

Complement Factor H
29-Apr-06 - 1:00 pm - 4:30 pm

Albert O. Edwards: I thought rather than go over my laboratory's role in studying the genetics of AMD that I would try to answer a simple question, one that I get asked often in the course of seeing patients, and just walking down the hall. It is "what is AMD?" And the first thing I'm going to talk about is the clinical features. AMD is a condition that starts at some point in life that is really unknown. We know from epidemiological studies that early changes can be seen in the forties and fifties. However there's some process where we go from normal to being unable to see just a few yellow spots called drusen and granularity. You'll notice that this color fundus photograph is a composite. It's a two-dimensional image of a three dimensional structure, and you can see on the inner surface of the retina, the retinal blood vessels, the retina itself is largely translucent, the pigment epithelium, and then the underlying choroidal vessels, which you can see coursing here. And you'll notice that there's kind of a smooth homogenous appearance to this, and this is even more apparent on an infrared image, which has a greater ability to detect drusen at a smaller size. And you can see the second structures, but notice this kind of smooth, glassy appearance. Now at some point in patient's who are destined to develop macular degeneration, we see these small yellow spots. I don't know if you can see them. It's fairly subtle. But with the infrared imaging, we can see a diffused disturbance of the macula that results from the accumulation of subretinal deposits that disrupt the topology of the RPE, Bruch's membrane interface. And this disease can progress in some patients fairly rapidly. We see here a lady who over a two-year period went from having several distinct, soft drusen, and some indistinct soft drusen. And I apologize, I'm pointing from memory here, because I can't see that. But you'll have to trust me, there's something over there. And over a two-year period, you can see this accumulation of diffused deposits underneath the retina in a very impressive manner. Now there is a Phenocopy here. This is a light burn from a cataract surgery. And it's one of the important points we want to bring up later is that these features are not necessarily diagnostic, and we have to be sure to be careful when we examine these patients. Now this maculopathy in and of itself can lead to some complications. For example, coalescent drusen can result in so-called drusenoid pigment epithelial detachments where patients can have metamorphopsia, or distorted vision, or perhaps mild decreases in vision, and certainly decreases in night vision and contrast sensitivity. In some patients they will develop a _____ for maculopathy where there's accumulation of photoreceptor outer segment debris between the subretinal - within the subretinal space, between the neuroretina and the RPE. And some patients later in life develop a diffuse mild atrophy of the retinal pigment epithelium. And some the disease progresses to the so-called late stages where one can have either death of

the retinal pigment epithelium as shown here, you can see the edge of the living and dead retinal pigment epithelium. This is called geographic atrophy. Some patients develop abnormal blood vessel growth, apparently as a reparative response. Here we see a patient with choroidal neovascularization external or outside of Bruch's membrane growing in the choriocapillaris. This is called idiopathic polypoidal choroidal vasculopathy, and it is frequently seen in Japan as a manifestation of AMD, and not infrequently seen here. Here we see a patient with these abnormal blood vessels growing between the retinal pigment epithelium shown by this red line on an OCT scan, and Bruch's membrane. This is a pigment epithelial detachment with choroidal neovascularization as so called a colt choroidal neovascular membrane. And some patients, they develop the blood vessels breakthrough the pigment layer, and grow in this theoretical space between the photoreceptor outer segments, and the retinal pigment epithelium as shown by this patient right here with this lacy network. And some patients will go on to develop severe scarring. This is called a disciform scar, and profound vision loss as a response to this choroidal neovascularization. As I mentioned these disease features are not classic for any particular disease. So here's for example a patient with extensive Drusen that has a mutation in the fibulin three, or this disease – this patient happens to be from the Leventin Valley of Switzerland. We called it dominant radio drusen or Malattia Leventinese. _____ called it retinal dystrophy is a branch of this – apparently a branch of this same family, and similar – the same mutation. Now here's a patient with so-called dominant Stargardt Macular Dystrophy that we and Zhang cloned the gene for this several years ago. And you can see in this patient, which arises from a dominant negative mutation in a gene called elongation of _____ fatty acids. It has some retinal spots, and central geographic atrophy of the macula. Here's a patient with the garden-variety myopia with focal depigmentation of the retinal pigment epithelium, and some retinal hemorrhage from a small classic choroidal neovascularization. We see a peripherin RDS with some retinal flex, and _____, and so forth. Recessive Stargardt Disease here. It's important to remember that many of these diseases do not have names, and they just show up in our clinics, and they frequently get labeled macular degeneration such as this patient. But I would submit to you that this patient does not have typical macular degeneration. He has some subretinal flex, and he has a little spot here I think you can see that is an area – a condition called RAP, Retinal Angiomatous Proliferation, which is where the neovascularization starts within the neuroretina, and then eventually grows toward the retinal pigment epithelium. And this can be seen frequently in patients with macular degeneration. So the way I think of macular degeneration is that there is this underlying trait, or the maculopathy. And there are abnormal biological pathways that at some point, perhaps from birth, or perhaps later after some initiating factor, lead to cellular

