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Interview with: **Michael J. Ackerman, M.D., Ph.D.**
Subject: CPVT
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1. **How many people are known to be affected by CPVT annually?**
   The real answer is: We have no idea. If we put CPVT in the category of cardiochannelopathies with Long QT Syndrome being the most common, Long QT Syndrome affects about 1 in 3,000 people. So, a best guess is that CPVT probably affects about 1 in 10,000 people.

2. **How many unknown deaths are suspected of being CPVT?**
   There we have a little more of a handle on this number from a series that we published, in part, with the contributions from the Hannah Wernke Foundation. We did an autopsy series of autopsy-negative sudden unexplained death, and we found in that series that 15 percent of those 'normal heart' sudden deaths were due to CPVT. If we translate that, there are probably on the order of several thousand such autopsy-negative sudden unexplained deaths, and what we are saying is that about 15 percent of these autopsy-negative sudden unexplained deaths may be CPVT related

3. **What is the ultimate goal of your research?**
   There are several aspects of the Sudden Death Genomics Laboratory, and as it relates specifically to CPVT, our goals are several fold:
   - To determine the various genetic causes for CPVT. We know that about two-thirds of CPVT is due to defects in a gene called RyR2. We do not know the causes for the remaining one-third of CPVT. So, one of the efforts is to eventually identify those causes.
   - The second effort, through our coroners program, is to conduct post-mortem genetic testing of the cardiac ryanodine receptor (RyR2), the first and the main CPVT gene to continue to provide that service for autopsy negative sudden death since there is no equivalent commercially available genetic test. One of the reasons why that is so important is the standard screening test will always miss diagnosing this condition. The standard ECG is always normal in this condition.

   And so I think beyond diagnosing this condition post-mortem with genetic testing, our ultimate goal is to figure out some sort of screening method for this condition, whether it be a genetic screening or some sort of screening evaluation, and then working toward a treatment solution. Right now the only treatment to this condition is to implant a defibrillator because the current medications are not adequately protective.
   So, the two-pronged goal is to identify CPVT's presence and then figure out better ways to treat it.

4. **How will the Hannah Wernke Memorial Foundation fund-raising efforts help impact CPVT research?**
   I think this funding will go toward all those aspects. Obviously the genetic testing is extremely expensive. In research costs, it costs about $2000 per genetic test. In terms of the number of post-mortem genetic tests we can conduct for CPVT, that's limited by our resources.
   Now we have a large CPVT program that's going on where this fund-raising effort helps provide directed dollars for CPVT, and I think the main thrust of it right now is to use it to provide CPVT genetic testing until research-based genetic testing is no longer needed. There is no commercially available clinical diagnostic test right now for this gene, so it's only done in labs like mine—research labs. Once a commercial test becomes available, then our services won't be needed to test living people.
   But, it will be a long time before insurance companies will pay for autopsy testing of those who have died. So, we'll see that a major component of their funds will be dedicated to post-mortem genetic testing effort.

5. **Have Hannah Wernke Memorial Foundation contributions increased your CPVT research budget or has Mayo lowered its portion and the level kept the same?**
   The Hannah Wernke Foundation has provided additional money directly for the CPVT research program.

6. **How many CPVT-causing genes have been discovered?**
   Currently, the number of CPVT-causing genes that have been established are two. RyR2 and the gene that encodes protein called Calstabin-2.
   The first, RyR2, is the most common and accounts for about 50-60 percent of the syndrome.
   The second gene is very very rare, and so about 40 percent of the syndrome remains genetically unexplained.

7. **How many CPVT-causing genes are suspected?**
   We have no idea how many genes are going to explain the balance of CPVT. We've got about 40 percent left to explain, and those could be explained by anywhere from 1 to 40 genes is my guess—probably closer to the latter. We haven't found a common second cause yet, and that suggests that all of the rest of the causes are going to be uncommon.

8. **What is the death rate for CPVT?**
   We don't really know for sure but it seems higher than in long QT syndrome. I would estimate it at about 5% per year risk of sudden death. To put in perspective, the risk of dying suddenly for a healthy teenager is about 0.3-0.5% per year risk.

