The Role of Genotype in Selectively Enriching Patients for Clinical Studies

Developing Treatments for Dry Age-Related Macular Degeneration (AMD): A Workshop

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AMD-associated Genes/Loci

Chromosome 1

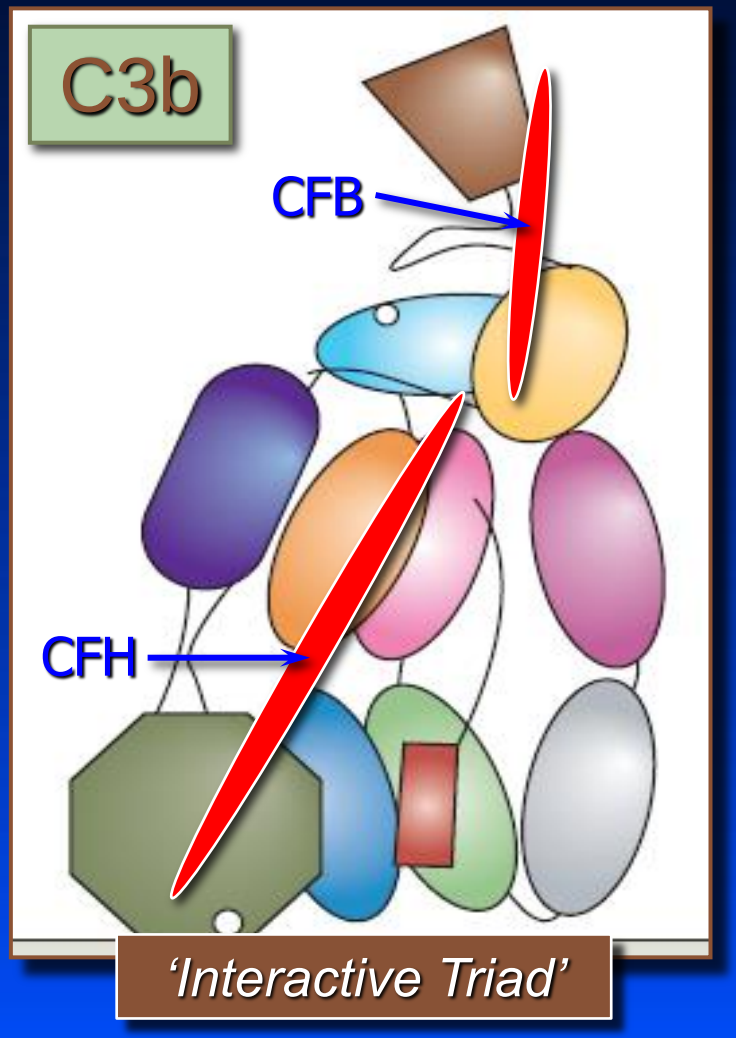
- *CFH*
- *CFHR1/CFHR3*

Chromosome 10

- *ARMS2/HTRA1*

Minor Gene Associations

- *GWAS 2013*
- *CFB/C2*
- *APOE*
- *LIPC*
- *CFI*
- *C3*



AMD-associated Genes/Loci

5.1% (161 of 3,166) of AMD cases grades 1B-4C from the combined Iowa/Utah/Melbourne cohort & 7.6% (60 of 444) of neovascular AMD cases in the combined NHS & HPFS cohorts carry no risk at *CFH* (Chr1), *ARMS2/HTRA1* (Chr10), or C3 (Chr6)