responses that result in accumulation of material underneath the pigment epithelium. This material includes fat, a variety of substances that Dr. Hageman and others will talk about today including Complement and Vimentin. And these deposits can lead to early disease complications, such as decreased visual acuity, loss of contrast sensitivity, loss of spacial discrimination, or hyper acuity, and so forth. And at some point there can be more advance complications, such as the abnormal blood vessels, and these lead - these disease end points lead to response to the tissue. And depending on how the eye responds, the patient may or may not suffer significant morbidity. We all have patients that have had choroidal neovascularization that for whatever reason still have 20/30 vision. They treated themselves, and we wish we knew how they did that. There are a number of risk factors from macular degeneration. Age is of course a classic one, and we can see here a slide I made over ten years ago showing the prevalence of macular degeneration from several population studies. Any macular degeneration defined as a single spot of sixty-three microns consistent with a soft drusen, starts in the forties and fifties, and progresses fairly rapidly in incident – I'm sorry prevalence. In terms of late AMD, it's less common starting in the sixties, and increasing rapidly thereafter. We know that the ocular features, that is the maculopathy, it's very important in predicting who will lose vision, and who will develop complications. A classic study from the macular photocoagulation study many years ago, showed that the five-year incidents of choroidal neovascularization in the second eye, as one eye already has choroidal neovascularization, the other eye does not. The five year incidents could be predicted based on four features: the number of drusen; the presence of pigmentation, which would be a sign of retinal damage; the size of the drusen, an indicator of the severity of the deposits, and then systemic hypertension. You can see that eighty five percent or more of people who had all four of those developed choroidal neovascularization over five years. And we now know that there are important genetic causes of macular degeneration. Multiple genes have been identified that – and some have stated that they explain up to seventy-five percent of AMD. I think we have to be careful with percents coming out of case control studies, because they tend to inflate the risk. But nonetheless it does demonstrate an important role. In one of the papers, the combination of two of these genes led to a fifty-seven-fold increase in the risk of AMD cases compared to controls without those homozygous risk half the types. And so we have two genes in the regulation of compliment that have been identified establishing this as a critical pathway, and it's likely that these genetic variants will impact each step of disease progression, and also a response to the disease in terms of developing morbidity. And we now know that the genetic and variance - variants interact with the environment. And there's some very exciting presentations here at ARVO this year that I will refer to later. In terms of environment, there are multiple risk

factors that have been reported: diet, lifestyle, exposures. The problem has been that these did not always show up in the same studies making it difficult to counsel patients. But we do know that some of these appear to be fairly important for maculopathy incidents, such as fatty fish consumption. And other seems to be more important, such as smoking and the development of complications, such as choroidal neovascularization. And data from the Rotterdam Study, and the Physicians Health follow up study suggests that these genetic variations interact with the environment, and give us the hope that in the not too distant future, we may be able to relate specific management recommendations at least based on epidemiological evidence to patients with individual genotypes. Looking at this in a little bit more detail, we see the complement factor H, and factor B involved in the – had been implicated in the regulation of the alternative – I'm sorry, they're established in the regulation of the alternative complement pathway, and have been established the risk factors for A and B at least the complement factor H. The factor B has been reported by one group. We find in our cohort a small non-significant association suggesting that it's either a modest overall effect, or perhaps a subgroup, which is what others will talk about more today, probably involved in AMD. And there's several reports now establishing genome chromosome ten, LOC387715, which is a theoretical gene, and there's a variation that has been found in multiple cohorts to be highly associated with AMD. And we know that others exist based on the linkage studies that have been performed to date. As an example of the gene environment interaction, if we look at smoking and the Rotterdam Study complement factor H, homozygotes, increase the risk eleven fold. You add smoking to that, and it went up to thirty-four fold. Similar findings were seen with obesity, and biomarkers systemic inflammation, such as C-reactive protein sed rate. Looking at smoking in a little bit more detail, we see that in the Rotterdam Study, the risk increased from eleven just with the genetics, add the smoking thirty-four as I mentioned earlier, and in the physician's follow up study, the risk of four to eleven. And we may have presentations later today talking about LOC387715 and smoking, which may explain some of the effect of smoking through this genetic variation. I'm going to skip this slide. So I think what this leads us to is an inflammatory hypothesis where we know there are multiple AMD genes that are involved, and some of these are very well established now. Others are in the process of being sorted out. There are possibly pro inflammatory genetic variance in CRP from the Rotterdam Study, possibly antiretinal antibodies tissue injury, and so forth may play a role in the initiation or the ongoing progression of the disease. And I think if we look at the epidemiological studies in bulk, I think we get this sense that factors that increase systemic inflammation, such as smoking, obesity, sedentary lifestyle, N minus 6, N minus 3 fatty acid ratios, increase the risk of both the incidents of the maculopathy, and the development of the complications. And