9. **If CPVT is found and the patient is being treated with either a pacemaker or beta blockers, what is the death rate?**
   We know from a couple of papers published over the last three years that beta blockers, which is the best medicine that we have available is not sufficiently protective. That is why, right now, the treatment of choice for CPVT is a defibrillator. We know that beta blockers in a patient who has a defibrillator seems to lower the shock rate, but not low enough that one would be confident in the medicine being a stand-alone therapy.
   I am not sure what the death rate is on therapy. The death rate with the defibrillator implanted ought to be extremely low, the ICD saves lives.
   The death rate on beta blockers is higher. Among our patients who we see and take care of with CPVT, when I compare those patients to the much larger population with Long QT Syndrome, the patients with CPVT have a much more aggressive course, much more family history of sudden death in CPVT families. CPVT seems to be a more sudden death predisposing condition than Long QT Syndrome. This could be, in part, 'a tip of the iceberg phenomenon' because CPVT is newer on the scene than Long QT Syndrome. When Long QT Syndrome was first discovered and first described, it was viewed as a universally lethal entity. Now it is understood to be far more common and far less lethal. It has only been about 10 years since CPVT was first described, and so the impression is that it is less common than Long QT Syndrome and more lethal. But, over time, that impression is probably going to change as well. It's probably going to turn

out to be more common than what we've guessed and not quite as lethal overall compared to what it seems right now. We're just seeing the worst of it coming to our attention right now because as physicians we are not as savvy yet to recognize it.

10. Symptoms we know can include: simple fainting, seizures or sudden death. Are there others?

The most important symptom that would make somebody think about CPVT is exercise induced sudden fainting. It is not the ordinary faint where you're light-headed and woozy and hot and bothered and going down — but rather the immediate faint. And these faints or seizures or sudden deaths are all triggered by exertion. So, exertion is the common trigger. We've found several patients whose activity exertion was swimming and so near drowning and unexplained drowning is potentially an indicator of CPVT. It seems to be a condition that is much more uniformly triggered by exercise. Although, one of the new things that we've discovered this year, through the Foundation's support, are mutations in CPVT in infants with crib death. It's hard to explain what they were doing in terms of exercise or exertion. We are finding that exercise can be defined in several ways, but the common denominator is an exercise or an exertional or an adrenalin-rush trigger event.

11. Can you confirm that 80 percent of the cases are inherited and 20 percent are spontaneous?

I'm not sure we really know the answer to that in terms of what percent of CPVT is inherited vs. spontaneous. That is probably as good a guess as there is out there right now. My impression has been that there is a greater tendency toward sporadic or spontaneous mutations in CPVT than in Long QT Syndrome, but that's just an educated guess from observations in the Clinic.

12. Is there a suspicion of what could cause a spontaneous mutation?

We don't really have any clue as to what causes spontaneous mutations. Basically, a spontaneous mutation results when a healthy egg and a healthy sperm come together and then, post-fertilization, there is an early strike in the gene. There are all kinds of speculated mechanisms for it. There is nothing unique about spontaneous mutations in CPVT genes compared to spontaneous mutations in any other genes.

13. Are there other topics that have not been covered that you would like to mention?

Mayo, in partnership with Mayo Clinic Health Solutions, have partnered together with a commercial company to move Long QT Syndrome genetic testing out of the research domain and into the clinical domain. Long QT genetic testing has been commercially available through a company called PGxHealth since May 2004.

We are similarly working to commercialize and develop CPVT genetic testing. Again, that is going to be started for the living and that is why there is still going to be a gap in terms of when there is a family who has already lost somebody suddenly and everyone else who is alive seems healthy—can you explain the deceased death? That's where funds for the post-mortem genetic testing effort are going to remain critical. I am optimistic that we should have genetic testing for the most common CPVT gene, RyR2, probably released in the next six months to a year. That is the pace that we are working at with the company right now.

Interestingly, the gene responsible for CPVT is one of the largest genes in the human genome. Right now the priority is to only do the "spell-check" for the region of the gene where mutations have been found already. But that only represents about one-third of that gene. So, one of the things we're doing in the research lab is continuing to search the rest of the gene to try to find out how many additional cases are explained by mistakes throughout the rest of the gene.

As the research lab, we are trying to get the discoveries made to the point that it entices or becomes justified to convert that *rare* disease to a disease that people want to develop a clinical test for. And one of the things that I have been doing in my relationship with the commercial company is trying to convince them that this condition, although rarer than Long QT Syndrome, warrants a commercially available genetic test to advance the field and to provide something for these families. As opposed to having families continue to rely on research labs, which by definition are research. The business of a research lab should be about discovery and discovering the next set of genes that should go on the test. And so we are trying to make that maturation for CPVT happen like we made it happen for Long QT Syndrome.

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