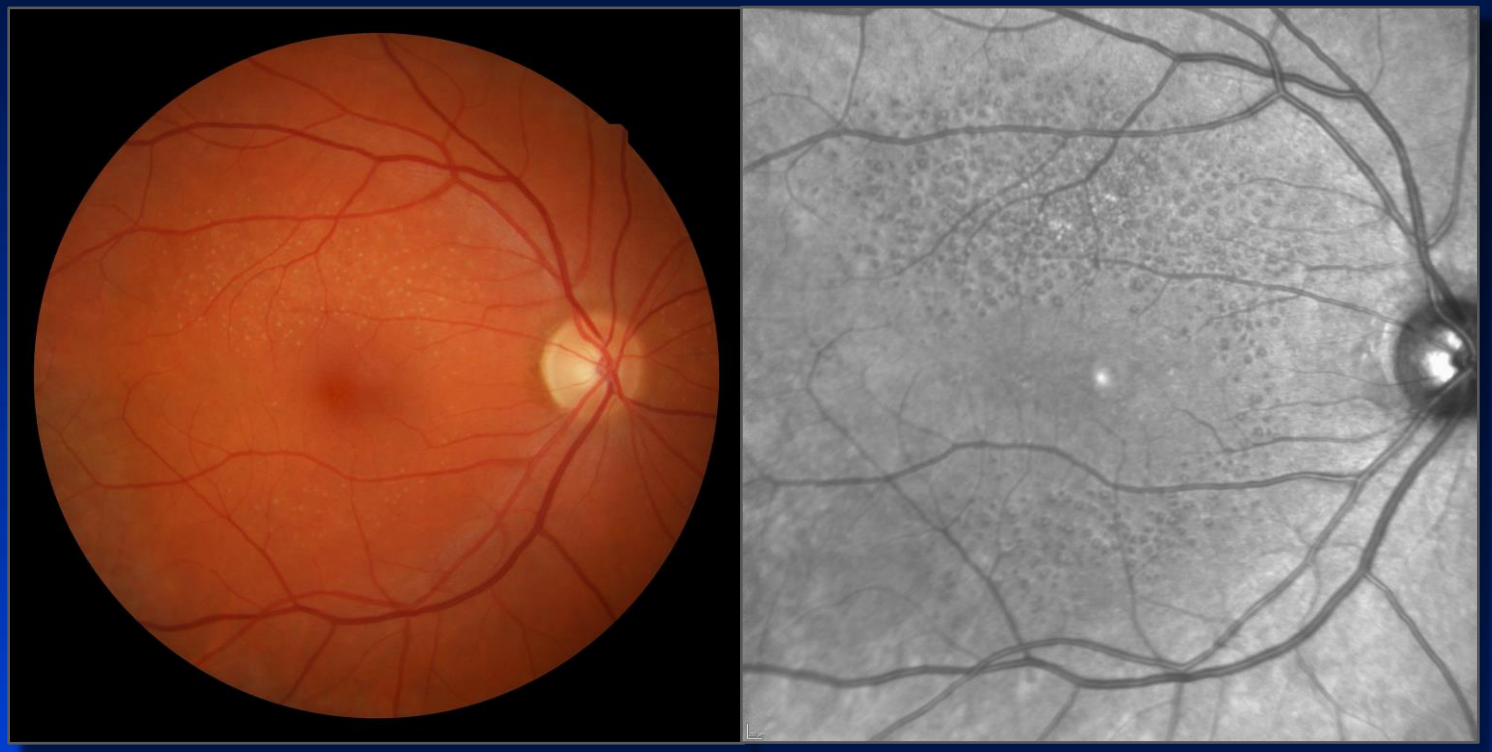
Age-related Macular Degeneration

AMD Phenotypes

Diverse clinical phenotypes of both early-stage ('drusen') & late-stage (GA, CNV, PPCV, RAP) AMD exist

Age-related Macular Degeneration

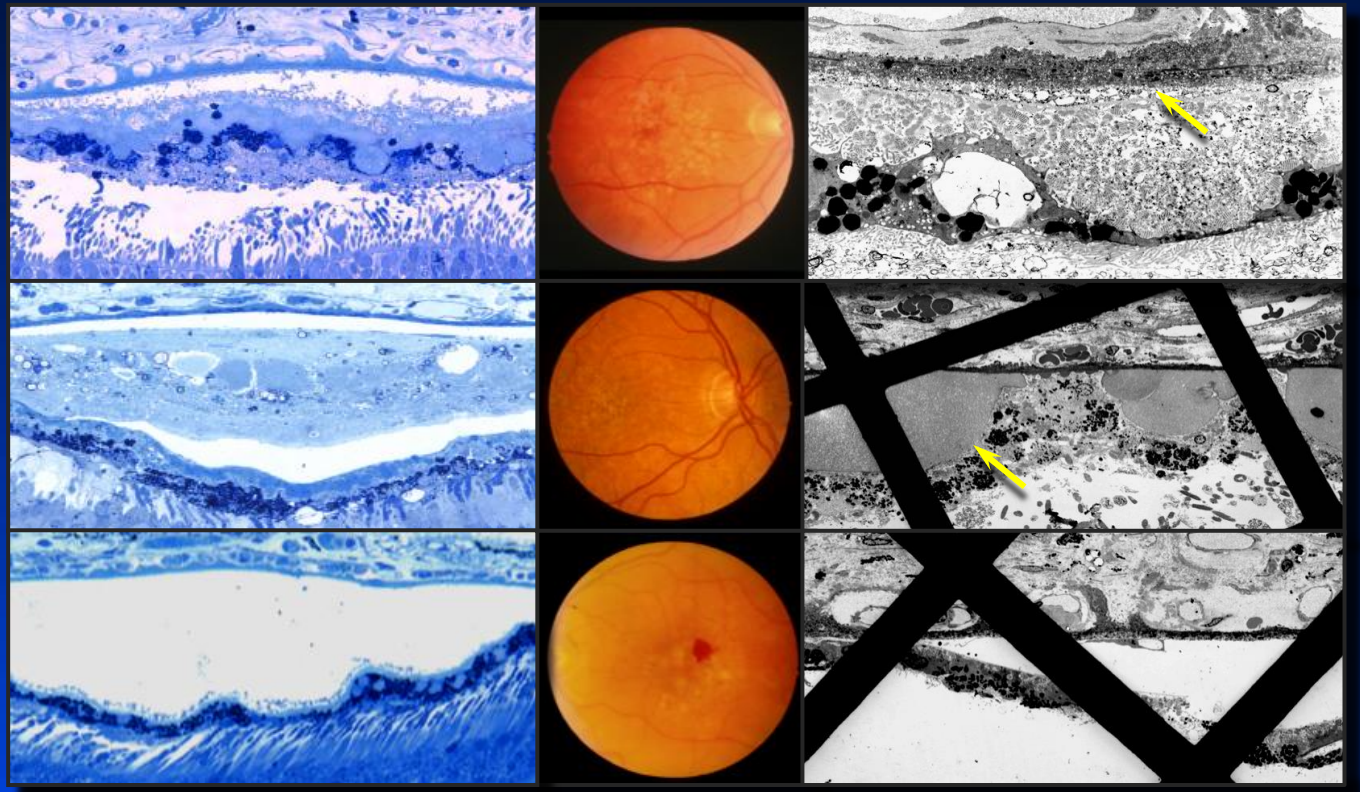
Macular 'Drusen'



'Drusen' are often 'lumped' into a single category without consideration of genotype, histological phenotype, etc.

