence, so to speak — was equally fruitless and failed to produce a consensus.

Without clear evidence to guide us and needing to make a decision swiftly, we turned to a new approach, using the data captured in our institution's electronic medical record (EMR) and an innovative research data warehouse. The platform, called the Stanford Translational Research Integrated Database Environment (STRIDE), acquires and stores all patient data contained in the EMR at our hospital and provides immediate advanced text searching capability.[1] Thro... could rapidly r... SLE cohort that ... patients with ... clinicians in ou... October 2004 a... "electronic coho... created for use ... plications assoc... ric SLE and exi... col approved by ... review board.

Of the 98 pa... atric lupus coho... veloped thromb... in the EMR, wh... ly ill. The prev... among patients ... tent nephrotic- ... and pancreatit... compared with ... lupus who did ... risk factors, the ... sis was 14.7 (9... terval [CI], 3.3 ... tients with pe... and 11.8 (95%... among those with pancreatitis. This automated cohort review was conducted in less than 4 hours by a single clinician. On the basis of this real-time, informatics-

Results of Electronic Search of Patient Medical Records (for a Cohort of 98 Pediatric Patients with Lupus) Focused on Risk Factors for Thrombosis Relevant to Our 13-Year-Old Patient with Systemic Lupus Erythematosus.*

Outcome or Risk Factor	Keywords Used to Conduct Expedited Electronic Search	Prevalence of Thrombosis	Relative Risk (95% CI)
		no./total no (%)	
Outcome — thrombosis	"Thrombus," "Thrombosis," "Blood clot"	10/98 (10)	Not applicable
Thrombosis risk factor			
Heavy proteinuria (>2.5 g per deciliter)			
Present at any time	"Nephrosis," "Nephrotic," "Proteinuria"	8/36 (22)	7.8 (1.7–50)
Present >60 days	"Urine protein"	7/23 (30)	14.7 (3.3–96)
Pancreatitis	"Pancreatitis," "Lipase"	5/8 (63)	11.8 (3.8–27)
Antiphospholipid antibodies	"Aspirin"	6/51 (12)	1.0 (0.3–3.7)

used to guide real-time clinical decisions. The rapid electronic chart review and analysis were not only feasible, but also more helpful and accurate than physi-

to her anticoagulation; truthfully, though, we may never really know. We will, however, know that we made the decision on the basis of the best data available

diagnosis of pediatric hypertension — an example of a new era of clinical research enabled by electronic medical records. AMIA Annu Symp Proc 2007;October 11:966.
4. Halevy A, Norvig P, Pereira F. The Unreasonable Effectiveness of Data. IEEE Intelli-

The basic researcher of the future will use EHR data…

Systematic comparison of phenome-wide association study of electronic medical record data and genome-wide association study data

Systematic comparison of phenome-wide association study of electronic medical record data and genome-wide association study data

Joshua C Denny[1,2], Lisa Bastarache[2], Marylyn D Ritchie[3], Robert J Carroll[2], Raquel Zink
Julie R Field[4], Jill M Pulley[4,5], Andrea H Ramirez[1], Erica Bowton[4], Melissa A Basford[4], D
Peggy L Peissig[7], Abel N Kho[8], Jennifer A Pacheco[9], Luke V Rasmussen[10], David R Cross
Jyotishman Pathak[13], Suzette J Bielinski[14], Sarah A Pendergrass[3], Hua Xu[15], Lucia A Hin
Rongling Li[16], Teri A Manolio[16], Christopher G Chute[13], Rex L Chisholm[17], Eric B Larso
Murray H Brilliant[18], Catherine A McCarty[19], Iftikhar J Kullo[20], Jonathan L Haines[21], Da
Daniel R Masys[22] & Dan M Roden[1,23]

Candidate gene and genome-wide association studies (GWAS) have identified genetic variants that modulate risk for human disease; many of these associations require further study to replicate the results. Here we report the first large-scale application of the phenome-wide association study (PheWAS) paradigm within electronic medical records (EMRs), an unbiased approach to replication and discovery that interrogates relationships between targeted genotypes and multiple phenotypes. We scanned for associations between 3,144 single-nucleotide polymorphisms (previously implicated by GWAS as mediators of human traits) and 1,358 EMR-derived phenotypes in 13,835 individuals of European ancestry. This PheWAS replicated 66% (51/77) of sufficiently powered prior GWAS associations and revealed 63 potentially pleiotropic associations with $P < 4.6 \times 10^{-6}$ (false discovery rate < 0.1); the strongest of these novel associations were replicated in an independent cohort ($n = 7,406$). These findings validate PheWAS as a tool to allow unbiased interrogation across multiple phenotypes in EMR-based cohorts and to enhance analysis of the genomic basis of human disease.

