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Genetic Risk Factors of Age-Related Macular Degeneration (AMD)

You are listening to ReachMD, The Channel for Medical Professionals. Welcome to the Revealing Retina presented by the American Retina Foundation, the charitable arm of the ASRS, the American Society of Retina Specialists. I am your host, Dr. Roy Levit, Chairman of The American Retinal Foundation and joining me is Dr. Albert Edwards. Dr. Edwards obtained his Ph.D. in cell biology and his M.D and ophthalmology residency at the Baylor College of Medicine in Houston, Texas. He did a 2-year fellowship in vitreoretinal disease and in ophthalmic genetics at the KCI Institute at Oregon Health Sciences University and following 8 years in Dallas as an Assistant Professor in ophthalmology at Southwestern Medical Center. He is now an Associate Professor and Senior Associate Consultant in the Department of Ophthalmology at the Mayo Clinic in Rochester, Minnesota. He specializes in the genetics of retinal disease and today we are going to talk about the genetics of age-related macular degeneration.

DR. ROY LEVIT:

Welcome to the revealing retina, Dr Edwards.

DR. ALBERT EDWARDS:

Thank you Roy.

DR. ROY LEVIT:

In the past on this show we discussed the different types of AMD including the more common dry type, the acute visually debilitating wet type and we also talked about some of the more common treatments. At this point, I would like for you to give us your take on the current state of AMD and what part genotyping is playing in this ocular disease.

DR. ALBERT EDWARDS:

Well, I look at AMD as a common complex trait meaning it is a disease that develops late in life and that has multiple risks including environmental exposures, demographic exposures, and genetic risk, and I view AMD as a maculopathy as a disease in which there are abnormal deposits that form underneath the retina and in some patients these deposits become severe enough or there are additional risks that lead them to develop complications such as death of the retina, arteriographic atrophy where the retina dies and patients gets these defects in their vision or wet disease where abnormal blood vessels grow in and leak fluid and bleed. If you look at the natural history of the disease or look animal models, I think that it is a good way of thinking about macular degeneration.

DR. ROY LEVIT:

These deposits that you mentioned how do they effect the survival of the retinal cells?

DR. ALBERT EDWARDS:

The deposits initially have fairly minimal impact on vision and function. They are composed of lipids, inflammatory proteins such as activated component of molecules, beta amyloids and a variety of proteins that respond to the inflammatory state such as vimentin and also a variety of debris apparently extruded from RPE cells such as undigestible byproducts of visual cycle. These deposits begin to build up slowly over time in many patients, and the visual effect tends to be a little bit of decrease in dark adaptation or difficulty seeing at night or especially difficulty transitioning from a bright room into say a dark room, for example going into the movie theater, and at some point patients begin to lose some of their photoreceptor cells, that happens normally during life, but the rate of loss goes up, and if the deposits get severe enough they can get thick enough in order to prevent the nutrients and oxygen coming from the blood stream to get to the pigment layer under the retina and on the retina itself and that can lead to this fairly advanced focal atrophy of cells called geographic atrophy.

DR. ROY LEVIT:

Now these deposits that occur, are they naturally occurring or just in excess in these patients?

DR. ALBERT EDWARDS:

That's a good question, in animal models for example in mice there are age-related changes in the retina which genes are involved in, leukocyte extravasation or the migration of leukocytes out of blood vessels into the eye and genes that involve in complement activation and another genes are upregulated as a function of age in mice and that translates into some deposition of complement proteins and build-up of a limited amount of deposits. I don't know if that is normal. In humans, we don't know really know the answer to that question yet, but what we do know is that in patients who have certain behaviors such as smoking or eating a high-fat diet or being obese for example not exercising, the patients who fit into that category epidemiologically and patients who has genetic risks are much more likely to have an extensive build-up of these deposits. So, I would hesitate to say that the build up is normal, but it is certainly common and those patients in general don't get disease, its patients who have a large amount of the build-up of deposits that get disease.

DR. ROY LEVIT:

This is related to their genome?

DR. ALBERT EDWARDS:

Yes it is there are a number of genetics risks that are very important in increasing the chance of getting macular degeneration. The first that was discovered was reported in 2005 and that was a variation or group of variations in the complement factor H. Now complement factor H is a down regulatory molecule in the complement pathway, it binds to a central enzyme, the C3 convertase that is responsible for forming the attack that pokes holes in cells and destroys them and complement factor H serves to down regulate the activity of that complex and essentially destroy it through 3 distinct mechanisms. That genetic variation in that locus probably accounts for somewhere between 40% and 50% of the risk of developing AMD and has an odds ratio of about 2 to 3 if you have 1 copy of risk allele and 5 to 7 if you have 2 copies of the risk allele. The second locus that was identified is chromosome 10 band Q26. This locus contains 3 genes in an area that is associated with increasing the risk of macular degeneration. We don't know exactly which variation in which gene exactly causes the disease, but we do know that there is an ancestral segment of DNA that is present in about 25% of Caucasians that results in a three to fourfold increase in risk if you have 1 copy and seven to tenfold if you have 2 copies. Now because that risk variant is less common, it is only about 25% compared to the complement factor H which is about 39%. Its overall impact is actually less, even though the odds ratios for a given individual is higher. So we don't know what the function in that region is yet. The

next locus that was identified is located in the complement factor C2 and the factor B region, those are 2 genes that arise next to each other and we still haven't been able to determine exactly which gene it is. In fact, there are some reports suggesting that well it may be it is another gene that's nearby, and the reason for this is that these regions of genome the various base pair changes often go along with each other and are inherited as blocks, so it can be difficult to sort it out. I would say that that locus is a relatively modest affect compared to the first 2, they tend to have odds ratios of 1.5 to 2 for a single variant.