Age-related Macular Degeneration

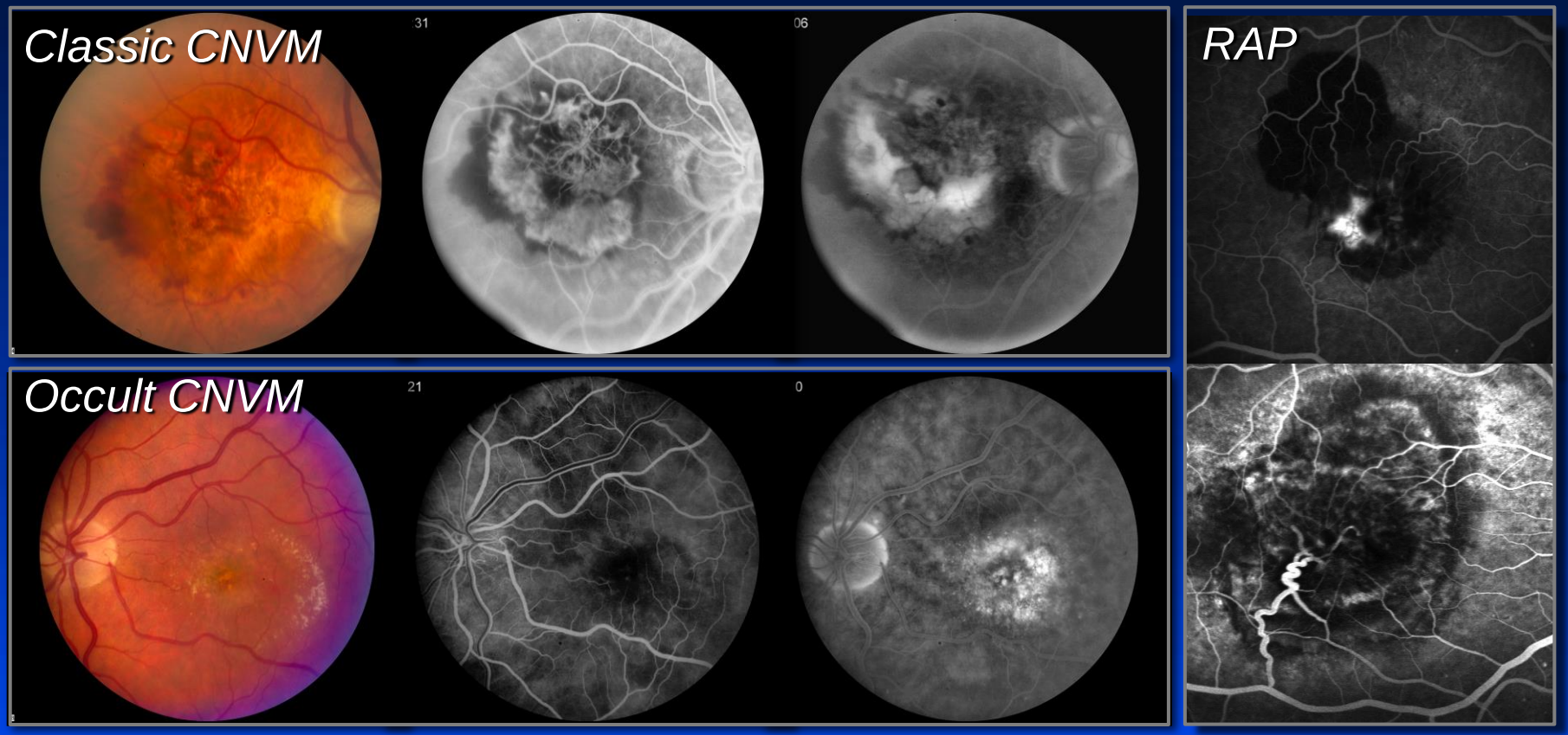
Macular 'Drusen'



In addition to clinical phenotypes, there are diverse histological, pathological, & likely functional phenotypes

Age-related Macular Degeneration

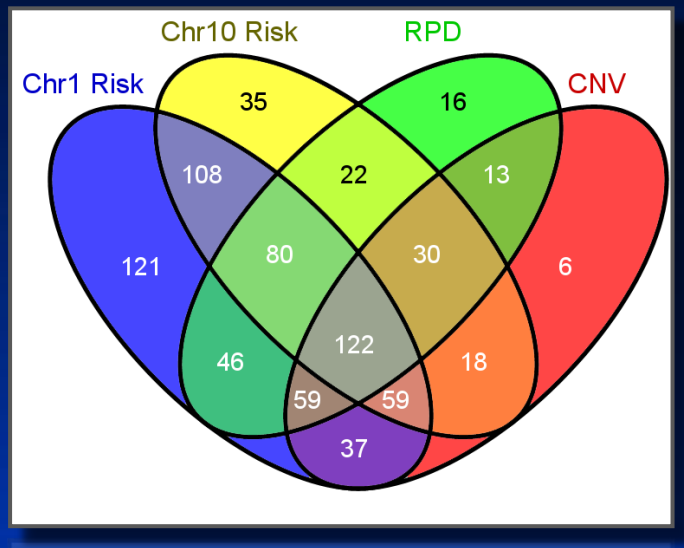
Neovascular Disease



The same is true for atrophic & neovascular phenotypes

Age-related Macular Degeneration

'Era of Refinement'



A refined understanding of genotype-phenotype associations in AMD will be crucial for the development of effective, gene-directed therapeutics

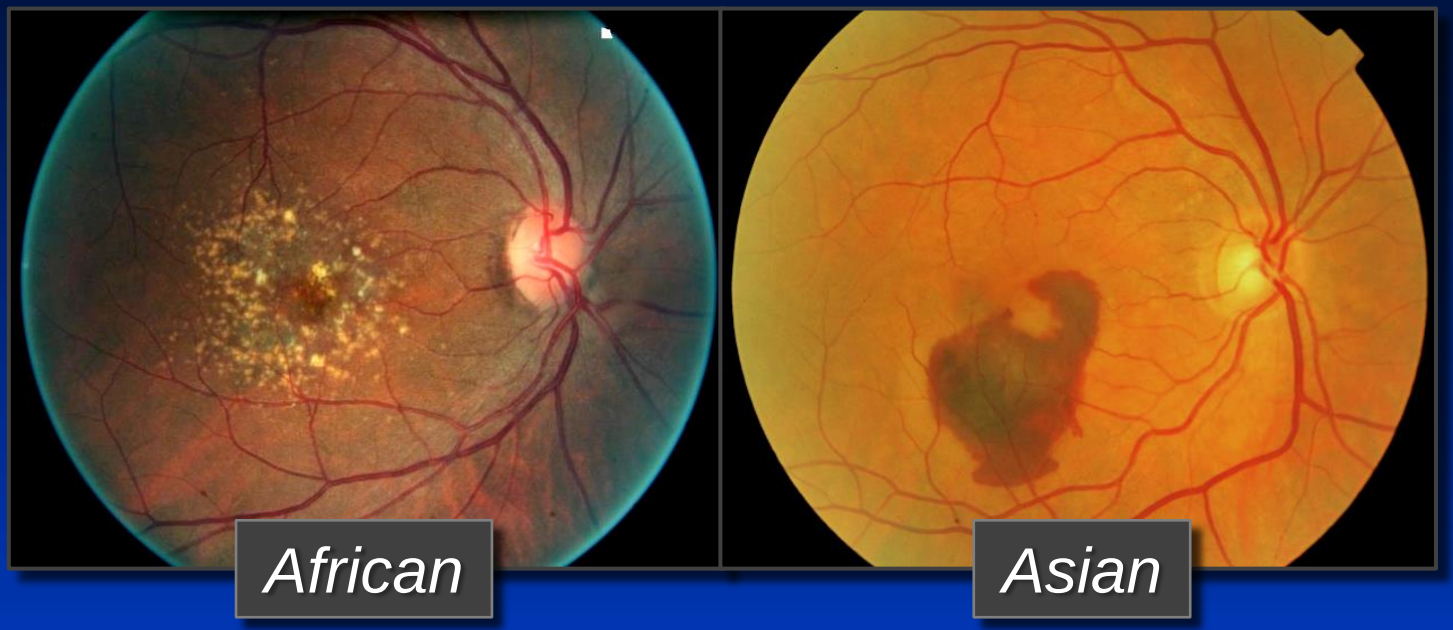
Let's not lose effective drugs for the wrong reasons!!

