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3 MAJOR SKILLS

THE SHORT READ

FEATURING GHOLSON LYON

2017
FRONT LINE GENOMICS

Welcome to The Short Read, our weekly peek behind the curtain at the people who make this amazing community tick. Make sure to check back every Tuesday for the latest installment.

Gholson Lyon is a geneticist, and a child, adolescent and adult psychiatrist at Cold Spring Harbor Laboratory where he studies the molecular basis of rare diseases. Gholson started his independent career in 2009 at the University of Utah, where he led one of the first groups to use exon capture and sequencing to identify the genetic basis of an entirely new, idiopathic disorder, which was named Ogden Syndrome. This discovery received wide press coverage in 2011, where Eric Topol predicted that this was just the beginning of a tidal wave of many more idiopathic disorders being investigated by exome and whole genome sequencing. This prediction has certainly come to pass, as many hundreds of researchers worldwide are identifying genetic mutations in many disorders.

Gholson also investigates the pathophysiological basis of neuropsychiatric conditions, with the goal of expanding access to preventive services and treatment for these disorders. Through public speaking, social media, and publications, he encourages open discussion and management of the ethical implications of human genetics research.

What are you working on right now?

Several years ago, we reported on the genetic basis of a X-linked, infantile lethal Mendelian disorder, involving a p.S37P missense mutation in NAA10, encoding the catalytic subunit of NatA, involved in amino terminal-acetylation (NTA) of proteins. Since that time, we and others have been identifying new families with mutations in this pathway, and we are currently delineating the genotype-phenotype relationships in these families. We are also collaborating on many functional analyses for this disorder, including mouse models and patient-derived cells. In a different project, I am working with some colleagues (Jesse Gillis and Sara Ballouz) to analyze gene expression differences in a new syndrome that we reported a couple of years ago, involving mutations in TAF1, and we are currently expanding the cohort of patients. We also have started collaborating on functional analysis of this gene, particularly as dysregulation of this gene has been implicated in a somewhat more common disease in the Phillipines, called X-linked dystonia parkinsonism (XDP). It has been a real pleasure to join and work with a consortium focused on trying to better understand XDP.

What's the biggest challenge you face in your work at the moment?

Stochasticity. There is a lot of randomness in development, which can lead to a substantial amount of variable expressivity for phenotypes of interest. I am working now with genetically engineered mouse models of human disease, but the expression of the phenotype is quite variable even on pure inbred genetic backgrounds. This is a well-documented phenomenon, of course, but this will complicate any efforts to predict genotype from phenotype in an outbred human population. I do work as a clinician as well right now, seeing mainly people with intellectual disability and/or autism, which constantly reinforces for me the enormous variability in these conditions. For diseases affecting the brain, a very long-term goal for the field would be to determine if CRISPR-mediated correction of mutations in somatic mosaic form delivered in vivo during infancy will ever work to at least ameliorate the conditions. There are obvious and enormous hurdles to this, including regulatory concerns, and I would not be surprised if such attempts occur first in other countries other than America (due to reduced regulatory burdens). Of course, this will likely result in harm to patients in those other countries first, prior to substantial success, and the field is first focusing on diseases that affect other organs (like the liver), where the chances of success are higher. Somewhat related to this, it is pretty much left unstated by most people that the field of medical genetics is substantially increasing the amount of prenatal diagnosis and termination of pregnancies.

Name one big development that you would like to see in your field in the next 18 months.

18 months is a very short time period! I have many long-term wishes, in terms of trying to free up more information and to enable better phenotyping of humans for longitudinal analyses, which is being enabled by social networking and the continuing education of the populace, particularly among the younger generations. I hope sincerely that society continues to advance, where more and more people become scientifically literate. But, all of this has a time-frame of 20-50 years, not 18 months!

What are you most proud of in your career?

Being a physician-scientist and discovering several rare diseases with mutations that contribute to the development of these diseases has been rewarding, in the sense that I have been able to give the families some clue regarding why their children have the illnesses that they have. However, it is still quite humbling to know that we still must understand mechanism and try to deliver on any sort of treatment. One pet peeve of mine is when geneticists announce that they have "solved" a case, when all they actually did was just find a mutation. I can guarantee you that no family on earth would say that you "solved" their child's condition by just finding a mutation! I just wish that these scientists announcing in talks and papers that they "solved" a case would realize this and become a bit more humble.