In recent years, GWAS have provided a powerful systematic method to investigate the impact of common genomic variations on human pathophysiology. Since 2005, more than 1,500 GWAS have identified genomic variants associated with nearly 250 diseases and traits[1];

large number of single variant–phenot
serendipitous identification of single
diseases, or pleiotropy. Notable examp
which were associated initially with ea
subsequently with intracranial aneurys
rysms[3]; variants in the human leukoc
IL23R, which were associated initially
ease[4] and subsequently with a variety o
and *PTPN22* R620W, which was asso
of Crohn's disease and subsequently
toid arthritis and other autoimmune
of the NHGRI catalog noted pleiotrop
single-nucleotide polymorphisms (SN
associations in the catalog[8].

An alternative and complementary
phenotype associations and to detect p
PheWAS, associations between a spec
range of physiological and/or clinical
be explored either by using algorith
analyzing data collected in observatio
small-scale EMR studies have provided
the EMR-based PheWAS to replicate i
associations and to uncover novel
whether EMR data or PheWAS meth
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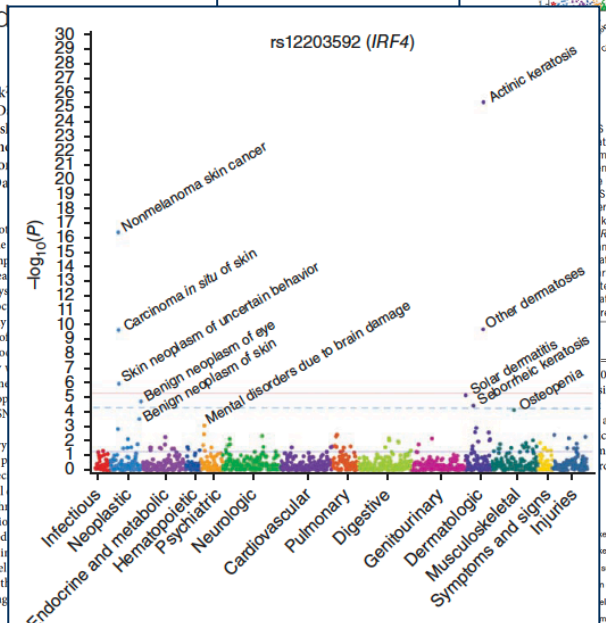
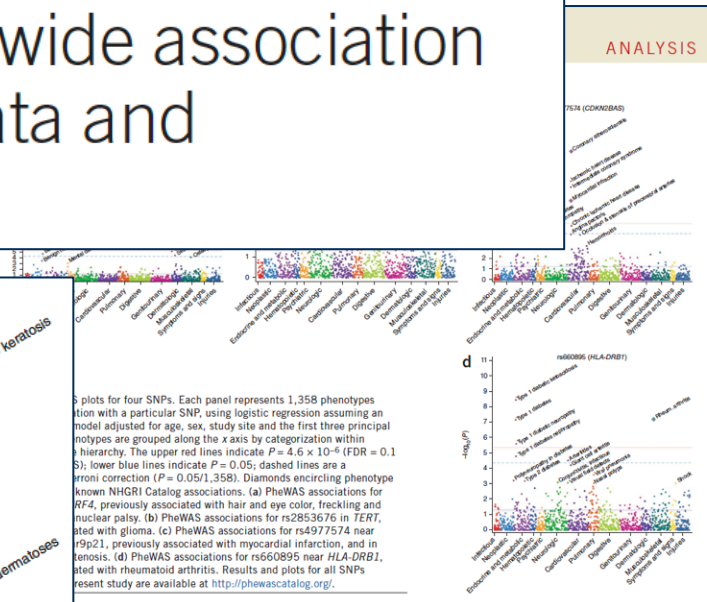
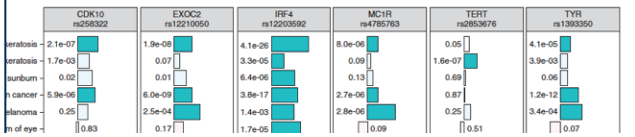