Chr1- & Chr10-directed Biology

- Assessment of genetic ‘outliers’ is providing a refined understanding of genotype-phenotype-pathway associations in AMD
- There is no evidence to support a direct biological interaction between AMD-associated Chr1 & Chr10 gene products

Chr1- & Chr10-directed Biology

Ethnicity-based Associations



- AMD in Ghanaian Africans is characterized by macular drusen; neovascularization is rare (paucity of ch10 risk alleles)
- AMD in Asians is primarily neovascular; macular drusen are uncommon (paucity of ch1 risk alleles)

Chr1 & Chr10 Associations

Utah, Iowa & Melbourne Cohorts (~6,000 samples)

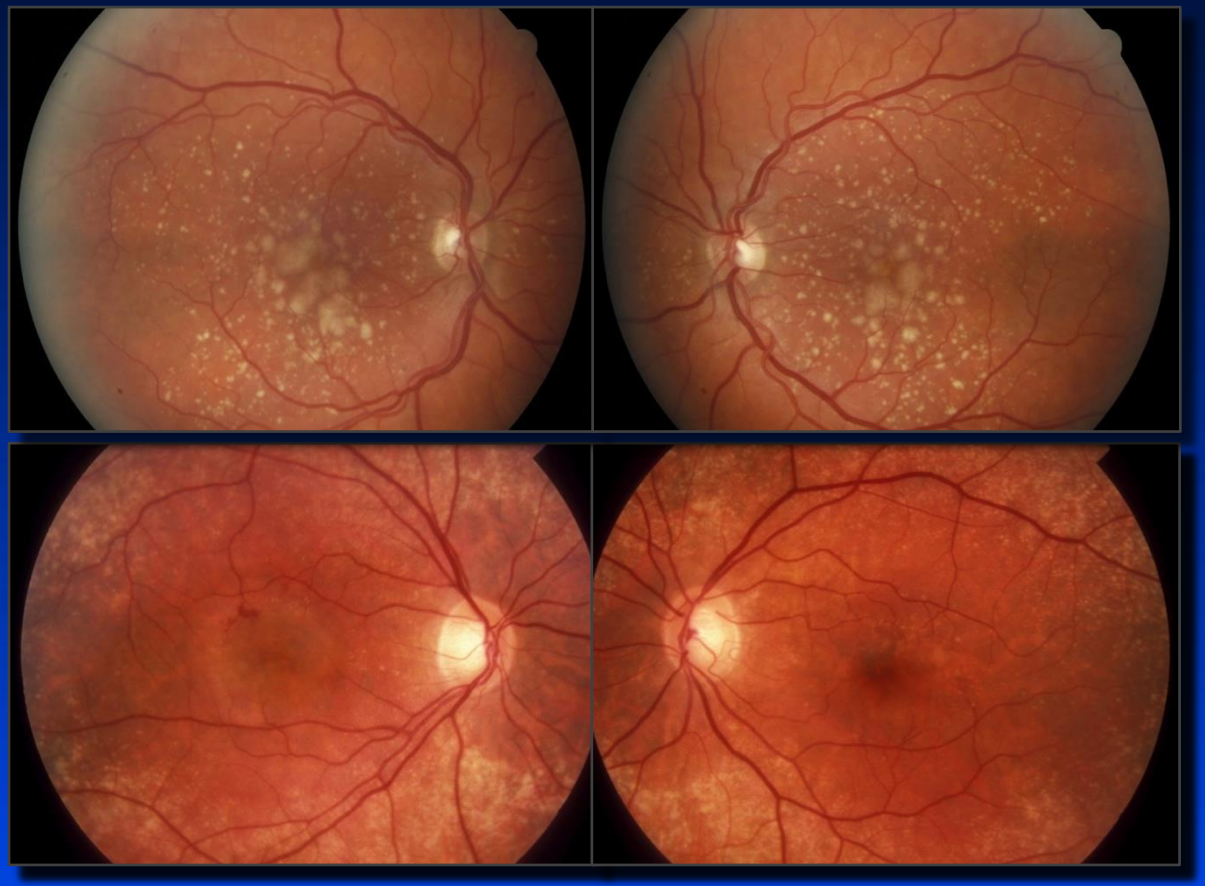
	Chr1 *(no risk @ Chr10)*	Chr10 *(no risk @ Chr1)*
	rs1061170 (Risk)	Rs10490924 (Risk)
All AMD	0.594, 0.397 **p=4.47E-25**	0.410, 0.203 **p=5.67E-18**
Early AMD (1b-3)	0.568, 0.397 **p=5.36E-10**	0.235, 0.203 p=0.3703
GA	0.565, 0.397 **p=3.17E-05**	0.398, 0.207 **p=2.72E-05**
CNV	0.613, 0.397 **p=3.56E-22**	0.465, 0.203 **p=4.86E-22**

