What is Asian Age-related macular degeneration and why does it matter?

Professor Gemmy Cheung
Lead Principal Investigator
Singapore Eye Research Institute

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Translational Asian Age-related macular degeneration Programme

NMRC National Medical Research Council Singapore
OPEN FUND - LARGE COLLABORATIVE GRANT

SINGAPORE EYE RESEARCH INSTITUTE
Singapore National Eye Centre SingHealth
DukeNUS Medical School
Tan Tock Seng Hospital National Healthcare Group
NUHS National University Health System
NANYANG TECHNOLOGICAL UNIVERSITY
Agency for Science, Technology and Research SINGAPORE

Translational Asian AMD Program (OF-LCG 2018-2024)

DukeNUS Medical School

Agency for Science, Technology and Research SINGAPORE

NANYANG TECHNOLOGICAL UNIVERSITY SINGAPORE

Tan Tock Seng HOSPITAL National Healthcare Group

NUHS National University Health System

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Our goals

Major impact on clinical care outcome of AMD in Asia and worldwide

Establish Singapore team as a key international center for AMD research

- Capacity building, training and development of local expertise
- Collaboration between institution within Singapore and internationally
- Income generation through partnering with industry and generation of IP
- Incorporation of digital technology and AI

Our Vision

- Address Unmet Clinical Needs and Scientific Gaps focusing on Asian-specific aspects
- Develop paradigm shifts in our understanding of Asian AMD, that will lead to novel classification and evidence-based cost effective diagnostics, prevention and treatment strategies
- Blindness reduction from AMD by 20% within 10 years.

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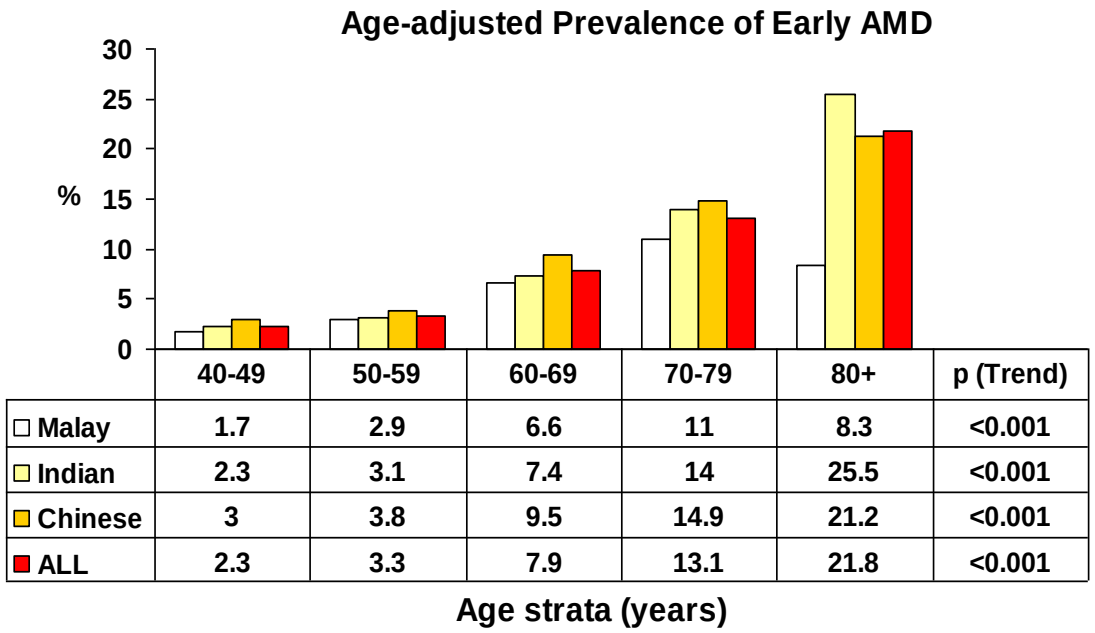
Age-related Macular Degeneration

One of the most common neurodegenerative conditions
Leading cause of blindness in US, UK; 2nd in Singapore



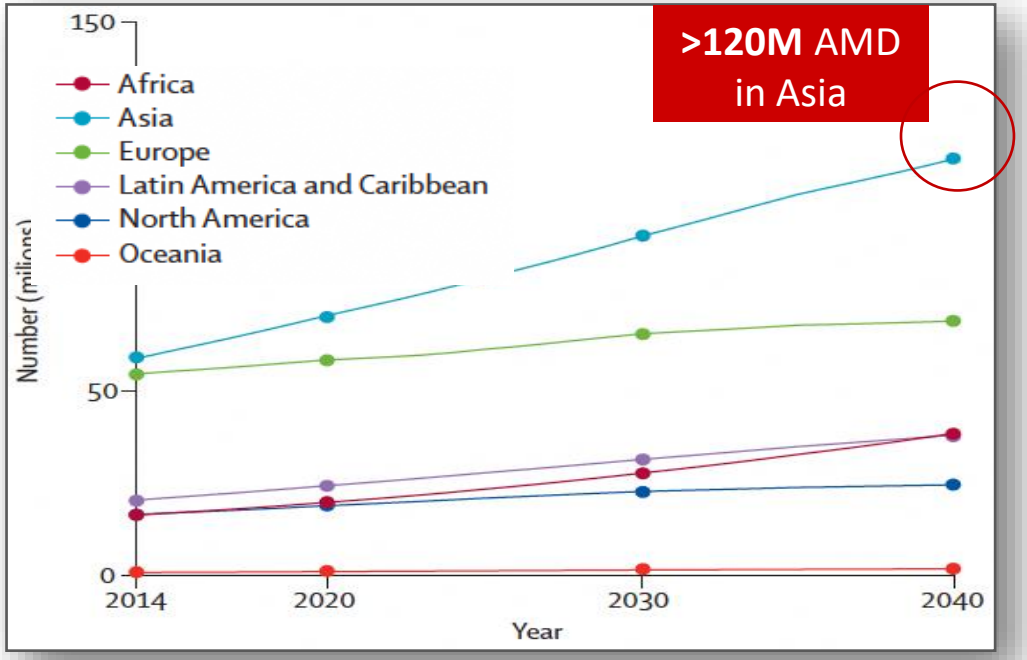
	40-49	50-59	60-69	70-79	80+	p (Trend)
Malay	1.7	2.9	6.6	11	8.3	<0.001
Indian	2.3	3.1	7.4	14	25.5	<0.001
Chinese	3	3.8	9.5	14.9	21.2	<0.001
ALL	2.3	3.3	7.9	13.1	21.8	<0.001

Cheung et al., Ophthalmology, 2014; 121(8):1598-603

Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis

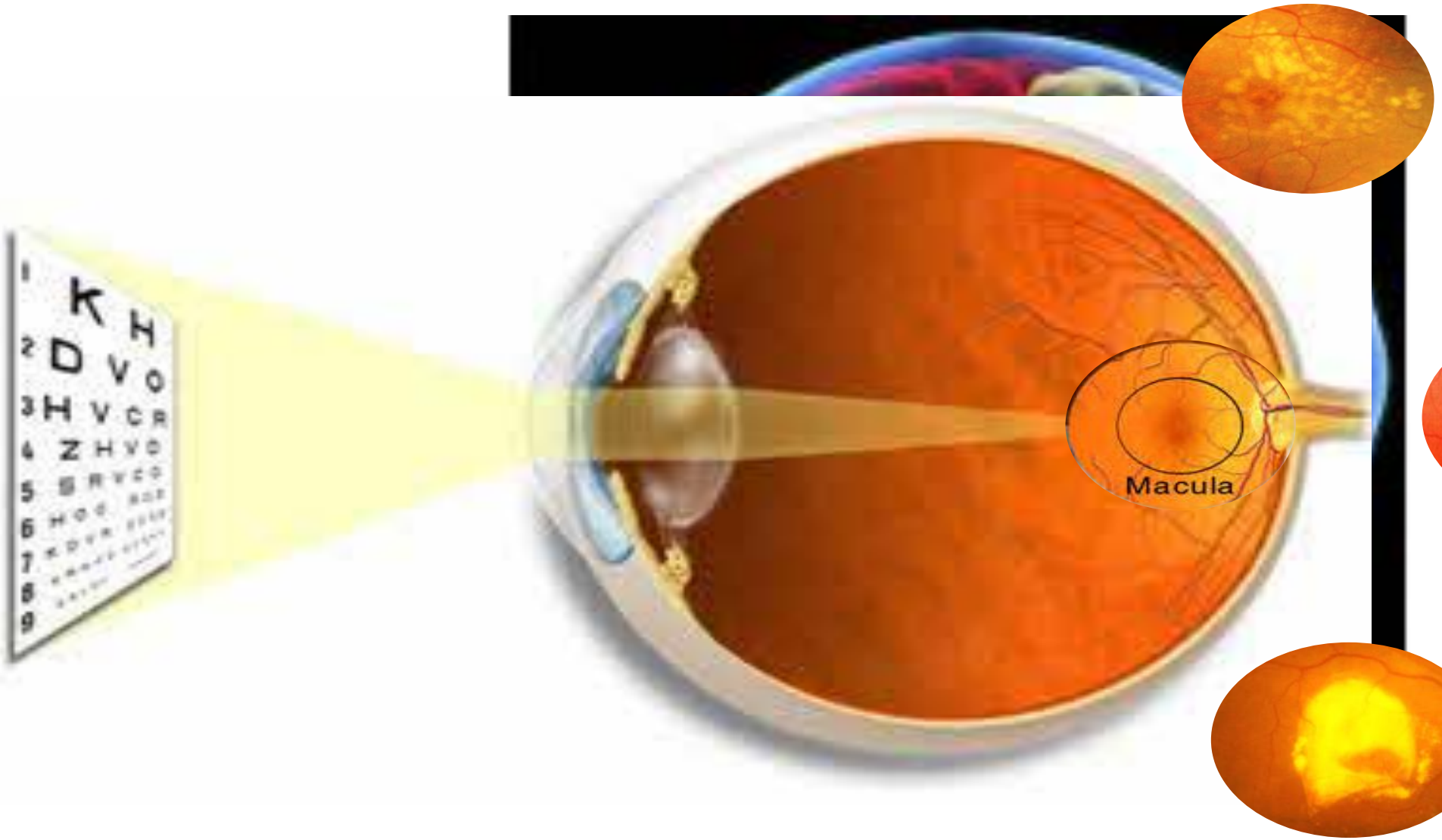
Wan Ling Wong, Xinyi Su*, Xiang Li, Chui Ming G Cheung, Ronald Klein, Ching-Yu Cheng†, Tien Yin Wong†*

Summary
Background Numerous population-based studies of age-related macular degeneration have been reported around the world, with the results of some studies suggesting racial or ethnic differences in disease prevalence. Integrating these resources to provide summarised data to establish worldwide prevalence and to project the number of people with age-related macular degeneration from 2020 to 2040 would be a useful guide for global strategies.



