IN THIS ISSUE

Joint efforts pinpoint new rare genetic disorder

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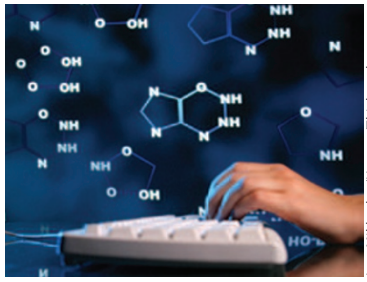

Ivan Mikhaylov/Hemera/Thinkstock

A combination of motivated parents, an Internet blog, whole-genome sequencing (WGS) technology, and traditional clinical genetics located the gene responsible for a newly described genetic disorder presented in this issue. Deficiency of N-glycanase 1 (NGLY1), a deglycosylating enzyme, is responsible for a unique constellation of symptoms of varying severity, as described by Enns et al. in a handful of patients. Perhaps the first-recognized congenital disorder of deglycosylation, NGLY1 deficiency, an inherited disorder of the endoplasmic reticulum–associated degradation pathway, is also the first to be identified that involves the cytosolic proteasome.

NYGLY1 is part of the quality-control system for targeting and degrading misfolded proteins, and the *NYGLY1* gene, which is highly conserved across species, is intolerant to any functional mutation. Presumably the rarity of such a mutation accounts for its not having been described previously. The advent of WGS no doubt made its discovery possible, but the speed with which data on far-flung isolated cases were collected required the doggedness of desperate parents who were able to connect the dots using shoe-leather detective work. Their story, outlined in an accompanying Commentary, may yield lasting lessons for the medical genetics community. Armed with knowledge of a gene candidate ascertained at Duke University, the father of one affected child recounted his family's odyssey in a blog post that was to be the catalyst for discovery. Other families recognized their own children's symptoms after reading the post and advocated for the gene sequencing that confirmed the culprit gene. These families are now calling for better bioinformatics tools and a national repository where families and scientists can search for clues in other unsolved genetic cases. The families' story did not stop with diagnosis, of course; they have moved on to searching for viable treatment options. The lesson here may be that the democratizing effect of the Internet and social media has created a valuable opportunity for motivated citizens to contribute meaningfully to the research enterprise. —*Karyn Hede, News Editor*

Incidental findings approach 9% in the NIH Undiagnosed Diseases Program

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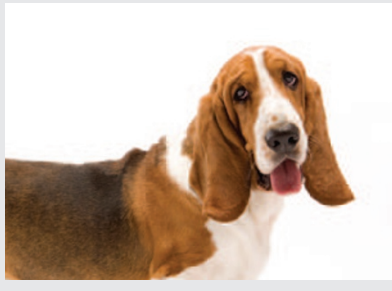
BRCA1, BRCA2, STK11, APC, VHL, RET, RB1, TSC1, TSC2, NF2, FBN1, TGFBR1, TGFBR2, SMAD3, ACTA2, MYLK, RYR2, KCNQ1, KCNH2, SCN5A, TP53, MLH1, MSH2, MSH6, PMS2, MUTYH, MEN1, PTEN, SDHD, SDHAF2, SDHC, SDHB, WT1, COL3A1, MYBPC3, MYH7, TNNT2, TNNI3, TPM1, MYL3, ACTC1, PRKAG2, GLA, MYL2, LMNA, PKP2, DSP, DSC2, TMEM43, DSG2, LDLR, APOB, PCSK9

The laudable efforts by the National Institutes of Health (NIH) to diagnose rare genetic diseases necessarily also raise the issue of managing the incidental findings. A recent examination of the rate of incidental findings among 159 families participating in the NIH Undiagnosed Diseases Program (UDP) revealed that nearly one in nine families carried variants that appear on the American College of Medical Genetics and Genomics list of reportable variants. Nine of the reportable variants involved minor children. Of these, five were associated with adult-onset conditions and four with childhood-onset conditions. The authors note that reporting decisions were guided by the choices made by participants or guardians during the informed-consent process by which individuals enrolled under the UDP protocol. The study revealed the limits of analysis based on annotations in public databases, which in some cases lacked well-curated information on segregation of variants with disease. Given the likely improvement of annotations in the future, the authors pose the question of whether there is an ethical duty to reanalyze such data regularly in the light of increasing information. —*Karyn Hede, News Editor*

NEWS BRIEFS

Genetic origins of Fido's floppy ears explained after 140 years

The very traits that make dogs and other domestic animals endearing to us—floppy ears, curly tails, shorter muzzles—have puzzled scientists since Charles Darwin. Many distinguished scientists have posited explanations for the constellation of traits that developed after domestication, but none has convincingly proposed a genetic basis that covers all the observed changes. However, a deceptively simple explanation has now been suggested, by an interdisciplinary team in the July 2014 issue of *Genetics*. Wilkins and colleagues hypothesize that the cluster of phenotypic traits has its origins in neural crest cells, a class of stem cells that appear during early vertebrate embryogenesis at the dorsal crest of the neural tube and then migrate through the cranium and the trunk. They also suggest that selection for the desired trait of "tameness" has unintended effects on other body systems, producing, for example, floppy ears. The authors maintain that these traits can all be explained by subtle genetic changes that lead to reduc-



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