DR. ROY LEVIT:

You are listening to the Revealing Retina on ReachMD 160, The Channel for Medical Professionals. I am Dr. Roy Levit and I am speaking with Dr. Albert Edwards and we are discussing the genetic influence on age-related macular degeneration.

Now we were just talking about the genes which are known that effect AMD. At this point, is it practical to do this sort of testing on patients that may have a family risk?

DR. ALBERT EDWARDS:

I think that it can be done. The question is what would we do with it, how useful would the information. So in addition to those 3 variants that I mentioned there is one other in C3 which has a modest odds ratio. So we have these 4 genetic variants and so we can stratify or rather we can account for the genetic risk, we can account for the risk of AMD up to about 75% to 80% with these variations that we know about already. Okay even the ones we don't know exactly what the disease-causing changes are, we can still incorporate those in the model. So we could at birth provide an estimate of lifelong disease risk and the question would be, would that information lead to a useful change in behavior and we know that behavioral changes that would reduce the risk of getting macular degeneration, so called modifiable risk factors. The first of those and probably most important is avoidance of smoking, the second is the consumption of fatty fish such as salmon, tuna, mackerel. That has a protective effect and then its other dietary and lifestyle factors that appear to be important, but for which there is not extensive evidence and those are low-fat diet, exercise, eating leafy green vegetables, and fruits. You get this picture that there are these people who live a healthy life, eat a healthy diet are much less likely to get disease and those who don't and that proportion of the disease risk is probably around 20% to 30%. So the question would be, would patients change their behavior if they knew that information given that we already recommend for a variety of reasons to eat that kind of diet and live that kind of lifestyle. That's an unknown question.

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DR. ROY LEVIT:

Another question I have been thinking about has to do with the AREDS formula which is a specific group of vitamins that has been shown to be beneficial in certain patients in reducing the progression of dry, age-related macular degeneration. Now is there any genetic correlation as to who would benefit more from this vitamin supplement regimen.

DR. ALBERT EDWARDS:

It is interestingly a recent study suggested that patient who had the high risk of alleles in the complement factor H locus had a reduced benefit. They still had a benefit, but it was reduced and because of the fairly modest size of the study and the fact that there is no other cohort to replicate that finding in, I would be very cautious about suggesting that patients not take the AREDS supplements because of that finding. One of the unfortunate realities of doing case control studies is that many findings ultimately prove not to be replicated in subsequent studies So although the study was done, it is an excellent study, it was done very well, and it is a valid finding in that study in that group of

patients, whether or not it is going to hold true across say the AREDS 2 trial that is going on right now, we don't know, and the effect wasn't large enough to say that we should treat these patients and also we haven't looked that all the other genetic variants to see how that factors out. So, I would say that that is a very exciting and interesting result, it gives us the suggestion that some day we may be able to tailor therapy to individual patients. Right now, we don't how to do that.

DR. ROY LEVIT:

If you had a patient that came to your office and he was between 50 and 60 years' old, no visual symptoms had a few drusen that were diagnosed and some suspicion of the possibility of dry AMD was there, would you suggest in this individual with no real family history to have genetic testing?

DR. ALBERT EDWARDS:

I personally would not, I would suggest that the patient modify his exposures and the reason for that is that we don't yet know. If we take this patient you described with they suggest almost early macular degeneration almost there, just several hard drusen may be 10 or 15 just not enough to call it, but it is very suspicious, and those are the people in the Beaver Dam study that were most likely to go on to have AMD 10 years later. So if we were to take that person and divide them into 2 categories say high genetic risk and low genetic risk, my question would be would I tell those patient anything differently, I think the answer today would be no, may be 10 years from now, 5 years from now, after we do some prospective studies based on the ongoing genetic and proteomic work, it may that we could tell those patients to do something differently, but today I would tell them exactly the same thing.

DR. ROY LEVIT:

Interesting. Iwouldlike totalkabout this further, but our timeis up. Dr. Albert Edwards, I would like to thank you for speaking with us about the genetic aspect of age-related macular degeneration.

DR. ALBERT EDWARDS:

Thank you Roy, it was a pleasure.

I am your host, Dr. Roy Levit, and I would like to thank you for listening to the Revealing Retina, presented by the American Retina Foundation. For more information, please visit us online at americanretina.org. We welcome your questions and comments about this or any other show, please send your e-mail to XM at ReachMD.com, or visit us at www.ReachMD.com. Our new on-demand and our new podcast features will allow you access to our entire program library. Again, thanks for listening.