Values represent case/control frequencies followed by p-values

- 'GA' & 'CNV' associate independently with both chromosome 1 & 10 risk variants & haplotypes (phenotypes?)
- Macular drusen are not significantly associated with chromosome 10-directed AMD

Chr1- & Chr10-directed Phenotypes

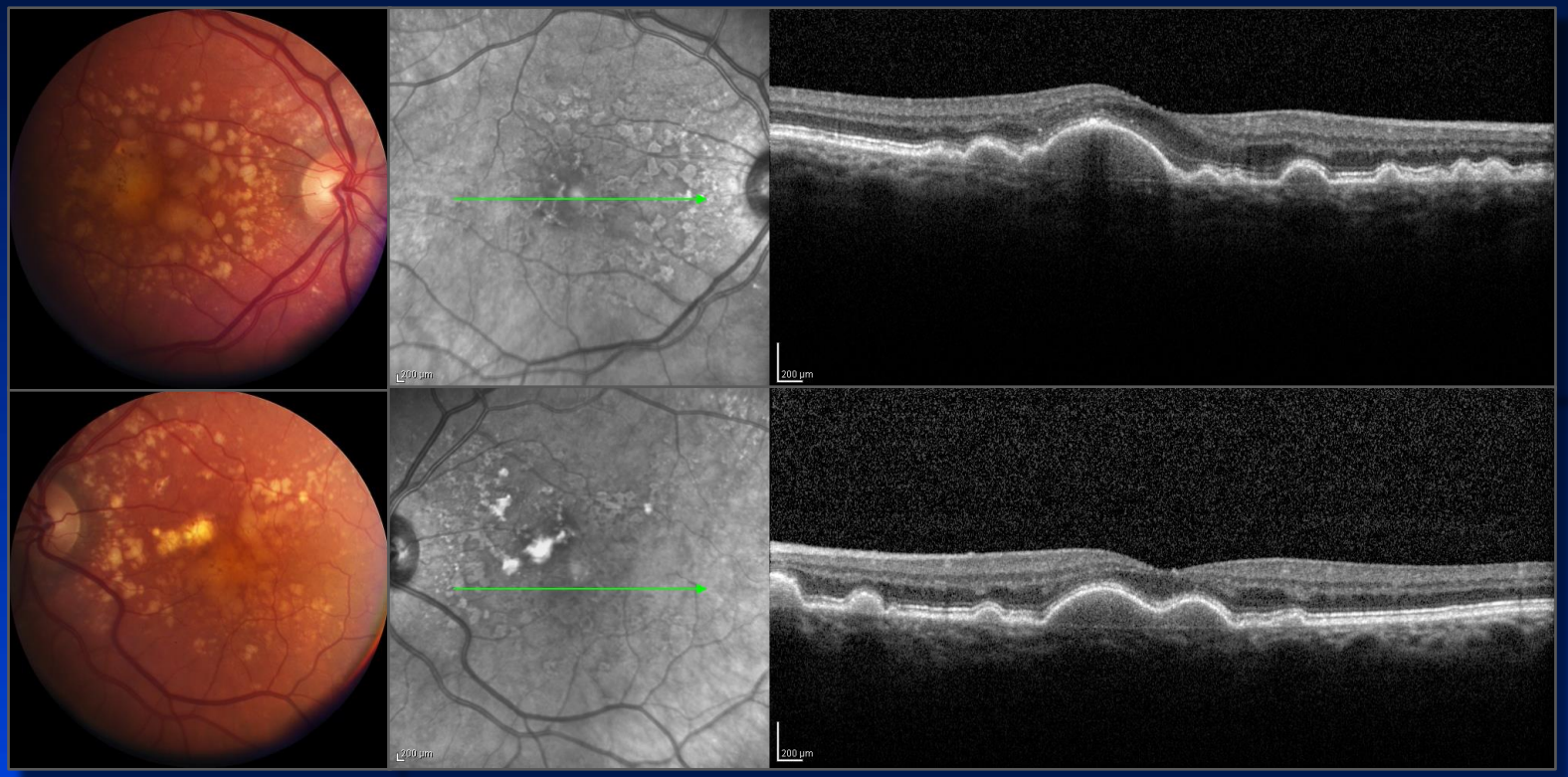
Clinical



Phenotypes of cases with Chr1- & Chr10-directed AMD exhibit distinct characteristics

Chr1-directed Phenotypes (Pre-GA/CNV)