plots for four SNPs. Each panel represents 1,358 phenotypes
tion with a particular SNP, using logistic regression assuming an
model adjusted for age, sex, study site and the first three principal
notypes are grouped along the *x* axis by categorization within
hierarchy. The upper red lines indicate $P = 4.6 \times 10^{-6}$ (FDR = 0.1
S); lower blue lines indicate $P = 0.05$; dashed lines are a
rroni correction ($P = 0.05/1,358$). Diamonds encircling phenotype
known NHGRI Catalog associations. (**a**) PheWAS associations for
RF4, previously associated with hair and eye color, freckling and
nuclear palsy. (**b**) PheWAS associations for rs2853676 in *TERT*,
ated with glioma. (**c**) PheWAS associations for rs4977574 near
r9p21, previously associated with myocardial infarction, and in
tenosis. (**d**) PheWAS associations for rs660895 near *HLA-DRB1*,
ated with rheumatoid arthritis. Results and plots for all SNPs
resent study are available at http://phewascatalog.org/.

$= 1 \times 10^{-12}$), acute myocardial infarction (OR =
0^{-8}) and abdominal aortic aneurysm (OR = 1.29,
istent with prior publications[3], but also with other
"vascular" phenotypes such as unstable angina,
and hemorrhoids. Associations with hemorrhoids,
c aneurysms and carotid stenosis all persisted when
odel was adjusted for coronary atherosclerosis or
rction as a comorbidity.

Our study replicated the association between rheumatoid arthritis and rs660895 near *HLA-DRB1* (**Fig. 3d**; OR = 1.56, $P = 6.7 \times 10^{-8}$). This SNP was also strongly associated with type 1 diabetes (OR = 1.44, $P = 7.1 \times 10^{-8}$) and potentially associated with inflammatory arthritides (OR = 1.64, $P = 3.1 \times 10^{-5}$), a parent phenotype of giant cell arteritis (OR = 1.94, $P = 6.3 \times 10^{-5}$). Both of these associations persisted when adjusting for rheumatoid arthritis ($P = 1.8 \times 10^{-7}$ for type 1 diabetes and $P = 2.3 \times 10^{-5}$ for inflammatory arthritides).

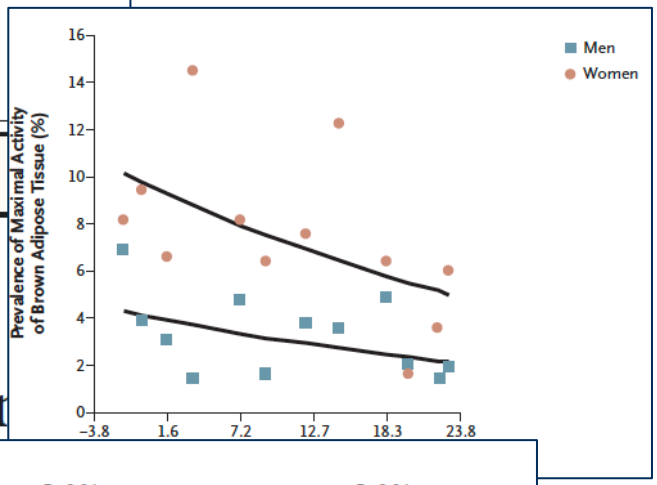


The clinical researcher of the future will use EHR data…

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Identification and Importance of Brown Adipose Tissue in Adult Human



and had maximal standardized uptake values of ^{18}F-FDG of at least 2.0 g per milliliter, indicating high metabolic activity. Clinical indexes were recorded and compared with those of date-matched controls. Immunostaining for UCP1 was performed on biopsy specimens from the neck and supraclavicular regions in patients undergoing surgery.

betes Center, 1 Joslin Pl., Boston, MA 02215, or at c.ronald.kahn@joslin.harvard.edu.