Wong et al. Lancet Global Health, 2014; 2(2): e106-16

Globally, **288M** persons with AMD by 2040



Amyloid,
Complement,
Lipid deposits

Ischemia
Angiogenesis

Fibrosis
Atrophy
Cell Death

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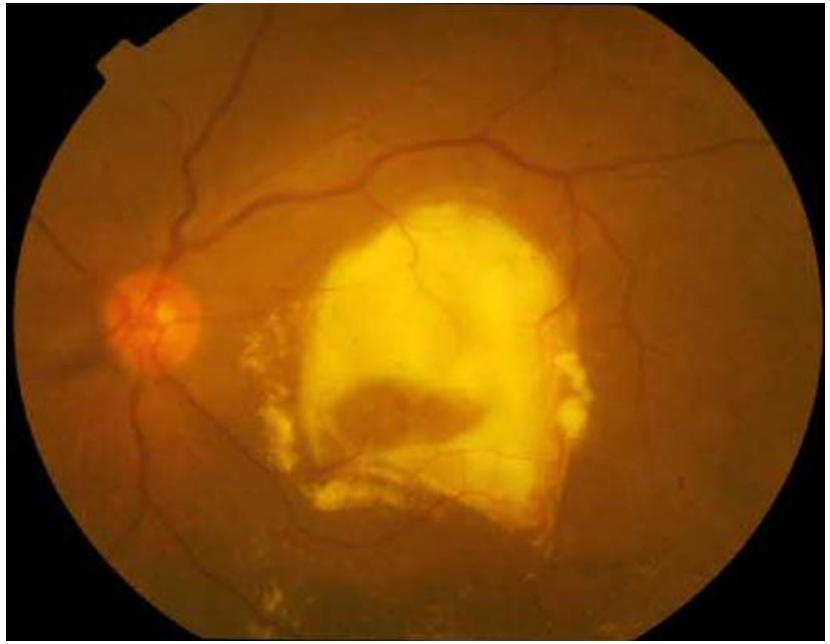
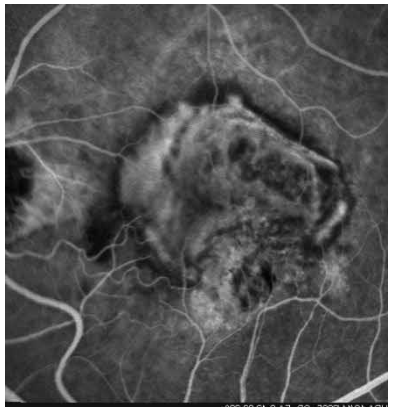
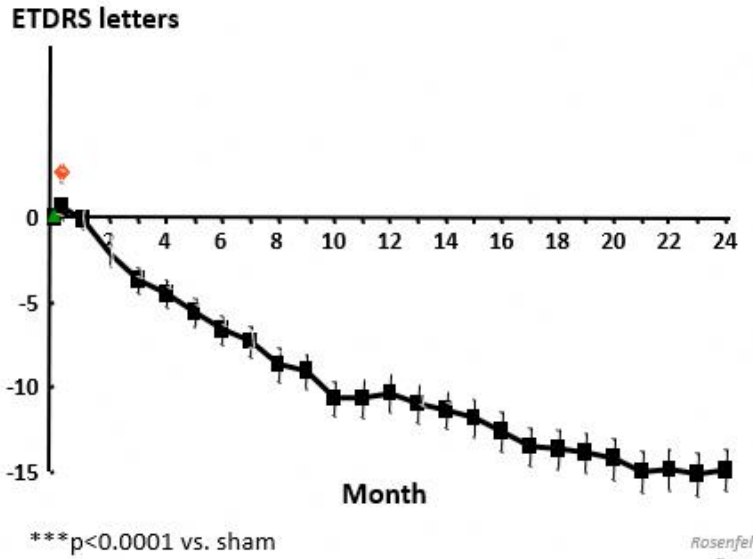
Age-related Macular Degeneration

Without treatment most sufferers progress to loss of all practical central vision in 2 years







Chakravarthy, U. et al. BMJ 2010;340:c981

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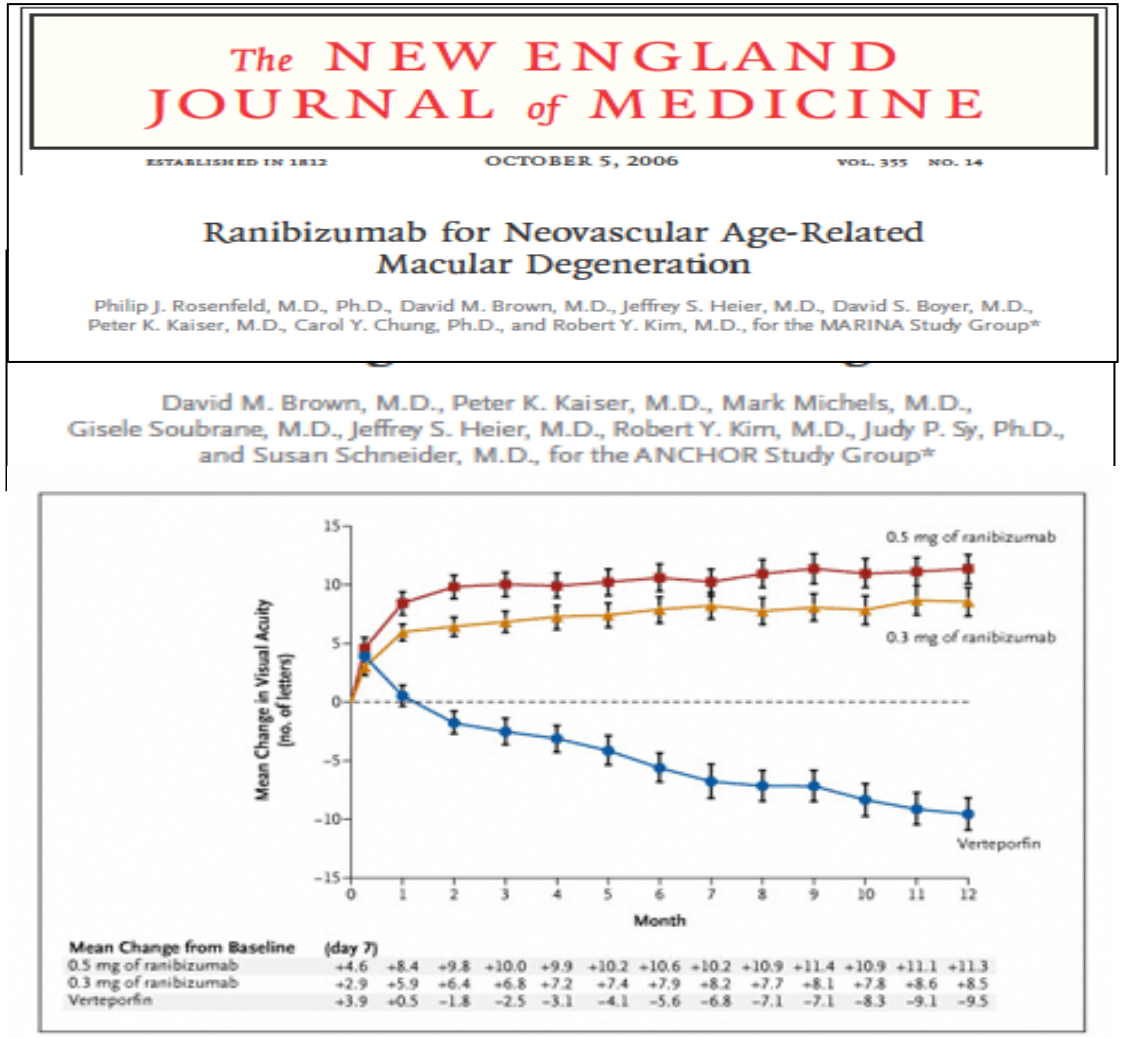
Game-changers



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 5, 2006 VOL. 355 NO. 14

Ranibizumab for Neovascular Age-Related Macular Degeneration

Philip J. Rosenfeld, M.D., Ph.D., David M. Brown, M.D., Jeffrey S. Heier, M.D., David S. Boyer, M.D., Peter K. Kaiser, M.D., Carol Y. Chung, Ph.D., and Robert Y. Kim, M.D., for the MARINA Study Group*

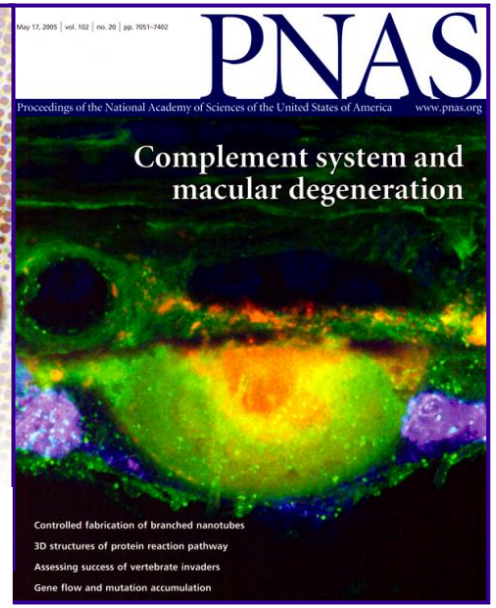
David M. Brown, M.D., Peter K. Kaiser, M.D., Mark Michels, M.D., Gisele Soubrane, M.D., Jeffrey S. Heier, M.D., Robert Y. Kim, M.D., Judy P. Sy, Ph.D., and Susan Schneider, M.D., for the ANCHOR Study Group*

Mean Change from Baseline	(day 7)												
0.5 mg of ranibizumab	+4.6	+8.4	+9.8	+10.0	+9.9	+10.2	+10.6	+10.2	+10.9	+11.4	+10.9	+11.1	+11.3
0.3 mg of ranibizumab	+2.9	+5.9	+6.4	+6.8	+7.2	+7.4	+7.9	+8.2	+7.7	+8.1	+7.8	+8.6	+8.5
Verteporfin	+3.9	+0.5	−1.8	−2.5	−3.1	−4.1	−5.6	−6.8	−7.1	−7.1	−8.3	−9.1	−9.5

Complement Factor H Polymorphism in Age-Related Macular Degeneration

Robert J. Klein,[1] Caroline Zeiss,[2]* Emily Y. Chew,[3]* Jen-Yue Tsai,[4]* Richard S. Sackler,[1] Chad Haynes,[1] Alice K. Henning,[5] John Paul SanGiovanni,[3] Shrikant M. Mane,[6] Susan T. Mayne,[7] Michael B. Bracken,[7] Frederick L. Ferris,[3] Jurg Ott,[1] Colin Barnstable,[2] Josephine Hoh[7]†

Age-related macular degeneration (AMD) is a major cause of blindness in the elderly. We report a genome-wide screen of 96 cases and 50 controls for polymorphisms associated with AMD. Among 116,204 single-nucleotide polymorphisms genotyped, an intronic and common variant in the complement factor H gene (*CFH*) is strongly associated with AMD (nominal *P* value $<10^{-7}$). In individuals homozygous for the risk allele, the likelihood of AMD is increased by a factor of 7.4 (95% confidence interval 2.9 to 19). Resequencing revealed a polymorphism in linkage disequilibrium with the risk allele representing a tyrosine-histidine change at amino acid 402. This polymorphism is in a region of CFH that binds heparin and C-reactive protein. The *CFH* gene is located on chromosome 1 in a region repeatedly linked to AMD in family-based studies.



Haines JL et al. *Science* 2005;308:419-21 Edwards A et al. *Science* 2005;308:421-4
Klein RJ et al. *Science* 2005;308:385-9 Hageman G et al , PNAS, 2005

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Asia Pacific Academy of Ophthalmology 2021

Polypoidal Choroidal Vasculopathy- Treat like Neovascular AMD?

