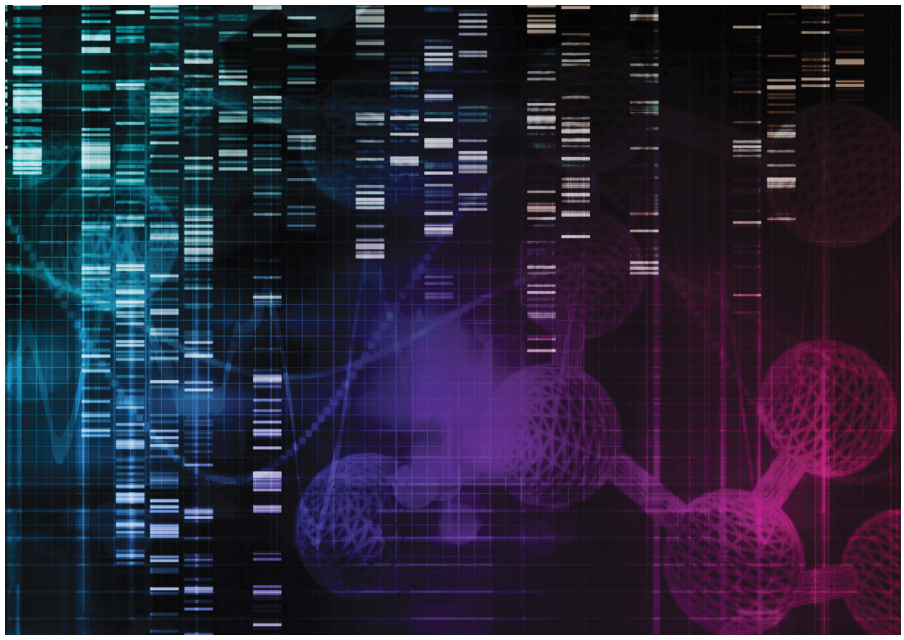
Bias against genetic case reports might compromise medicine



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Rare readouts: Although cases may be uncommon, not all of them have been published.

In February 2013, a 34-year-old Pakistani man went to see a rheumatologist at the Brigham and Women's Hospital in Boston. At age five, he had been diagnosed with juvenile rheumatoid arthritis—the most common form of arthritis seen in children. Damage to his joints persisted, and in his twenties, it became so severe that he underwent a series of operations: a double hip replacement, a double knee replacement and spinal surgery. Yet the joint pain and movement problems did not go away.

His rheumatologist ordered a series of tests—and surprisingly, they all came back negative for rheumatoid arthritis. So the rheumatologist took the case to a team of clinical geneticists. Clues from his family history suggested that his condition might be genetic. After sequencing the man's DNA, the doctors diagnosed him with progressive pseudorheumatoid arthropathy of childhood (PPAC), a rare condition that affects approximately one in a million individuals. It is caused by mutations in the *WISP3* gene, which encodes a protein involved in bone growth and the maintenance of cartilage.

"At first, we didn't have a specific name for the disorder. But when we sequenced the patient's genome and found this variant—a specific gene mutation—it turned out we had two other matching cases. Our case had some interesting findings and described some of the clinical variability that kept us from initially understanding and recognizing the disease," says Christopher Cassa, a geneticist at the Harvard Medical School in Boston, who helped to diagnose the man. Cassa was keen to publish a description of the PPAC case to spread knowledge about this disease.

Two other cases of this PPAC variant had already been published in the medical literature, which made Cassa and his colleagues reluctant to submit their report for publication. It is difficult, he says, to persuade research journals to publish repeat observations of clinical cases. "We saw that the writing was already on the wall. Publishing a finding like this would be difficult and time-consuming," Cassa says.