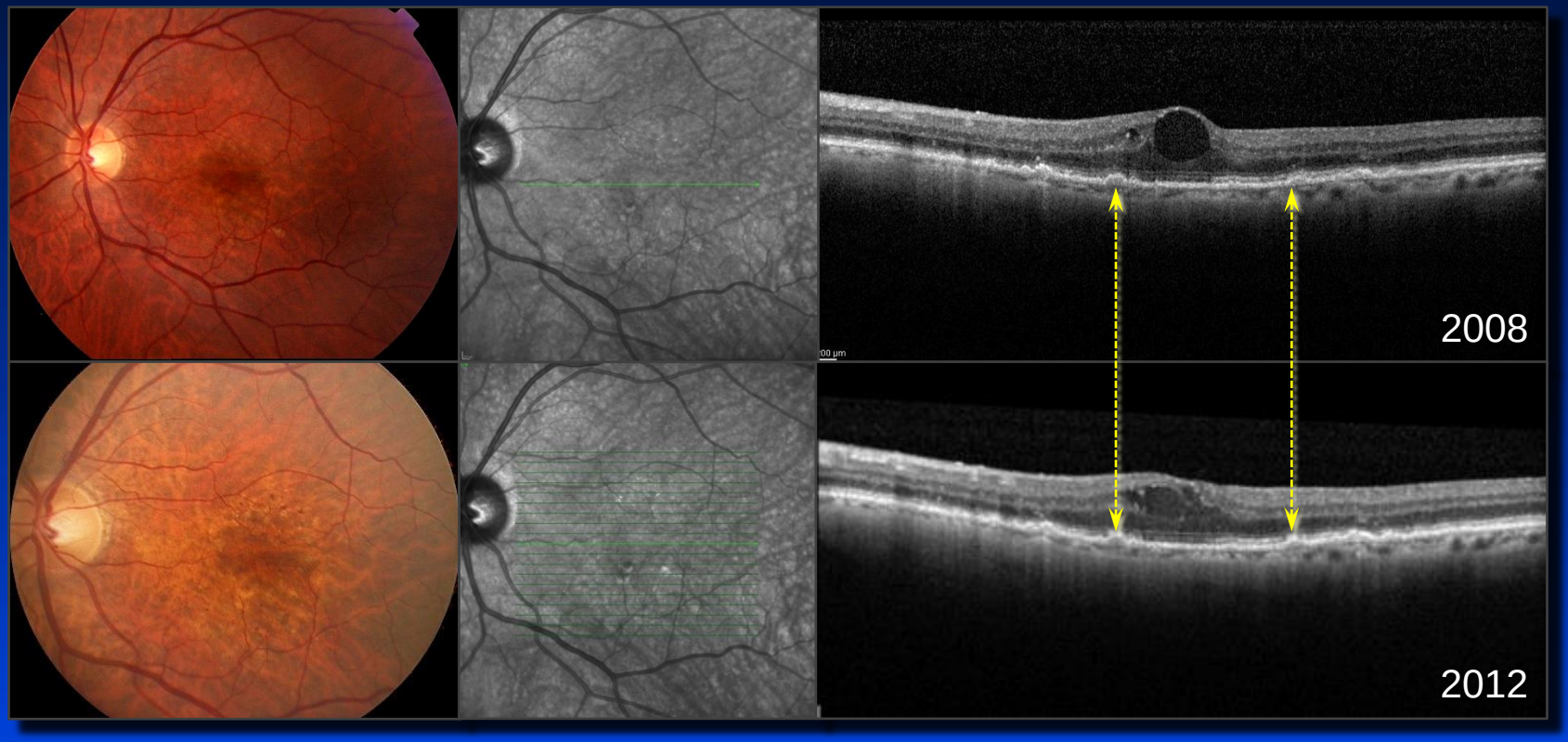
Homozygous Risk at Chromosome 1 (464-10)



'Typically' characterized by large soft, coalescing drusen/ PEDs, as compared to Chr10-directed phenotypes

Chr10-directed Phenotypes (Pre-GA/CNV)

Homozygous Risk at Chromosome 10 (560-11)



'Typically' characterized by fewer & smaller macular drusen, as compared to Chr1-directed phenotype