Dr. Gemmy Cheung

Head and Senior Consultant, Medical Retina Department, S

Professor, Duke-NUS Medical School, National University o

EURETINA 2015

Asian Macular Degeneration & Polypoidal Vasculopathy

Same or Different diseases?

Dr. Gemmy Cheung FRCOphth
Singapore National Eye Centre

SINGAPORE EYE RESEARCH INSTITUTE
Singapore National Eye Centre SingHealth
NUS

Controversies in Ophthalmology 2021

PCV TREATMENT TYPICALLY SHOULD COMBINE ANTI-VEGF AND PDT ??

Gemmy Cheung

Professor, National University of Singapore

Head, Medical Retinal Department, Singapore National Eye Centre

The NEW ENGLAND JOURNAL of MEDICINE

Ranibizumab and Bevacizumab for AMD

TO THE EDITOR: Bevacizumab is the predominant agent used for the treatment of neovascular age-related macular degeneration (AMD) worldwide, and the study by the Comparison of AMD Treatments Trials (CATT) research group (May 19 issue)[1] should have far-reaching influence on global practice patterns.[2] However, considerable uncertainty is likely to remain in Asia, whose population was not addressed by CATT. The unfortunate truth remains that 80% of all new drugs are discovered in the United States and Europe, are tested in subjects of European descent, and are then administered to Asians on the presumption of similar therapeutic response.[3] In-

8%).[4] Bevacizumab monotherapy (as evaluated in CATT) is less efficacious in patients with polypoidal choroidal vasculopathy than in those with classic neovascular AMD.[4] In China alone, there may be 1.68 million patients with neovascular AMD,[5] and of these patients, nearly 900,000 will have polypoidal choroidal vasculopathy. Treatment of these patients will continue to rely on data from uncontrolled studies or from extrapolation trials testing interventions in subjects of European descent until such time as clinical trials are conducted that specifically target neovascular AMD in Asian populations.

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Dr. Wong reports serving on advisory boards for Allergan, Bayer, Novartis, Pfizer, and Solvay and receiving travel, honorarium, and research support from these companies. No other potential conflict of interest relevant to this letter was reported.

1. The CATT Research Group. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med 2011;364:1897-908.
2. Rosenfeld PJ. Bevacizumab versus ranibizumab for AMD. N Engl J Med 2011;364:1966-7.
3. Light DW. Global drug discovery: Europe is ahead. Health Aff (Millwood) 2009;28:w969-w977.
4. Laude A, Cackett PD, Vithana EN, et al. Polypoidal choroidal vascul
5. Ka
related
meta-a

THE AUTHORS REPLY: Cheung and Wong write that our results may not apply to Asian populations because of the higher prevalence of polypoidal choroidal vasculopathy. We agree with this assertion.

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Since publication of their article, the authors report no further potential conflict of interest.

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What Is Asian AMD and why does it matter?

- Phenotypic variations and management implications

- Develop novel therapies targeting genetic and functional alterations

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Building Strategic Partnerships and Enabling Translational Research

- Phenotypic variations and management implications
  - Phenotypic comparison (International academic, devices)
  - Therapeutic Implications (Industry partners)
  - Management Guidelines (Professional bodies)

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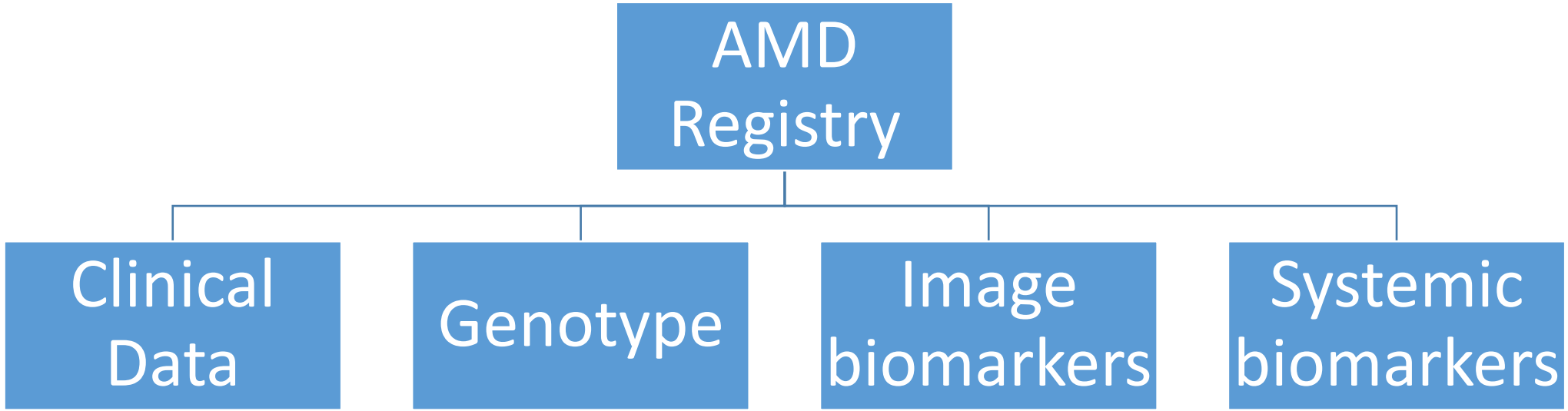
Phenotyping Asian AMD study (NIG 2009)



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Multimodal Imaging Comparison of Polypoidal Choroidal Vasculopathy Between Asian and Caucasian Populations

FEDERICO CORVI, SHRUTI CHANDRA, ALESSANDRO INVERNIZZI, LUCIA PACE, FRANCESCO VIOLA, SOBHA SIVAPRASAD, GIOVANNI STAURENGHI, CHUI MING GEMMY CHEUNG, AND KELVIN YI CHONG TEO

• PURPOSE: Differences in multimodal imaging features between Asian and Caucasian eyes may contribute to our understanding of the etiology of the polypoidal choroidal vasculopathy (PCV). The purpose of this study was to compare the multimodal imaging features of Asian and Caucasian eyes with PCV.

• DESIGN: Cross-sectional, retrospective, multicenter, observational case series.

• METHODS: Con... diagnosed with PCV b... aphy in accordance wi... aphic and multimodal i... ndus photography, spec... ogra- phy, fluorescein a... n an- giography were gr...

• RESULTS: A tot... (128 Asian vs 122 C... uded. Asian participants presented with lower best corrected visual acuity (mean ± SD: 0.7 ± 0.6 logMAR vs 0.4 ± 0.3 logMAR; $P < .001$) compared with Caucasian participants. More Asian eyes had subretinal hemorrhage (mean ± SD: 53.9% vs 24.6%; $P < .001$) and larger areas of hemorrhage (mean ± SD: 7.5 ± 15.2 mm^2 vs 1.3 ± 3.3 mm^2; $P < .001$). More Asian eyes had pachyvessels (84.4% vs 28.7%; $P < .001$), choroidal vascular hyperpermeability (70.3% vs 17.2%; $P < .001$), and widespread polypoidal lesions (19.5% vs 8.2%; $P = .005$), and Caucasian eyes had more drusen (79.5% vs 49.2%; $P = .02$).

Singapore
Italy
UK

Phenotypic and genetic variations between Asian and Caucasian polypoidal choroidal vasculopathy

Janice Marie Jordan-Yu,[1,2] Kelvin Teo,[1,2] Qiao Fan,[3] Jose Carlos Gana,[2] Anna Karina Leopando,[2] Sandrina Nunes,[4,5] Cláudia Farinha,[4,6] Patricia Barreto,[4,5] Joana Barbosa Melo,[7,8] Isabel Carreira,[7,8] Joaquim Neto Murta,[4,5] Rufino Silva,[4,5,9] Chui Ming Gemmy Cheung[1,2]

ABSTRACT

Purpose To compare phenotypic a... in polypoidal choroidal vasculopathy... Caucasian and Asian patients.

Methods We analysed phenotypic... from two sites, Association for Innov... Research on Light and Image, Portu... National Eye Centre, Singapore. Baseline fundus photography, spectral domain-optical coherence tomography, indocyanine green and fluorescein angiography scans were analysed by respective reading centres using a standardised grading protocol. Single nucleotide polymorphisms across 8 PCV loci were compared between cases and controls selected from each population.

Results One hundred and forty treatment-naïve PCV participants (35 Portuguese and 105 Singaporean) were included. The Portuguese cohort were older (72.33±8.44 vs 68.71±9.40 years, p=0.043) and were comprised of a lower proportion of males (43% vs 71%, p=0.005) compared with the Singaporean cohort. Differences in imaging features include higher prevalence of soft drusen (66% vs 30%, p=0.004), lower prevalence of subretinal haemorrhage (14% vs 67%, p<0.001), smaller polypoidal lesion (PL) area (0.09±0.09 vs 0.76 ±0.93 mm^2, p<0.001), lower ratio of PL to branching

Singapore
Portugal

characteristic polypoidal dilatations, and is often ...with a paucity of drusen and choroidal ...

...differences in phenotypes between ... Caucasian PCVs have previously been ... PCV vascular lesions are commonly ...e peripapillary area in Caucasians versus the predominantly macular lesions in Asians.[4,5] PCV lesions have also been reported to overlap with typical manifestations of nAMD in Caucasians such as the presence of soft drusen, findings which are uncommon in Asian PCV eyes.[6,7] Heterogeneity in allele frequencies, as well as difference in causal genetic variants in PCV, has been proposed to underly phenotypic variations across ethnic groups.[8] However, these inter-ethnic variations have not been elucidated in detail before.

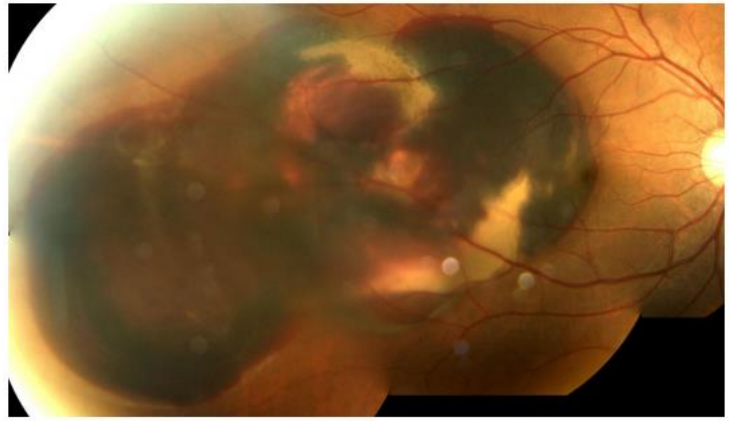
A number of genetic loci have been identified to be associated with AMD. Most of these results have been reported in studies mainly including Caucasian patients. In our previous study comprising 2119 cases and 5691 controls in East Asian populations, we confirmed the association for AMD at *ARMS2-HTRA1*, *CFH*, *ADAMTS9*, *CETP and C2-CFB*, whereas the variant CETP rs2303790 (D442G)

RETINA
CLINICAL UPDATE

American Academy of Ophthalmology EyeNet

Polypoidal Choroidal Vasculopathy, Part 1: Diagnosis

...asculopathy ...se days? If ...studies have ...re of under- ...y among ...ought to be ...e learned a ...t 10 years," ..., MMM, at ... Honolulu. ...is a subtype ...macular ...l that, if left ...ogress to ...Just a bit ...acula with



BLEEDING RISK. *PCV can cause subretinal hemorrhage, as seen here in this fundus*