Whereas research journals are more inclined to publish novel findings, clinical geneticists are interested in repeated observations because knowledge gleaned from additional cases can enable them to diagnose a rare condition accurately. "Often, case reports relate to unusual clinical presentations or unexpected clinical problems. These types of reports can alert clinicians to look for a broader phenotype than what is described in textbooks," says Sharon Plon, a geneticist at Baylor University in Houston. Sharing these findings will ultimately help doctors to better diagnose and treat these conditions.

"There have been several examples where a single patient had an uncommon mutation that was found to be identical to another patient with very similar symptoms in a large study from another country," Plon adds. "It's only by publication or some type of public data sharing that you might be able to find similar patients."

Database dilemma

In 2013, the US National Institutes of Health funded ClinGen, a resource to help doctors understand the links between mutations and diseases. The project collects reports on variants from research labs to submit to the separately funded and separately maintained repository, ClinVar. Since its launch, the database has acquired more than 170,000 submissions from more than 300 international institutions and is used not only by researchers, but also by patients. Earlier this year, Cassa presented data at the American College of Medical Genetics and Genomics (ACMG) annual meeting in Salt Lake City, Utah, showing that the number of annual cases reported to ClinVar is outpacing the annual number of case reports published in the scientific literature—a trend that is expected to continue.

"ClinVar has become a household term at this point," says Heidi Rehm, one of the principal investigators of ClinGen. Initially, researchers were concerned that individual labs would report data differently, and that these inconsistencies would then be reflected in a ClinVar entry. ClinGenhas worked with the ACMG and the Association for Molecular Pathology, both in Bethesda, Maryland, to standardize, for example, the language used to describe how strongly a mutation correlates with disease (*Genet. Med.* **17**, 405–423, 2015).

This fall, Cold Spring Harbor Laboratory Press launched a new journal entitled *Molecular Case Studies*. The journal publishes individual reports of rare diseases identified using advanced molecular techniques, including whole-genome sequencing and metabolomic and proteomic approaches, says John Inglis, the publisher's executive director. According to Rehm, ClinVar is also working to integrate previously published cases and information from smaller gene repositories into ClinVar to supplement the existing entries.

As for the Pakistani patient, his case is among those now catalogued in ClinVar, providing additional information about a rare condition so that scientists and doctors can learn more about it in the future.

Wudan Yan

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renamed Pfizer Plc, and Pfizer will leave its US-based headquarters and move to Dublin. "By combining with Allergan, we will be able to enhance our pipeline capabilities in both new molecular entities and product-line extensions," said Ian Read, the CEO of Pfizer and future head of Pfizer Plc, in a statement. Should the deal receive approval from regulators, Brent Saunders, current CEO of Allergan, will serve as Pfizer Plc's chief operating officer. Starting in 2018, the annual cash flow for the merged companies is expected to exceed $25 billion.

Dengue approval

On **9 December**, Mexico became the first country in the world to approve a vaccine for dengue. The vaccine, called Dengvaxia and manufactured by Sanofi Pasteur in Lyon, France, is the only available vaccine for dengue fever, a disease that afflicts nearly 400 million people annually worldwide. Dengvaxia protects against the four serotypes of dengue-causing virus, and it will be made available in Mexico early this year. In clinical trials of adults and children, Dengvaxia was shown to reduce the likelihood of dengue infection by more than 65%, and it reduced hospitalizations from the disease by 80%. "Today, with this first marketing authorization of Dengvaxia, we have achieved our goal of making dengue the next vaccine-preventable disease," said Olivier Brandicourt, CEO of Sanofi, in a press release.

Sponsor switch

A study published on **15 December** reported a decrease in the percentage of clinical trials funded by the NIH, but an increase in trials funded by industry (*JAMA* **314**, 2566–2567, 2015). The study's authors, based at Johns Hopkins University, found that the number of trials registered on clinicaltrials.gov rose from roughly 9,000 in 2006 to more than 18,000 in 2014. In the same time span, the number of trials receiving funding from the pharmaceutical industry increased by 43%, whereas the number funded by the NIH decreased by 24%. In addition, funding for clinical trials from other sources, such as universities, individuals and nonindustry, nongovernment agencies, increased by more than 225%. A decreased NIH budget could explain this trend, the authors suggested. When adjusted for inflation, "The 2014 NIH budget is 14% less than the 2006 budget," they wrote.