Chr1- & Chr10-directed Phenotypes

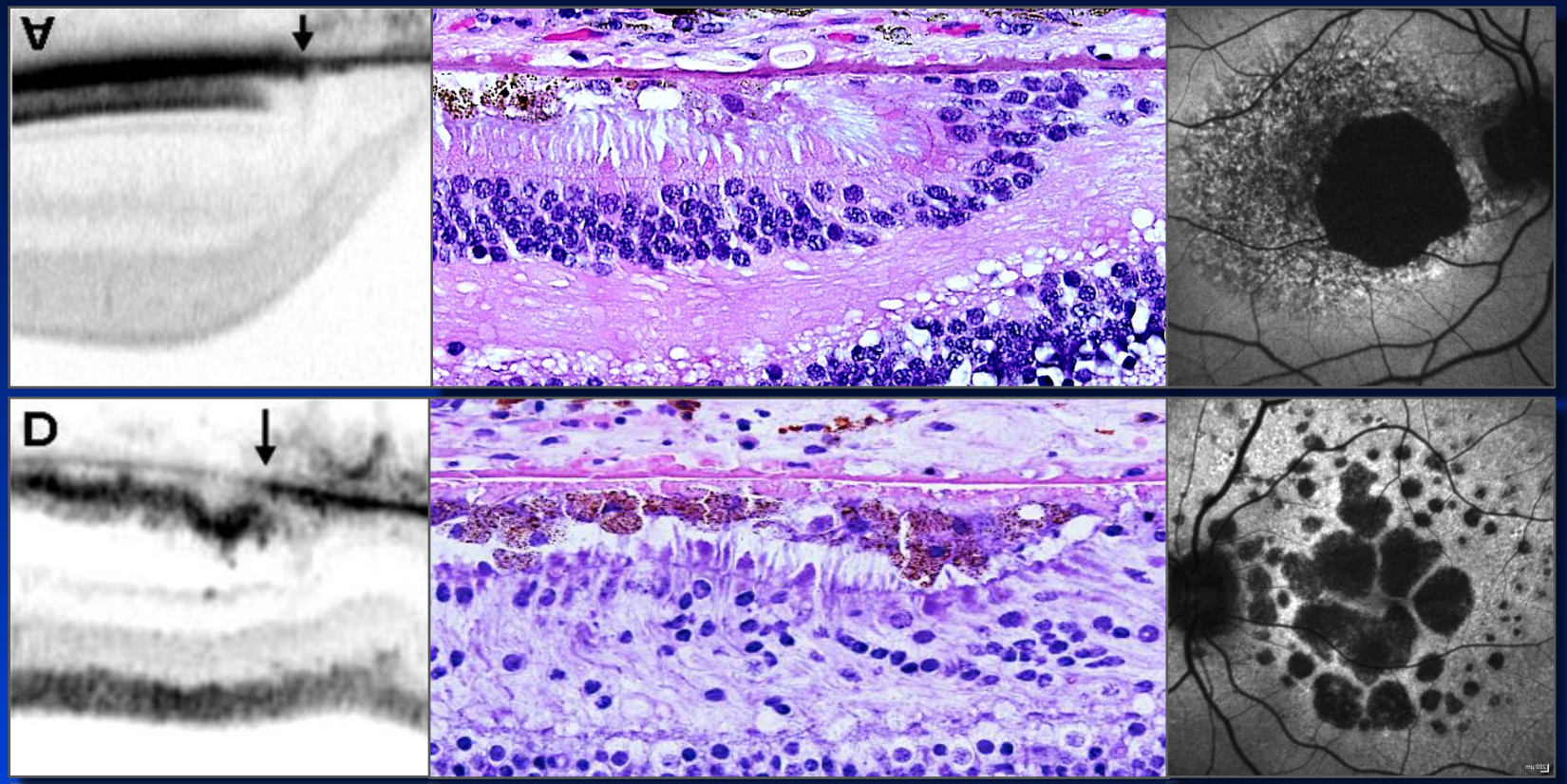
Utah, Iowa & Melbourne Patient Cohorts

	CC/GG	TT/TT
Grade	Risk @ Chr1	Risk @ Chr10
Unaffected (0)	**23%**	7%
Early (1B-3)	**34%** (**45%** AREDS grade 3)	17% (8% AREDS grade 3)
GA (4A)	7%	**12%**
CNV (4B)	34%	**60%**
GA & CNV (4C)	2%	4%
Ave Age Initial CNV	78.6 years	**72.8 years**

- Drusen are more common in Chr1 patients (phenotype?)
- CNV & GA are more prevalent in Chr10 patients
- Average age of initial CNV is younger in Chr10 patients

Chr1- & Chr10-directed AMD

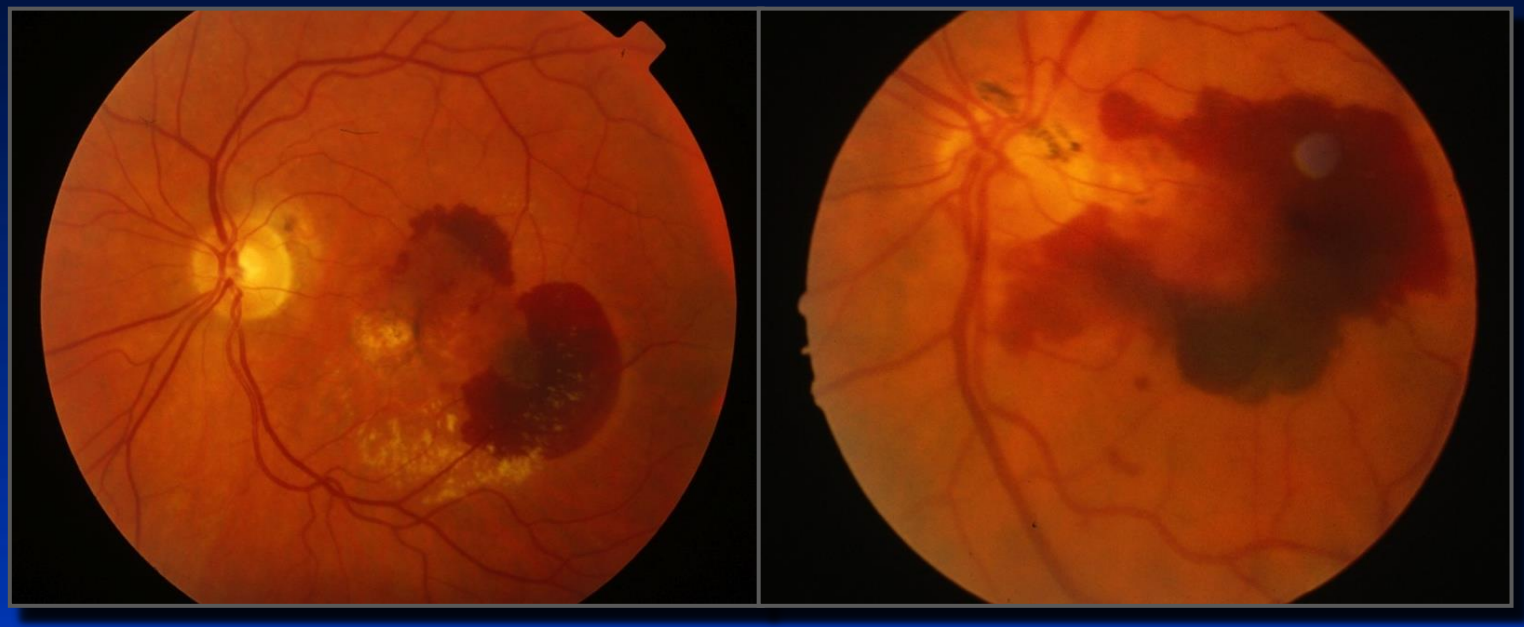
Geographic Atrophy



Chr1- & Chr10-directed geographic atrophy may also be distinct…stay tuned

Chr1- & Chr10-directed Biology

Overview



- *The biological manifestations of 'Chr1-directed' AMD are also distinct from those of 'Chr10-directed' AMD*
  - ✓ *Gene expression (patient samples & eye repository)*
  - ✓ *Serum biomarkers (patient samples)*
  - ✓ *Histology (eye repository)*