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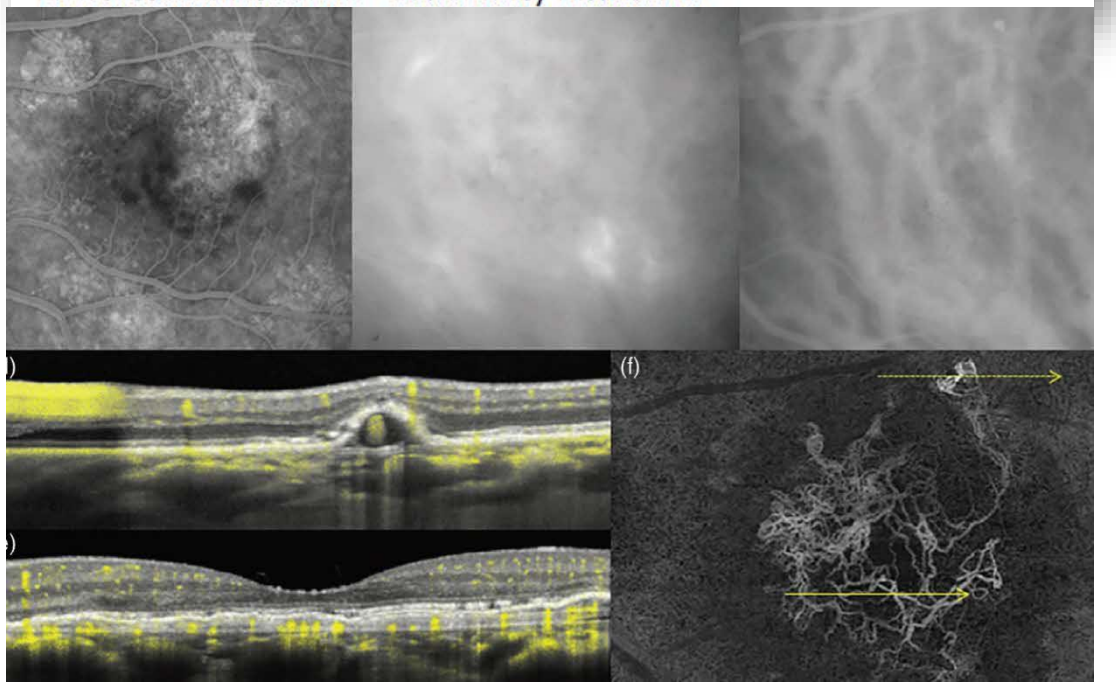
Understanding aneurysmal type 1 neovascularization (polypoidal choroidal vasculopathy): a lesson in the taxonomy of 'expanded spectra' – a review

Kunal K Dansingani MA FRCOphth,[1,2] Orly Gal-Or MD,[3,4,5] Srinivas R Sadda MD,[6,7] Lawrence A Yannuzzi MD[3,4] and K Bailey Freund MD[3,4]

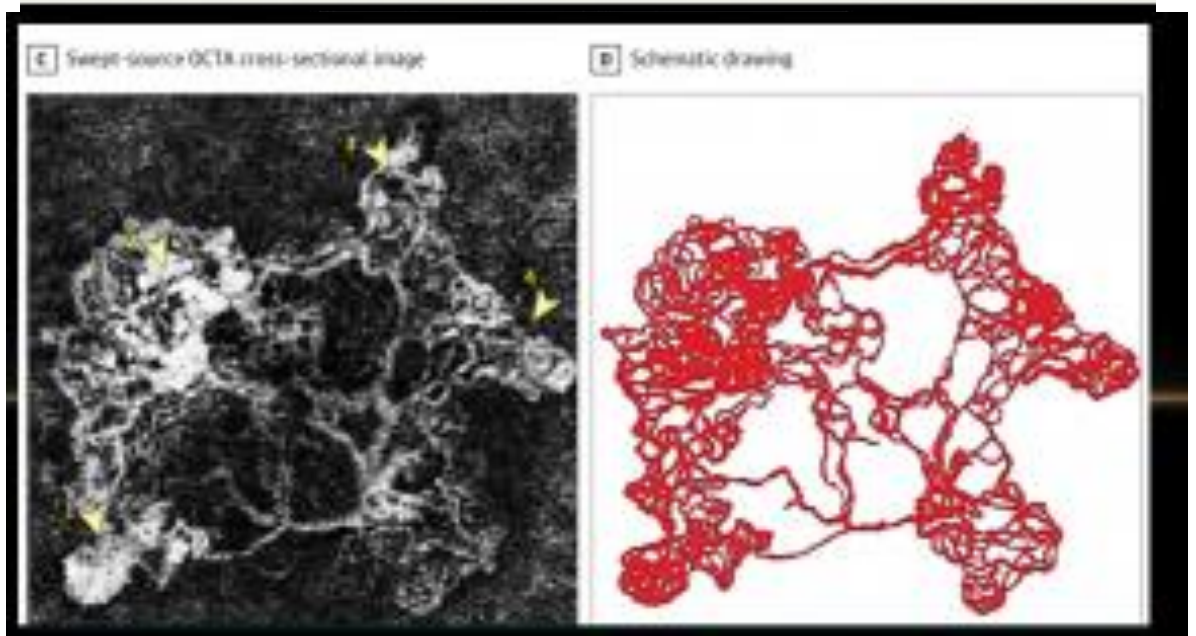


JAMA Ophthalmology | Original Investigation

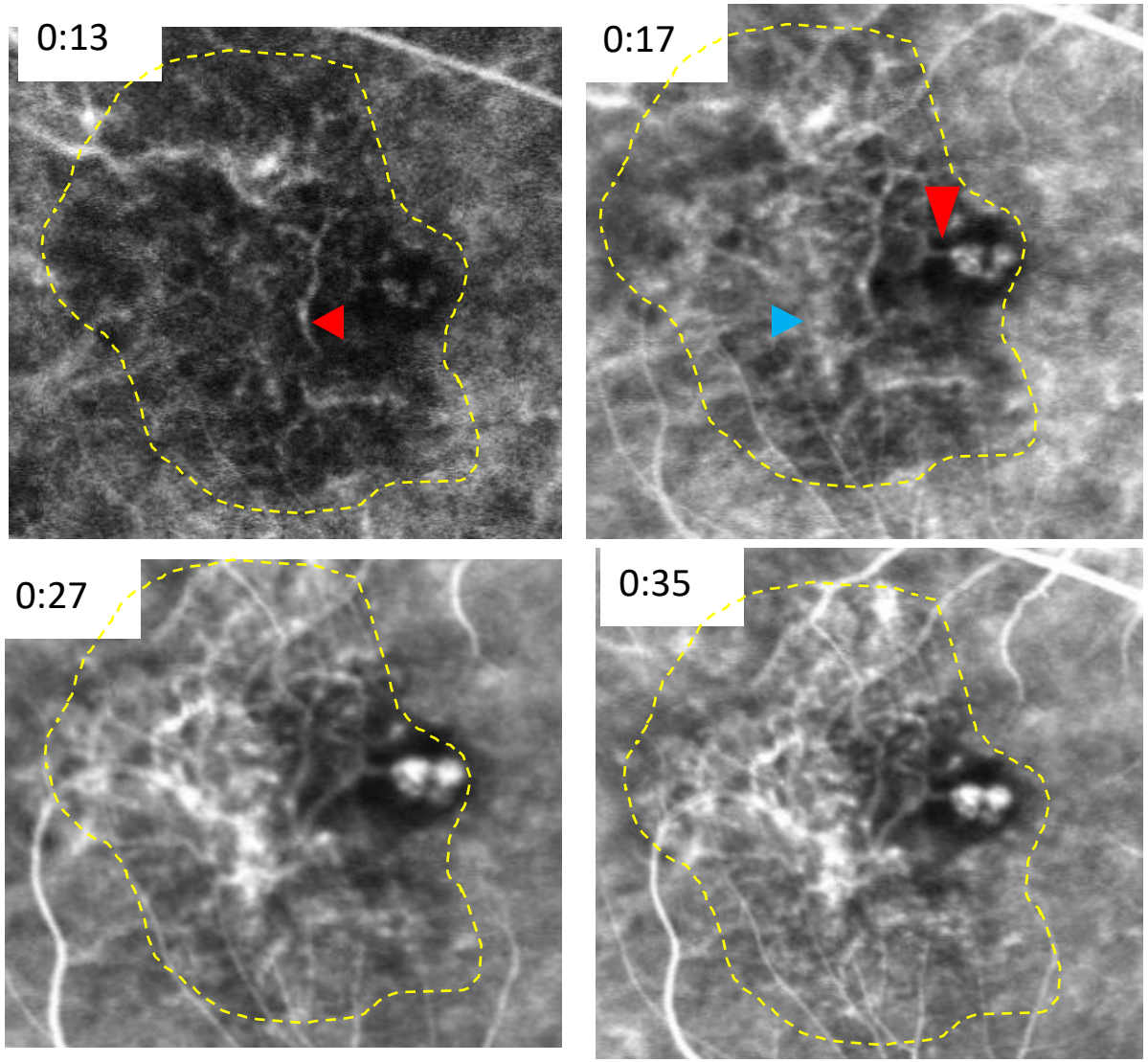
Appearance of Polypoidal Lesions in Patients With Polypoidal Choroidal Vasculopathy Using Swept-Source Optical Coherence Tomographic Angiography