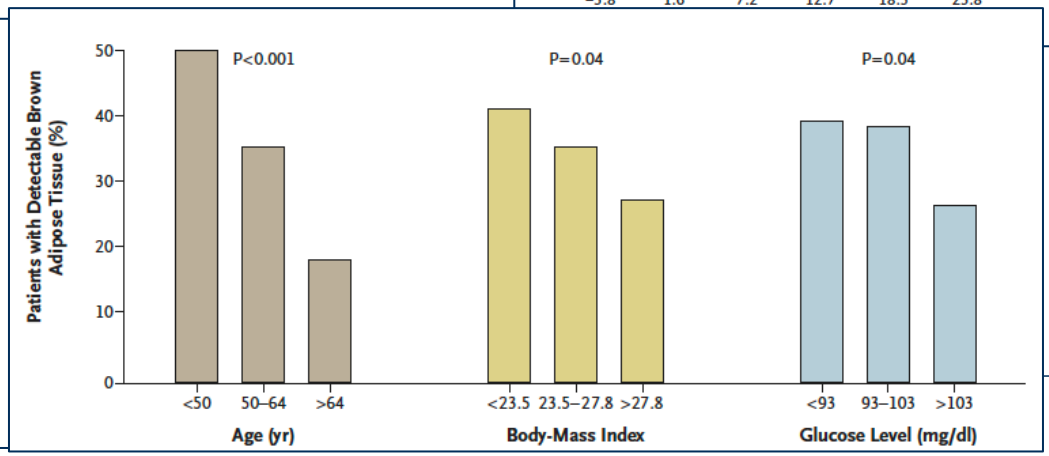
N Engl J Med 2009;360:1509-17.

RESULTS

Substantial depots of brown adipose tissue were identified by PET–CT in a region extending from the anterior neck to the thorax. Tissue from this region had UCP1-immunopositive, multilocular adipocytes indicating brown adipose tissue. Positive scans were seen in 76 of 1013 women (7.5%) and 30 of 959 men (3.1%), corresponding to a female:male ratio greater than 2:1 (P<0.001). Women also had a greater mass of brown adipose tissue and higher ^{18}F-FDG uptake activity. The probability of the detection of brown adipose tissue was inversely correlated with years of age (P<0.001), outdoor temperature at the time of the scan (P=0.02), beta-blocker use (P<0.001), and among older patients, body-mass index (P=0.007).

CONCLUSIONS

Defined regions of functionally active brown adipose tissue are present in adult humans, are more frequent in women than in men, and may be quantified noninvasively with the use of ^{18}F-FDG PET–CT. Most important, the amount of brown adipose tissue is inversely correlated with body-mass index, especially in older people, suggesting a potential role of brown adipose tissue in adult human metabolism.



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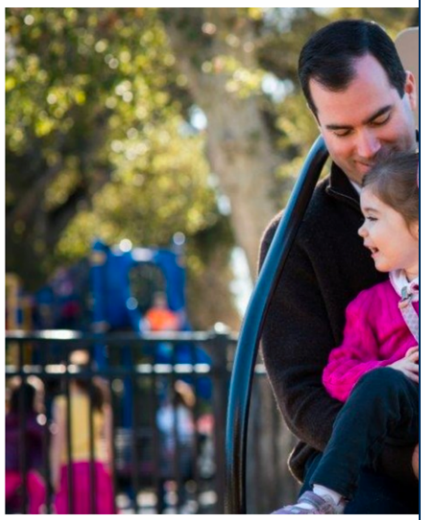
The patient of the future will need their EHR data…

CNN Health » Diet + Fitness | Living Well | Parenting + Family Live TV

Kids who don't cry: New genetic disorder discovered

By Jacque Wilson, CNN
Updated 2:53 PM ET, Thu March 20, 2014



Grace Wilsey was born with NGLY1 deficiency, w

The paper identifies NGLY1 deficiency as an inherited genetic disorder, caused by mutations in the NGLY1 gene. The researchers have confirmed eight patients with these mutations who share several symptoms, including developmental delays, abnormal tear production and liver disease.

And they credit an "Internet blog" with bringing the patients and scientists together.

Grace's genome

Grace Wilsey's parents knew something was wrong right away. Their newborn daughter was lethargic. Her eyes seemed hollow and unfocused. She refused to eat. Doctors at the hospital ran multiple tests, but couldn't come up with a diagnosis.

“With great power comes great responsibility”

“With great power comes great responsibility”

— Uncle Ben, Spider-Man