RESEARCH

Targeted editing

In a study published on **1 December**, scientists from the Broad Institute of MIT and Harvard revealed a way to reduce the off-target effects of gene editing done with clustered regularly interspersed short palindromic repeat (CRISPR)-Cas9 technology (*Science*, doi:10.1126/science.aad5227, 2015). Whereas CRISPR-Cas9 has shown high efficiency when it comes to targeted editing, a major concern has been the number of off-target edits seen when using the technology. Given that DNA, as a negatively charged molecule, binds to positively charged amino acids in the Cas9 protein, the scientists replaced three such amino acids with neutrally charged molecules. They found that this made the incidence of off-target binding nearly undetectable. Cas9 comes from the *Streptococcus pyogenes* bacterium, which led the team to call the new protein 'enhanced *S. pyogenes* Cas9 enzyme', or eSpCas9. "We hope the development of eSpCas9 will help address some of [the off-target] concerns, but we certainly don't see this as a magic bullet," Feng Zhang, the study's lead author, said in a press release.

Modified mosquitoes

In a study published on **7 December,** researchers at Imperial College London reported the successful modification of malaria-transmitting mosquitoes to curb the insects' fertility (*Nat. Biotechnol.*, doi:10.1038/nbt.3439, 2015). The scientists used CRISPR-Cas9 technology to disrupt one copy of an egg-producing gene in female *Anopheles gambiae*, the mosquito species that is responsible for most malaria infections in Africa. By using a phenomenon known as gene drive, in which a gene is passed on from one generation to the next at a higher frequency than the typical probability of 50%, the researchers were able to achieve a near-100% inheritance rate of the modified gene in both male and female *Anopheles* offspring; this happens because the intact chromosome, which contains the CRISPR construct in the middle of the gene, is copied to the modified chromosome during gamete formation and thereby increases the likelihood of producing offspring with both copies disrupted. This renders females infertile and thus should restrict mosquito populations. "The huge potential of this technology is very exciting and should have far-reaching consequences for the control of malaria," Tony Nolan, an author of the study, told *Nature Medicine*.

PEOPLE

New director

The US Office of Research Integrity (ORI), which is responsible for monitoring the use of government-issued research funds and for overseeing any research misconduct investigations, announced on **8 December** that it has appointed Kathy Partin as its new director. The position has largely been vacant since David Wright, the previous director of ORI, resigned in March 2014. Partin was formerly the director of the research integrity and compliance office at Colorado State University, and she has been training biomedical scientists in responsible research conduct for nearly 20 years. "She has been involved with academic research misconduct proceedings since 2002, first as a faculty member and later as an administrator, and has been an active member of the national Association of Research Integrity Officers since its inception," read a statement from ORI announcing Partin's appointment. As *Nature Medicine* went to press, Partin was due to join her post on **28 December**.

Corrections

In the December 2015 issue, the piece "Drugs that made headlines in 2015" (*Nat. Med.* **21**, 1382, 2015) did not specify that the different doses of aducanumab were compared with placebo, and that they were all conducted as part of the same study. The error has been corrected in the HTML and PDF versions of this article.

In the December 2015 issue, the piece "Bias against genetic case reports might compromise medicine" (*Nat. Med.* **21**, 1378, 2015) incorrectly described the relationship between ClinVar and ClinGen. ClinVar is maintained by staff at the US National Center for Biotechnology Information (NCBI) at the National Institutes of Health (NIH) and is supported with intramural funding. In contrast, ClinGen comprises many groups and is funded by grants from the National Human Genome Research Institute. The error has been corrected in the HTML and PDF versions of this article.