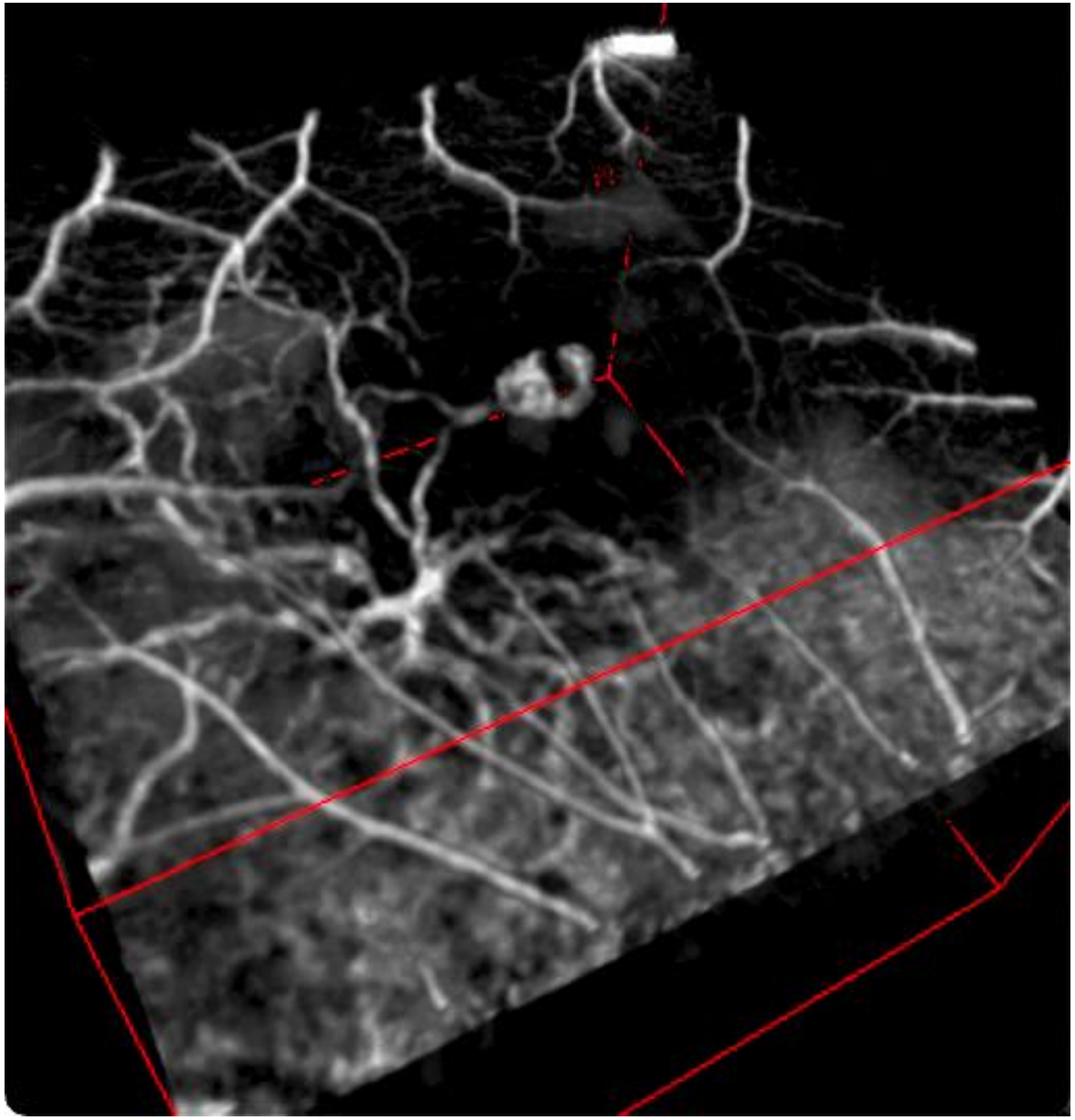
Qiyu Bo, MD; Quan Yan, MD; Mengxi Shen, MD; Minlu Song, MD; Mengsha Sun, MD; Yang Yu, BS; Philip J. Rosenfeld, MD, PhD; Fenghua Wang, MD; Xiaodong Sun, MD, PhD

CONCLUSIONS AND RELEVANCE In eyes with PCV undergoing SS-OCTA imaging, previously described polypoidal lesions may appear as tangled vascular structures associated with BVN or type 2 neovascularization. The identification of polypoidal lesions in patients with PCV as neovascular tangles rather than actual polypoidal lesions or aneurysmal dilatations may help facilitate understanding of their pathogenesis and response to treatment.



Collaboration with Zeiss





Collaboration with Duke University


Sina Farsiu


Jessica Loo

Joint Multimodal Deep Learning-based Automatic Segmentation of Indocyanine Green Angiography and OCT Images for Assessment of Polypoidal Choroidal Vasculopathy Biomarkers

Jessica Loo, PhD,[1] Kelvin Y.C. Teo, MD,[2,3] Chinmayi H. Vyas, MD,[2] Janice Marie N. Jordan-Yu, MD,[2] Amalia B. Juhari, MD,[2] Glenn J. Jaffe, MD,[4] Chui Ming Gemmy Cheung, MD,[2,3] Sina Farsiu, PhD[1,4]

Purpose: To develop a fully-automatic hybrid algorithm to jointly segment and quantify biomarkers of polypoidal choroidal vasculopathy (PCV) on indocyanine green angiography (ICGA) and spectral domain-OCT (SD-OCT) images.

Design: Evaluation of diagnostic test or technology.

Participants: Seventy-two participants with PCV enrolled in clinical studies at Singapore National Eye Center.

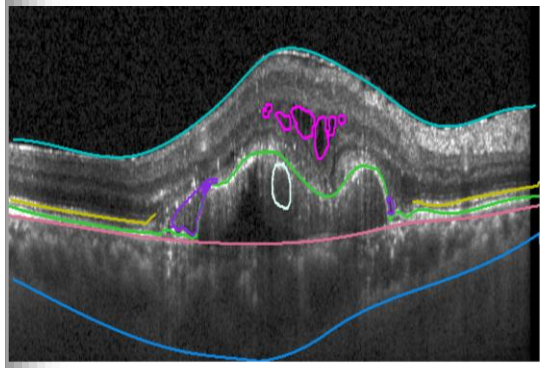
Methods: The dataset consisted of 2-dimensional (2-D) ICGA and 3-dimensional (3-D) SD-OCT images which were spatially registered and manually segmented by clinicians. A deep learning-based hybrid algorithm called PCV-Net was developed for automatic joint segmentation of biomarkers. The PCV-Net consisted of a 2-D segmentation branch for ICGA and 3-D segmentation branch for SD-OCT. We developed fusion attention modules to connect the 2-D and 3-D branches for effective use of the spatial correspondence between the imaging modalities by sharing learned features. We also used self-supervised pretraining and ensembling to further enhance the performance of the algorithm without the need for additional datasets. We compared the proposed PCV-Net to several alternative model variants.

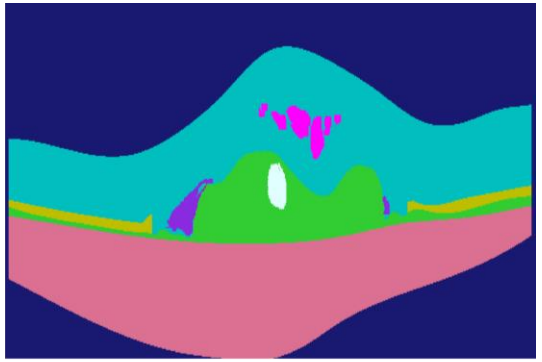
Main Outcome Measures: The PCV-Net was evaluated based on the Dice similarity coefficient (DSC) of the segmentations and the Pearson's correlation and absolute difference of the clinical measurements obtained from the segmentations. Manual grading was used as the gold standard.

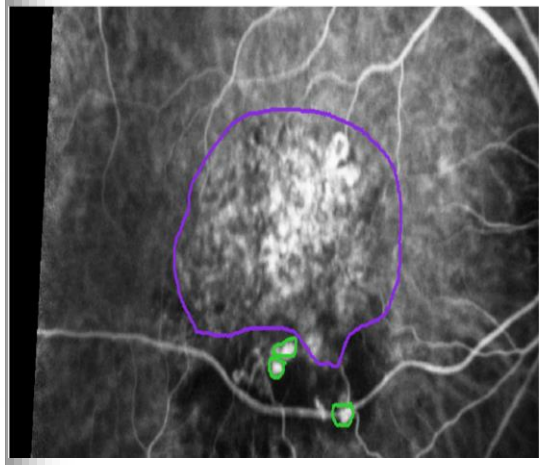
Results: The PCV-Net showed good performance compared to manual grading and alternative model variants based on both quantitative and qualitative analyses. Compared to the baseline variant, PCV-Net improved the DSC by 0.04 to 0.43 across the different biomarkers, increased the correlations, and decreased the absolute differences of clinical measurements of interest. Specifically, the largest average (mean ± standard error) DSC improvement was for intraretinal fluid, from 0.02 ± 0.00 (baseline variant) to 0.45 ± 0.06 (PCV-Net). In general, improving trends were observed across the model variants as more technical specifications were added, demonstrating the importance of each aspect of the proposed method.

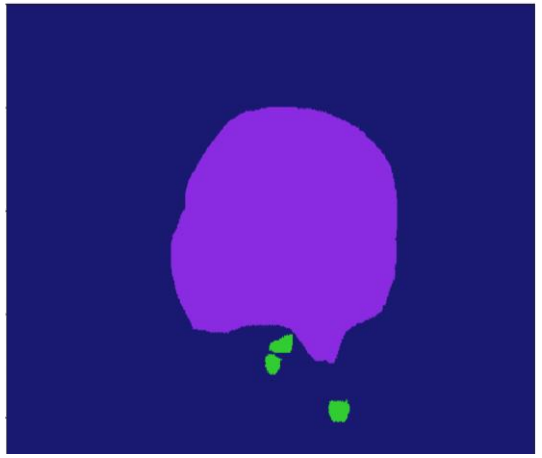
Conclusion: The PCV-Net has the potential to aid clinicians in disease assessment and research to improve clinical understanding and management of PCV.

Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references. *Ophthalmology Science 2023;3:100292*