factors such as exercise in Johanna's Sedens cohort study, and low fat diet, fatty fish, vegetables, fruit, nuts, antioxidants, all these things that have been found in different studies, not necessarily in the same studies, seem to be protective. And these can be argued as factors that would decrease CRP levels, and erythrocyte sedimentation rate. So in my last eight seconds, I would like just to give a brief summary of current treatment, as I think that is sort of related to what is AMD. So currently we have no clinical trials that teach us how to manage or prevent early AMD. We have epidemiological studies that suggest fatty fish, and a hard healthy diet and lifestyle could be beneficial, and there was a report from the Rotterdam Study and New Engl – sorry the Journal of American Medical Association this year providing further evidence for that. And we have no known treatment to reverse it in terms of geographic atrophy, smoking has been implicated, but again we have no known treatment. And in terms of exudation, we have very firmly established evidence that in patients at high risk for developing choroidal neovascularization that the A red supplements, particularly the Zinc, reduce that risk significantly. And we have good evidence from epidemiological studies that these lifestyle changes we've been talking about are important. And then we have a number of drugs and expanding lists that are used to manage patients with that disease. And with that I'll go ahead and close. Thank you. Are there any questions? I talk too fast.

Q: Let me throw in a simple question. What would you recommend then at this point as far as genetic susceptibility, and a workup go? Let's say the average person – let's say I want to know if I have a gene that makes me susceptible to macular degeneration. What genes should I get worked up for or sequenced, and how much would it cost?

A: Well I'll tell you the answer to that asks several questions, but the first question is, what would you do differently if you knew your genotype? So if you were to give me a blood sample, and we could do it for, it's mostly the labor costs, and my costs, but it could be done fairly inexpensively. Look at the complement factor A's, look at the B factor, look at the To4, the LOVO4, and the LOC387715. Let's say we look at that, and we come up with some estimate of risk. What are you going to do differently today that I would not have told you as your physician to do differently already? I'm already telling you to eat fatty fish, keep your N minus 3, N minus 6 ratio in balance. That's a recommendation of the American Heart Association. I'm already telling you to eat a healthy diet, lots of fruits, vegetables. I'm already telling you to exercise. I'm already telling you not to watch too much TV, a marker of a systemic – sedentary lifestyle. So what I would say to you today is I don't have a reason to do that testing, because I can't tell you how I would tell you to live your life differently.

Q: Well maybe I'd get scared enough to start exercising?

A: That would be the value. But you know, I haven't found scaring patients very effective. I've tried it, but it doesn't work very well. They just get mad at you and don't come back. Yes sir?

Q: On your last slide you mentioned cataract surgery. Is that a positive or a negative risk factor?

A: Yes I've gone over by fifty-eight seconds, so I wanted to – didn't talk about that, but the cataract surgery story is very interesting. Some reports out of Israel uncontrolled had suggested a very high increased risk of choroidal neovascularization after cataract surgery. And then some of the prevalent studies came out and found minimal to no risk, and then they pulled their data and found a modest risk. And then most recently, and I think the best study is the A red study, because again it's a cohort study, and this is where people like me who seek cohorts in our clinic, and the epidemiologists differ a little bit, but I like the cohort studies, because those are the people that come into the clinics and see us. And the A red study found no association with cataract surgery and progression of AMD to extrusion. So I think right now what I tell patients is it may play a role. It's probably a modest role. And I tell them if they need to see better they should have cataract surgery. If they don't need to see better, just wait. I have I guess fifty more seconds.

Q: My question is about the – our accuracy in determining the phenotype of AMD. I mean after using thirty years, we now realize that actually AMD has at least different phenotypes. And to my surprise I saw that you included idiopathic polypoidal into the AMD category about excluded RAPs, which to me they have both distinct features. So what do you think about the exclusion of all this genotype in the view that AMD, or these diseases have different phenotypes, and we are not very quite sure about what phenotype we are dealing with?

A: Well first I didn't intentionally mean to exclude RAP. I just didn't have room on that slide to put it on there. So you know, what I would say is that it is a, it's a constellation of features. I mean I think if we try to say that if you RAP you don't have AMD, or if you have polyportal changes, you don't have AMD. I mean certainly there are diseases with polyportal, and there are diseases with RAP that are not AMD. And I think that your question's a very good one. And the reason why in our genetic studies, we have a very high threshold for what AMD is. And the reason for that is exactly the points you bring up. So we require a large amount of drusen and no atypical features. So I don't think that problem is going to change, and I certainly don't have an answer for it. Thank you.