Which scientists, living, dead, or fictional, would you invite to dinner, and why?

There are of course many very famous deceased scientists that would be interesting to meet, although many of them have written quite a bit of autobiographical or “career advice” material that allows one to meet them somewhat through their writings. I am thinking here of the likes of Charles Darwin, Ramon y Cajal, Francis Galton, and Alexander von Humboldt. There is relatively little such material written by Gregor Mendel, so it would be interesting to meet him, mainly as a way to get to know what sort of person he really was, including aspects of his personality. Other somewhat more recent scientists that I would love to have met would have been Barbara McClintock, Erwin Chargaff and/or Oswald Avery, mainly due to the fact that they seemed to be thoughtful, hype-free, and perhaps interesting to talk with in person. I currently live at Cold Spring Harbor Laboratory in the same apartment that Barbara McClintock occupied for many years; I have read many of her papers and I frequently imagine what a conversation with her would be like. These days, I am also becoming more interested in engineering and technology development, so I would love to meet someone like Nikola Tesla (deceased) or Elon Musk (alive), perhaps as a way to try to catalyze ideas and projects about how to better study embryonic development with more precision.

What advice do you wish someone had given you at the start of your career?

Unfortunately, doing good science in a lab (with assistants) is much harder these days, as the technology and necessary reagents are much more expensive. This means having to obtain funding for the research, but that now means being incredibly networked, given that much of the funding these days is parceled out by peer review, in which the peers must really know about and like what you are doing. Imagine if any of the deceased scientists I mentioned above would have had to write a grant in the current environment in order to fund themselves or their project during their early years? I sincerely doubt any of them would have been funded in this current funding climate, as doing this kind of science is all about venturing into the unknown, so how is it remotely possible to predict what you will discover over the next five years? These days, grants are evaluated by peers who appear mainly interested in knowing where you published your papers (i.e. “high-impact journal”), but who give no indication that they actually read any of your papers. But, of course, getting papers published in high-impact journals usually relies on having long-standing relationships with certain editors, along with working in a very narrowly defined field in which the reviewers are very likely to know you personally. In terms of funding, most members of NIH study sections know each other from meetings that are usually set up to focus on fairly narrow topics, and they are inclined (consciously or unconsciously) to fund junior people either working on similar topics of study and/or having been mentored by colleagues that they know. This reinforces fashionable trends in science, but hugely disadvantages the discovery of new fields and areas of research.

... This also currently sets up positive selection for people who are very good at networking, hype, and self-promotion, sometimes to the detriment of good science . So, the advice I wish someone had given to me at the start of my scientific career (and which is now even more important) is the following:

Get to know yourself. Figure out if you must get major credit for your discoveries and/or if you like hype and self-promotion. If you only want to focus on the science and you do not care about credit, then you should try to become a staff scientist in a well-established lab or institute where you can be part of a larger team and where you do not necessarily have to worry as much about funding. This will obviate substantial need at least for you to engage in hype and networking, assuming that you do not like doing such things. However, if you do want to get the lion's credit for discoveries that you make, then that means having to become a triple threat in terms of being a great scientist, a great communicator, and a great networker. All three of these skills will be equal to each other in importance, as you will likely need all three of these to survive in today's funding climate. It will also help you tremendously if you at least begin your career with a mentor who is great at all three of these things AND also supportive of your development so that you have a decent chance of launching your independent career with funding made possible in part by your mentor's reputation. Of course, this means struggling to become truly independent and to get credit for making your own discoveries, but that is really the best chance for getting funding these days. But, really, if what you want to do is work at the bench doing science, without caring about credit, then seriously consider the option of becoming a staff scientist in a well-established lab, or institute. Of course, there are a host of other problems for people training to become physician-scientists, given that you are constantly bouncing back and forth between the clinical and research worlds, which are unfortunately quite different from each other.

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