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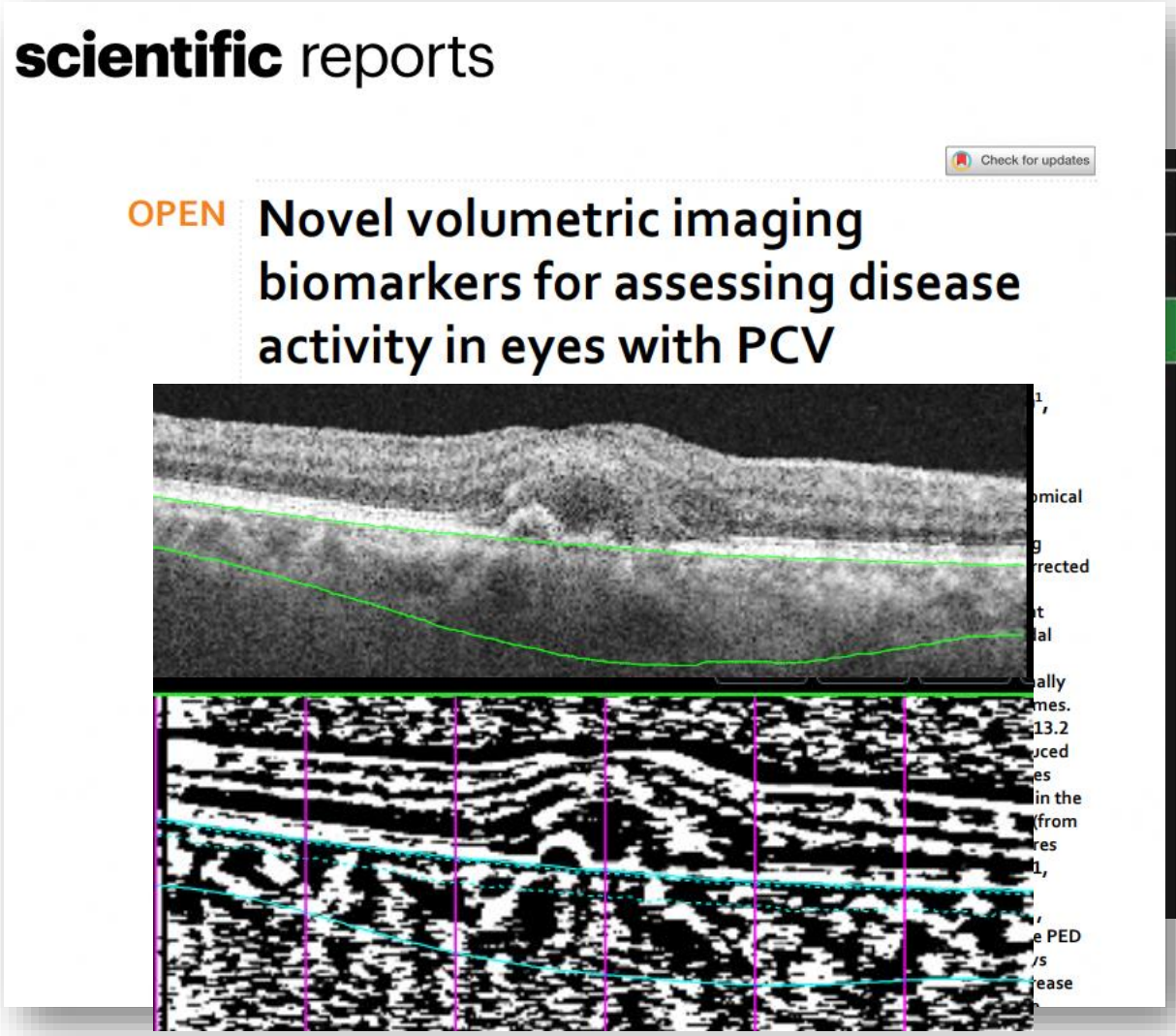
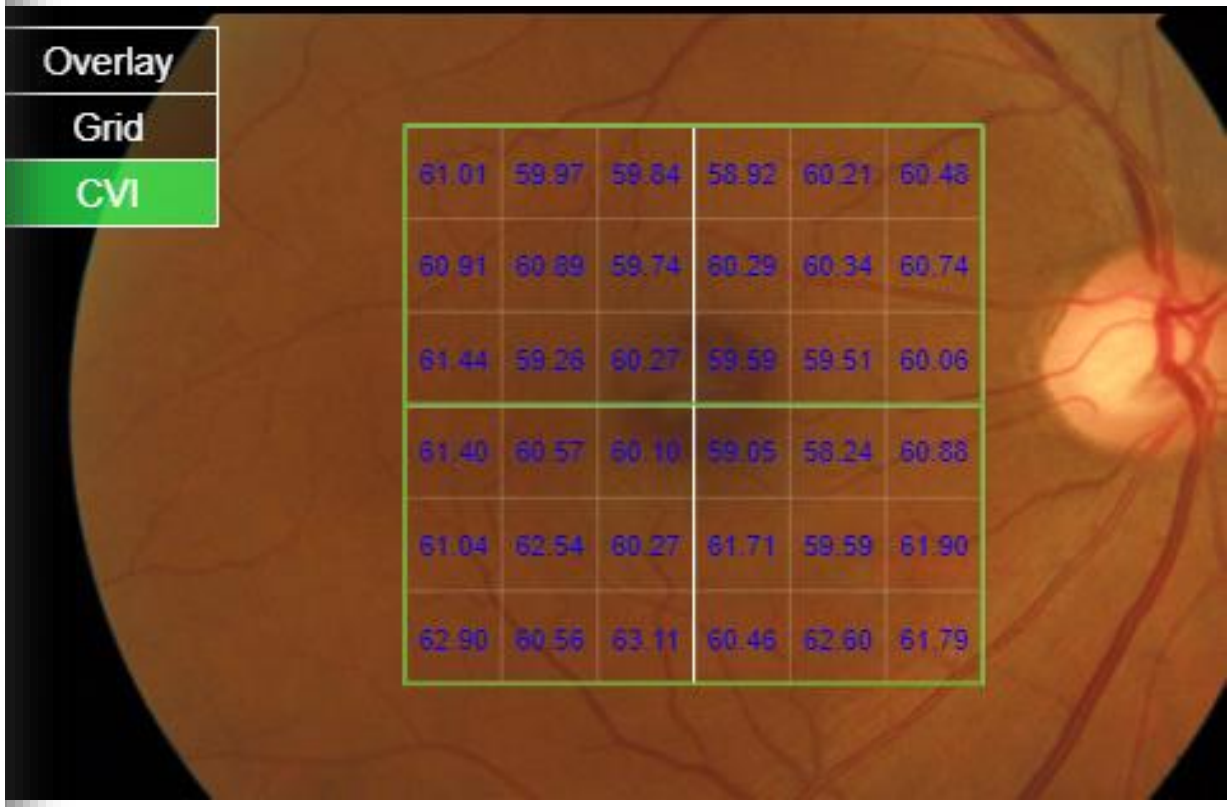
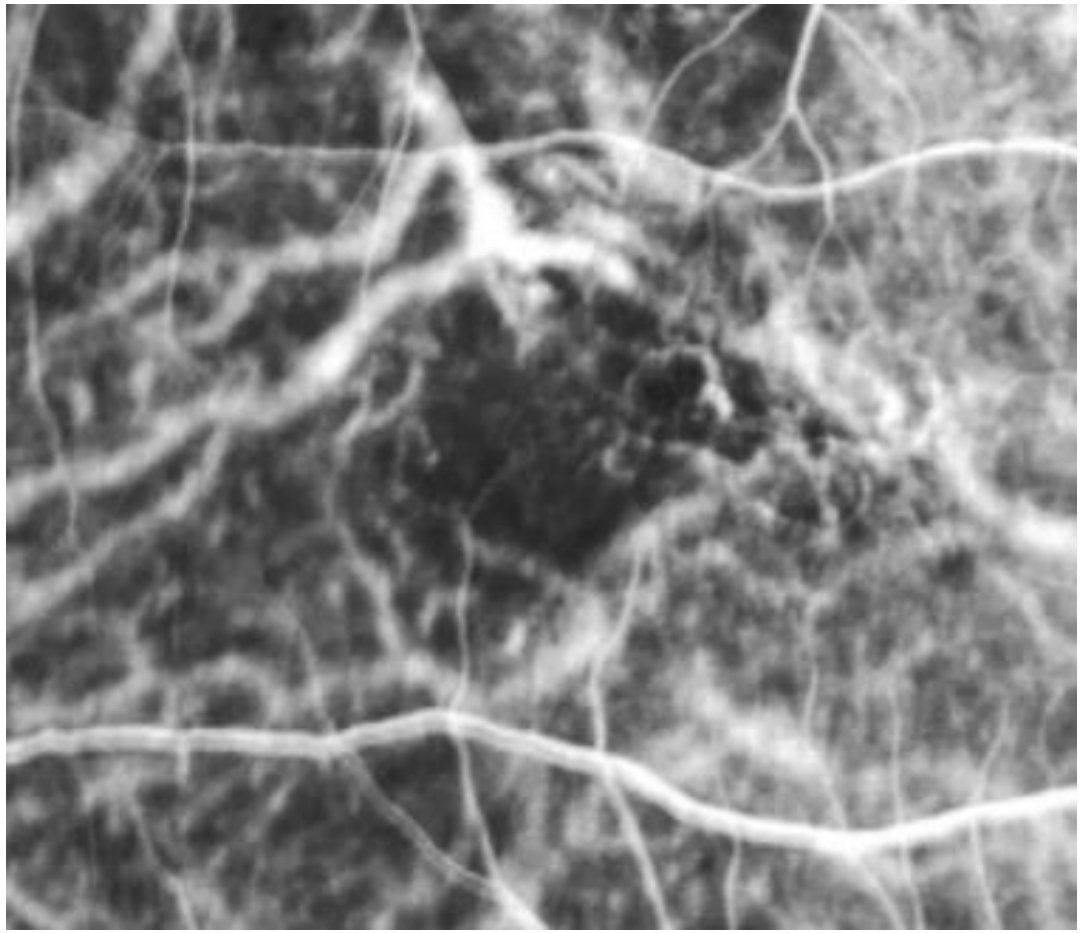
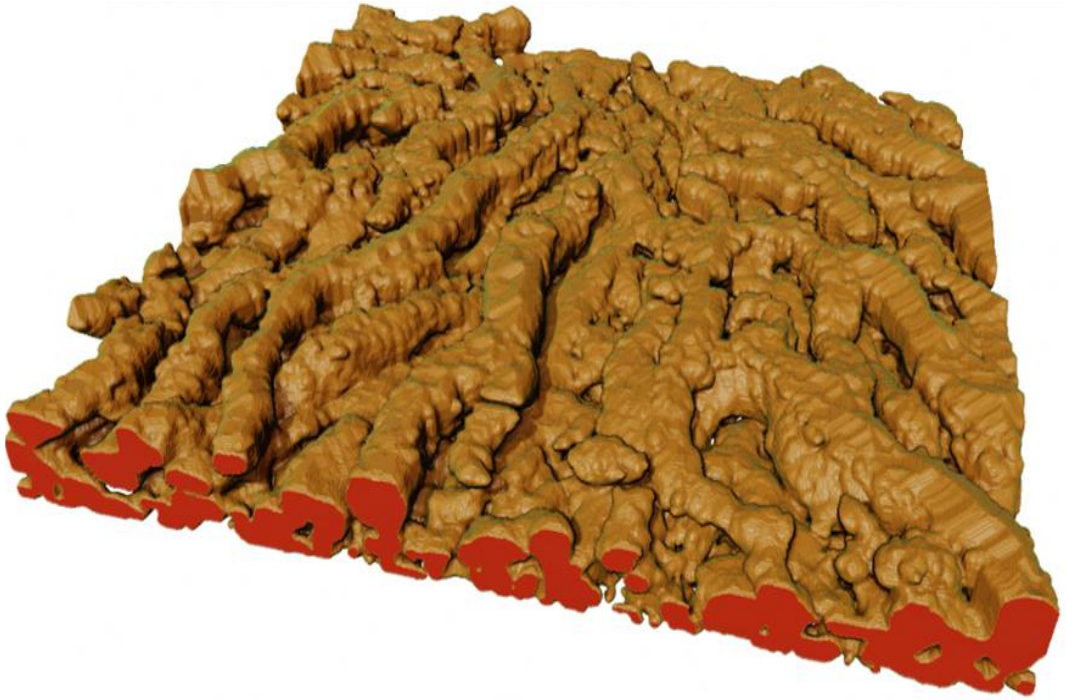
Collaboration and co-funding with Topcon: Automated Volumetric Choroidal vascularity index Map





Novel imaging- Choroidal segmentation





Translational Asian Age-related macular degeneration Programme

AMERICAN ACADEMY OF OPHTHALMOLOGY

Polypoidal Choroidal Vasculopathy

Consensus Nomenclature and Non–Indocyanine Green Angiograph Diagnostic Criteria from the Asia-P Imaging Society PCV Workgroup

Chui M. Gemmy Cheung, FRCOphth,[1,2] Timothy Y.Y. Lai, FRCOphth,[3] Kelvin Teo, M
Paisan Ruamviboonsuk, MD,[4] Shih-Jen Chen, MD,[5] Judy E. Kim, MD, PhD,[6] Fumi Go
Adrian H. Koh, MD,[1,2,8] Gregg Kokame, MD,[9] Janice Marie Jordan-Yu, MD,[1] Federico
Alessandro Invernizzi, MD,[10,11] Yuichiro Ogura, MD, PhD,[12] Colin Tan, MD,[13] Paul M
Vishali Gupta, MD,[15] Jay Chhablani, MD,[16] Usha Chakravarthy, MD, PhD,[2,17] Srinivas
Tien Y. Wong, MD, PhD,[1,2] Giovanni Staurenghi, MD,[10] Won Ki Lee, MD[19]

APOIS: Imaging
14 countries
Singapore, HK, Korea
Thailand, Taiwan, Japan
US, Italy, UK, Australia