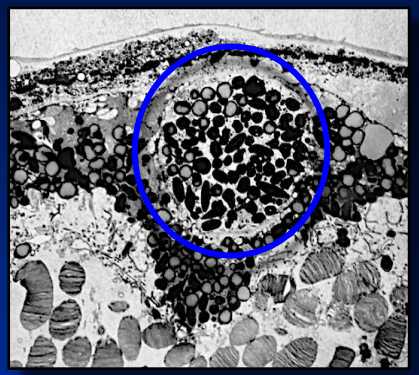
Chr1- & Chr10-directed Biology

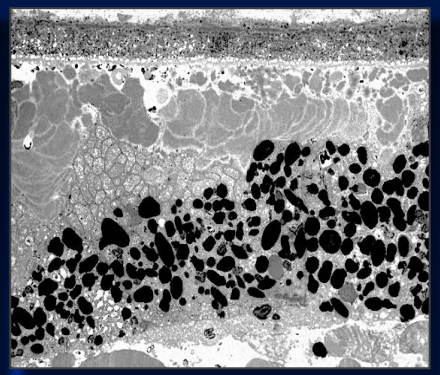
Histological Associations

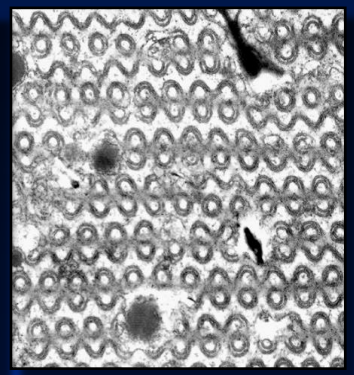
There is marked histological variation between chromosome 1- and chromosome 10-directed AMD

Morphometric data generated from >700 pairs of human donor eyes

Multivariate regression model corrected for gender & age







Feature	P Value	
	Ch1 Risk	Ch10 Risk
Macular drusen	**1.8×10^{-5}**	0.023
Thickened Bruch's membrane	**0.0027**	0.43
RPE 'spheres'	**0.0071**	0.11
Sub-RPE BLD (grade 3)	0.44	**1.8×10^{-12}**
Choriocapillaris ghosts	0.44	**2.6×10^{-5}**
Choroidal fibrosis	0.24	**0.0053**
Basal linear deposits	0.52	0.054

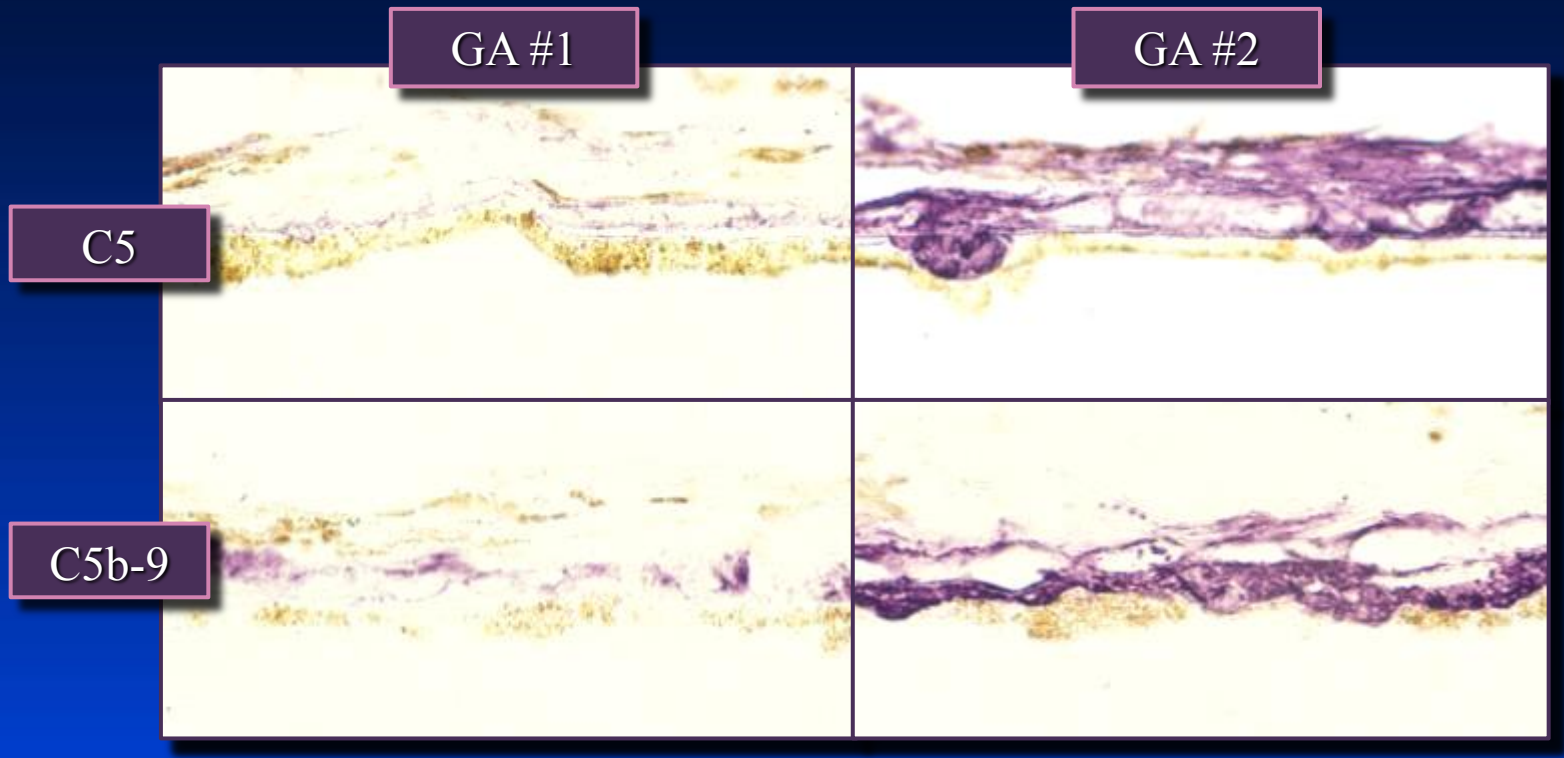
Age-related Macular Degeneration

'Take Home' Messages

- New insights into the underpinning biology of AMD suggest that it is multiple, distinct biological diseases rather than a single, complex trait disease
- A refined understanding of genotype-phenotype associations will be critical to the identification of gene-directed pathways & targets, the development of therapeutics & the design of clinical trials
- Major implication – an individual may have more than one disease

AMD (GA) & MAC (C5b-9)

RPE-Choroid Interface



The levels of C5 & C5b-9 at the macular RPE-choroid interface are low &/or non-existent in a subset of donors with AMD