AMERICAN ACADEMY OF OPHTHALMOLOGY

Prevalence and Pattern of Geographic Atrophy in Asia

The Asian Eye Epidemiology Consortium

Tyler Hyungtaek Rim, MD, PhD,[1,2,*] Ryo Kawasaki, MD, PhD,[3,4,*] Yih-Chung Tham, PhD,[1,2]
Se Woong Kang, MD, PhD,[5] Paisan Ruamviboonsuk, MD,[6] Mukharram M. Bikbov, MD, PhD,[7]
Masahiro Miyake, MD, PhD,[4,8] Jie Hao, PhD,[9] Astrid Fletcher, PhD,[10] Mariko Sasaki, MD, PhD,[4,11]
Vinay Nangia, MD,[12] Charumathi Sabanayagam, MD, PhD,[1,2] Marco Yu, PhD,[1] Kohta Fujiwara, MD, PhD,[4,13]
Raba Thapa, MD, PhD,[14] Ian Y. Wong, FRCOphth,[15] Takamasa Kayama, MD, PhD,[16]
Shih-Jen Chen, MD, PhD,[17] Tung-Mei Kuang, MD,[17] Hidetoshi Yamashita, MD, PhD,[16]
Periasamy Sundaresan, PhD,[18] Jonathan C. Chan, MBBS, FRCSEd,[19] G.H.M.B. van Rens, MD, PhD,[20]
Koh-Hei Sonoda, MD, PhD,[21] Ya Xing Wang, MD,[9] Songhomitra Panda-Jonas, MD,[22] Sei Harada, MD, PhD,[23]
Ramasamy Kim, DO, DNB,[24] Suganeswari Ganesan, MS,[25] Rajiv Raman, MS, FRCS
Kenji Yamashiro, MD, PhD,[8,26] Timur R. Gilmanshin, MD,[7] Watanee Jenchitr, MD,[27]
Kyu Hyung Park, MD, PhD,[28] Chui Ming Gemmy Cheung, MD, PhD,[1,2] Tien Yin W
Ningli Wang, MD, PhD,[9] Jost B. Jonas, MD,[29] Usha Chakravarthy, MD, PhD,[30] Ching-
Yasuo Yanagi, MD, PhD,[1,4,31,**] for The Asian Eye Epidemiology Consortium[‡]

AEEC: Epidemiology
23 sites across Asia

A Multicountry Comparison of Real-World Management and Outcomes of Polypoidal Choroidal Vasculopathy

Fight Retinal Blindness! Cohort

Kelvin Yi Chong Teo,[1,2,3] David M. Squirrell,[4] Vuong Nguyen,[5] Gayatri Banerjee,[5,6] Amy Cohn,[7]
Daniel Barthelmes,[8] Chui Ming Gemmy Cheung,[1,2,9,10] Mark Gillies[4]

FRB!: Clinical Databases
Singapore, Australia,
Switzerland, New Zealand

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Building Strategic Partnerships and Enabling Translational Research

- Phenotypic variations and management implications
  - Phenotypic comparison (International academic consortia)
  - Therapeutic Implications (Academic & Industry partners)
  - Management Guidelines (Professional bodies)

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PCV therapies

Recruiting	Comparing Intravitreal Aflibercept Monotherapy vs Aflibercept Combined With Reduced Fluence PDT in PCV Treatment	• **Polypoidal Choroidal Vasculopathy**	• Drug: Aflibercept + reduced fluence photodynamic therapy (RF-PDT) • Drug: Aflibercept + sham reduced fluence photodynamic therapy	• Singapore National Eye Centre Singapore, **Singapore** • National University Hospital Singapore, **Singapore**
Recruiting	Long-term Outcomes, Recurrence Rates, and Treatment Needs in **Polypoidal Choroidal Vasculopathy** (PCV)	• **Polypoidal Choroidal Vasculopathy**	• Diagnostic Test: Indocyanine Green Angiography	• Singapore National Eye Centre Singapore, **Singapore** • Tan Tock Seng Hospital Singapore, **Singapore** • National University Hospital Singapore, **Singapore**

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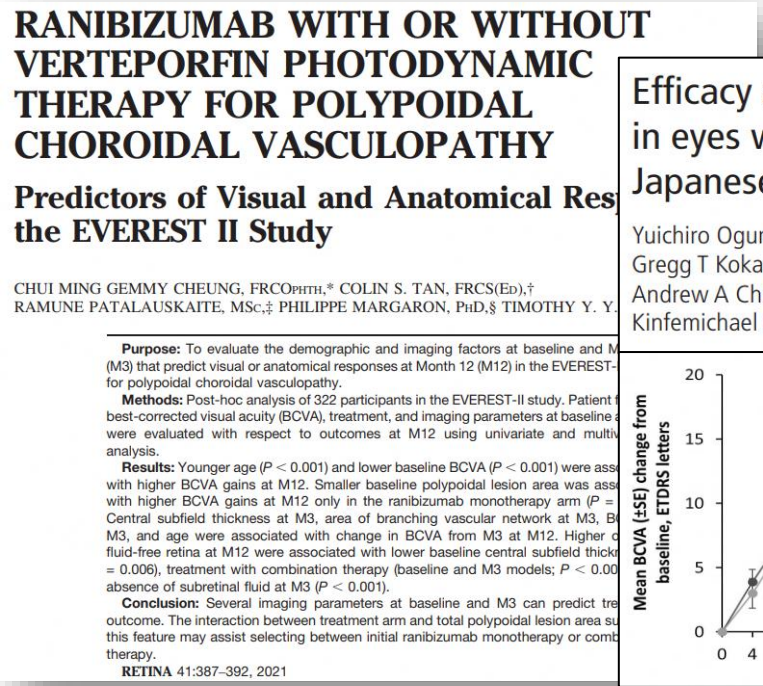
Collaboration with Industry and funding (*)

Industry partner		Project
Novartis	Visudyne	Prognostic biomarkers from Phase 3b/4 RCT
Novartis	Brolucizumab	Subgroup analysis of Asian patients in Phase III RCTs
Bayer*	Aflibercept	Efficacy in PCV in Caucasian patients



RANIBIZUMAB WITH OR WITHOUT VERTEPORFIN PHOTODYNAMIC THERAPY FOR POLYPOIDAL CHOROIDAL VASCULOPATHY

Predictors of Visual and Anatomical Res
the EVEREST II Study

CHUI MING GEMMY CHEUNG, FRCOPHTH,* COLIN S. TAN, FRCS(ED),†
RAMUNE PATALAUSKAITE, MSC,‡ PHILIPPE MARGARON, PHD,§ TIMOTHY Y. Y.

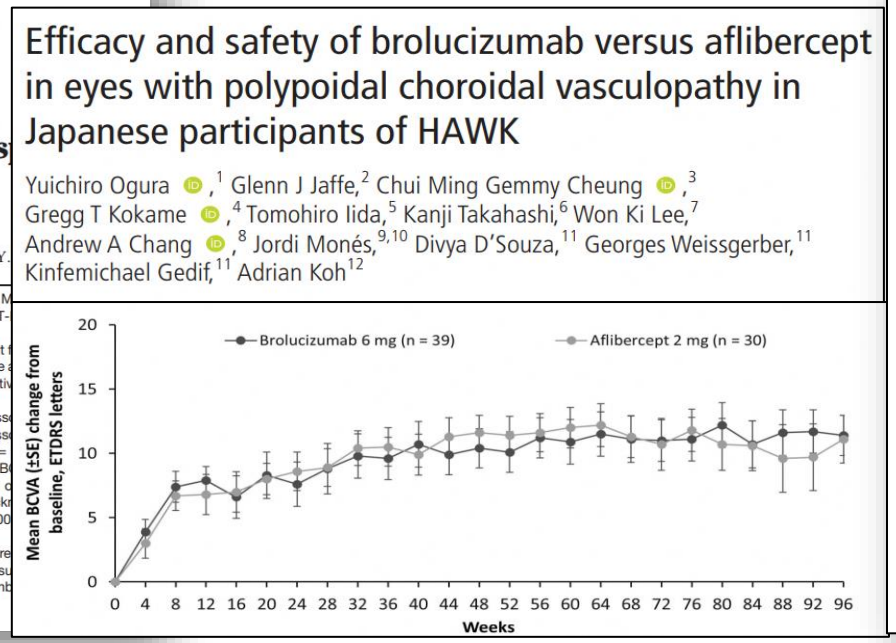
Purpose: To evaluate the demographic and imaging factors at baseline and M (M3) that predict visual or anatomical responses at Month 12 (M12) in the EVEREST- for polypoidal choroidal vasculopathy.

Methods: Post-hoc analysis of 322 participants in the EVEREST-II study. Patient best-corrected visual acuity (BCVA), treatment, and imaging parameters at baseline were evaluated with respect to outcomes at M12 using univariate and multiv analysis.

Results: Younger age ($P < 0.001$) and lower baseline BCVA ($P < 0.001$) were ass with higher BCVA gains at M12. Smaller baseline polypoidal lesion area was ass with higher BCVA gains at M12 only in the ranibizumab monotherapy arm ($P =$ Central subfield thickness at M3, area of branching vascular network at M3, B M3, and age were associated with change in BCVA from M3 at M12. Higher c fluid-free retina at M12 were associated with lower baseline central subfield thickn = 0.006), treatment with combination therapy (baseline and M3 models; $P < 0.00$ absence of subretinal fluid at M3 ($P < 0.001$).

Conclusion: Several imaging parameters at baseline and M3 can predict tre outcome. The interaction between treatment arm and total polypoidal lesion area su this feature may assist selecting between initial ranibizumab monotherapy or comb therapy.

RETINA 41:387–392, 2021



Efficacy and safety of brolucizumab versus aflibercept in eyes with polypoidal choroidal vasculopathy in Japanese participants of HAWK

Yuichiro Ogura ,[1] Glenn J Jaffe,[2] Chui Ming Gemmy Cheung ,[3] Gregg T Kokame ,[4] Tomohiro Iida,[5] Kanji Takahashi,[6] Won Ki Lee,[7] Andrew A Chang ,[8] Jordi Monés,[9,10] Divya D'Souza,[11] Georges Weissgerber,[11] Kinfemichael Gedif,[11] Adrian Koh[12]

Karger

Ophthalmologica

Ophthalmologica , DOI: 10.1159/000518235
Received: December 7, 2020
Accepted: July 2, 2021
Published online: July 12, 2021

Efficacy and safety of Intravitreal Aflibercept Vs Verteporfin Photodynamic Therapy in a Caucasian Population with Polypoidal Choroidal Vasculopathy: A Randomized Clinical Trial.

Silva R, Arias L, Nunes S, Farinha C, Coimbra R, Maques JP, Cachulo ML, Figueira J, Barreto P, Madeira MH, Pires I, Sousa JC, Distefano L, Rosa P, Carneiro Â, Vaz-Pereira S, Meireles A, Cabrera F, Bures A, Mendonça L, Fernandez-Vega Sanz A, Barrão S, Koh A, Cheung GMG, Cunha-Vaz JG, Murta J

Collaboration with Industry and funding (*)

Industry partner		Project
Roche	Faricimab	Subgroup analysis of Asian patients in III RCTs
Roche*	Faricimab	PCV grading of Phase II & III RCTs
Roche*	Faricimab	Phase 3b/4 multi-centre study in PCV in Asia
Roche* + University of Sydney	Faricimab	Investigator initiated trial: multicenter, international study for ‘switched’ patients

SNEC Ocular Reading Center

- Developed PCV-associated biomarkers, choroidal morphology grading, fibrosis grading and macular atrophy grading

Kelvin Teo

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Collaboration with Industry and funding (*)

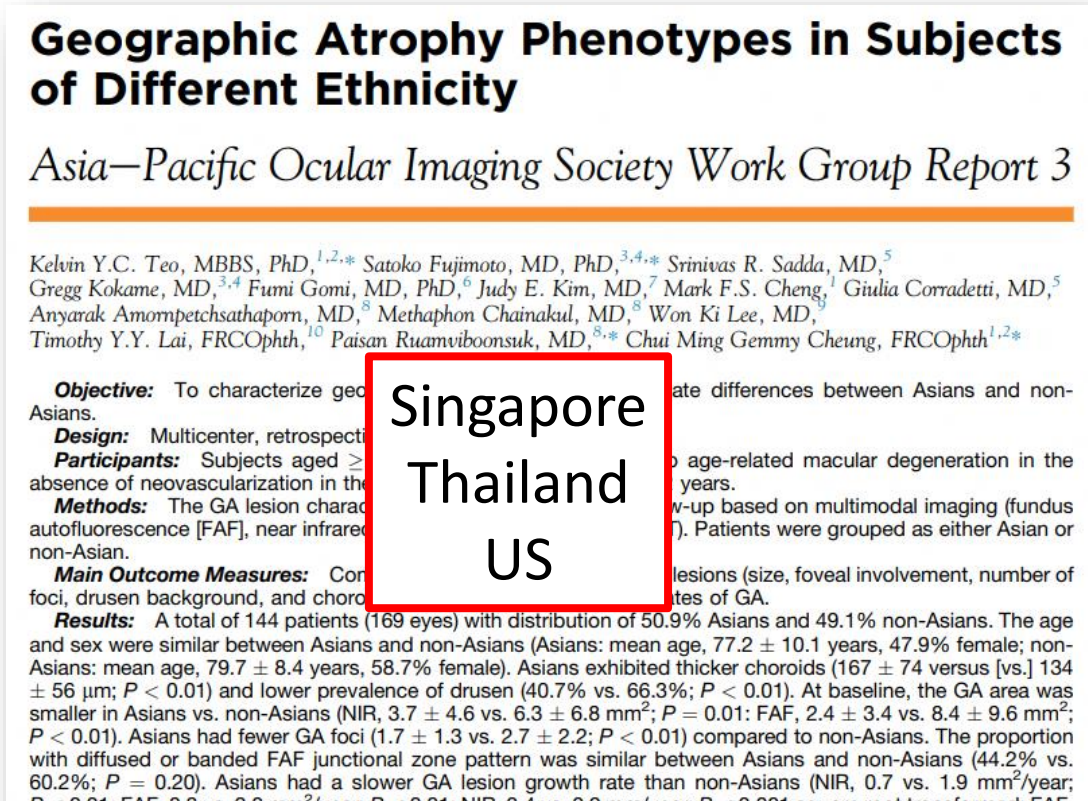
Industry partner	Project
Boehringer Ingelheim *	Phenotyping and progression of Geographic Atrophy in a multi-ethnic Asian Cohort from Singapore

February 17, 2023 | 1 min read SAVE

FDA approves Syfovre – first treatment for geographic atrophy, a leading cause of blindness

ADD TOPIC TO EMAIL ALERTS

Apellis Pharmaceuticals announced the FDA approved its product Syfovre, also known as pegcetacoplan injection, for the treatment of geographic atrophy secondary to age-related macular degeneration, according to the press release.



Geographic Atrophy Phenotypes in Subjects of Different Ethnicity

Asia–Pacific Ocular Imaging Society Work Group Report 3

Kelvin Y.C. Teo, MBBS, PhD,[1,2,] Satoko Fujimoto, MD, PhD,[3,4,*] Srinivas R. Sadda, MD,[5] Gregg Kokame, MD,[3,4] Fumi Gomi, MD, PhD,[6] Judy E. Kim, MD,[7] Mark F.S. Cheng,[1] Giulia Corradetti, MD,[5] Anyarak Amornpetchsathaporn, MD,[8] Methaphon Chainakul, MD,[8] Won Ki Lee, MD,[9] Timothy Y.Y. Lai, FRCOphth,[10] Paisan Ruamviboonsuk, MD,[8,*] Chui Ming Gemmy Cheung, FRCOphth[1,2,*]*

Singapore
Thailand
US

Objective: To characterize geo… ate differences between Asians and non-Asians.

Design: Multicenter, retrospecti…

Participants: Subjects aged ≥ … o age-related macular degeneration in the absence of neovascularization in th… years.

Methods: The GA lesion charac… w-up based on multimodal imaging (fundus autofluorescence [FAF], near infrare…). Patients were grouped as either Asian or non-Asian.

Main Outcome Measures: Cor… lesions (size, foveal involvement, number of foci, drusen background, and chor… tes of GA.

Results: A total of 144 patients (169 eyes) with distribution of 50.9% Asians and 49.1% non-Asians. The age and sex were similar between Asians and non-Asians (Asians: mean age, 77.2 ± 10.1 years, 47.9% female; non-Asians: mean age, 79.7 ± 8.4 years, 58.7% female). Asians exhibited thicker choroids (167 ± 74 versus [vs.] 134 ± 56 μm; $P < 0.01$) and lower prevalence of drusen (40.7% vs. 66.3%; $P < 0.01$). At baseline, the GA area was smaller in Asians vs. non-Asians (NIR, 3.7 ± 4.6 vs. 6.3 ± 6.8 mm^2; $P = 0.01$: FAF, 2.4 ± 3.4 vs. 8.4 ± 9.6 mm^2; $P < 0.01$). Asians had fewer GA foci (1.7 ± 1.3 vs. 2.7 ± 2.2; $P < 0.01$) compared to non-Asians. The proportion with diffused or banded FAF junctional zone pattern was similar between Asians and non-Asians (44.2% vs. 60.2%; $P = 0.20$). Asians had a slower GA lesion growth rate than non-Asians (NIR, 0.7 vs. 1.9 mm^2/year;

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- Phenotypic variations and management implications
  - Phenotypic comparison (International academic)
  - Therapeutic Implications (Industry partners)
  - Management Guidelines (Professional bodies)

TAAP
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Management Guidelines

AMERICAN ACADEMY OF OPHTHALMOLOGY*

Polypoidal Choroidal Vasculopathy

Consensus Nomenclature and Non–Indocyanine Green Angiograph Diagnostic Criteria from the Asia-Pacific Ocular Imaging Society PCV Workgroup

Chui M. Gemmy Cheung, Fl
Paisan Ruamviboonsuk, MD,
Adrian H. Koh, MD,[1,2,8] Gr
Alessandro Invernizzi, MD,[10]
Vishali Gupta, MD,[15] Jay Ch
Tien Y. Wong, MD, PhD,[1,2]

Purpose: To develop co
develop and validate a set c
entiating PCV from typical ne
and color fundus photograp
Design: Evaluation of di
Participants: Panel of r
Methods: As part of the
discussed the published lite
proposed an updated cons
histologic reports. The workg
photographs for PCV that m
combinations of these non-I
the use of ICGA. The final re
Main Outcome Measure
based criteria to differentiate
Results: The workgroup
the 2 key lesion component
(sub–retinal pigment epithel
PED) achieved an area unde
in a separate subset 80 eye
Conclusions: We propo
these lesions and is based
spectral-domain OCT result
ICGA is not performed rout

Non-ICGA treatment criteria for Suboptimal Anti-VEGF Response for Polypoidal Choroidal Vasculopathy: APOIS PCV Workgroup Report 2

Kelvin Yi Chong Teo, MBBS, MMed (Ophth),[1,2,6] Srinivas R. Sadda, MD,[3]
Chui Ming Gemmy Cheung, FRCOphth,[1,2] Usha Chakravarthy, MD, PhD,[2,4] Giovanni Staurenghi, MD,[5]
Alessandro Invernizzi, MD,[5,6] Yuichiro Ogura, MD, PhD,[7] Paisan Ruamviboonsuk, MD,[8] Shih-Jen Chen, MD,[9]
Vishali Gupta, MD,[10] Colin Tan, MD,[11] Jay Chhablani, MD,[12] Federico Corvi, MD,[5] Judy E. Kim, MD, PhD,[13]
Fumi Gomi, MD,[14] Adrian H. Koh, MD,[1,2,15] Gregg Kokame, MD,[16] Paul Mitchell, MD, PhD,[17]
Tien Y. Wong, MD, PhD,[1,2] Won Ki Lee, MD,[18] Timothy Y.Y. Lai, FRCOphth[19]

Purpose: To develop and validate OCT and color fundus photography (CFP) criteria in differentiating polypoidal choroidal vasculopathy (PCV) from typical neovascular age-related macular degeneration (nAMD) in eyes with suboptimal response to anti–vascular endothelial growth factor (VEGF) monotherapy and to determine whether OCT alone can be used to guide photodynamic therapy (PDT) treatment.

Design: Clinical study evaluating diagnostic accuracy.

Participants: Patients with nAMD who received 3-month anti-VEGF monotherapy but had persistent activity defined as subretinal fluid or intraretinal fluid at month 3 assessments.

Methods: In phase 1, international retina experts evaluated OCT and CFP of eyes with nAMD to identify the presence or absence of features due to PCV. The performance of individual and combinations of these features were compared with ICGA. In phase 2, these criteria were applied to an independent image set to assess generalizability. In a separate exercise, retinal experts drew proposed PDT treatment spots using only OCT and near-infrared (NIR) images in eyes with PCV and persistent activity. The location and size of proposed spot were compared with ICGA to determine the extent of coverage of polypoidal lesions (PLs) and branching neovascular network (BNN).

Main Outcome Measures: Sensitivity and specificity of CFP and OCT criteria to differentiate PCV from nAMD and accuracy of coverage of OCT-guided PDT compared with ICGA.

Results: In eyes with persistent activity, the combination of 3 non–ICGA-based criteria (sharp-peaked pigment epithelial detachment [PED], subretinal pigment epithelium [RPE] ring-like lesion, and orange nodule) to detect PCV showed good agreement compared with ICGA, with an area under the receiver operating characteristic curve of 0.85. Validation using both an independent image set and assessors achieved an accuracy of

Polypoidal Choroidal Vasculopathy

Definition, Pathogenesis, Diagnosis, and Management

Chui Ming Gemmy Cheung, FRCOphth,[1,2] Timothy Y. Y. Lai, MD,[3] Paisan Ruamviboonsuk, MD,[4]
Shih-Jen Chen, MD,[5] Youxin Chen, MD,[6] K. Bailey Freund, MD,[7,8] Fomi Gomi, MD,[9] Adrian H. Koh, MD,[10]
Won-Ki Lee, MD,[11] Tien Yin Wong, FRCS, PhD[1,2]

REVIEW ARTICLE

OPEN

Treat-and-Extend Regimens for the Management of Neovascular Age-related Macular Degeneration and Polypoidal Choroidal Vasculopathy: Consensus and Recommendations From the Asia-Pacific Vitreo-Retina Society

Voraporn Chaikitmongkol, MD, Min Sagong, MD, PhD†, Timothy Y.Y. Lai, MD, FRCOphth‡§,*
*Gavin S.W. Tan, MD, PhD¶, Nor Fariza, MD||, Masahito Ohji, MD**, Paul Mitchell, MD††*
Chang Hao Yang, MD, PhD‡‡, Paisan Ruamviboonsuk, MD§§, Ian Wong, MBBS, MMed¶¶,
*Taiji Sakamoto, MD, PhD||||, Anand Rajendran, FRCS, DNB***, Youxin Chen, MD†††,*
Dennis S.C. Lam, MD‡‡‡, Chi Chun Lai, MD§§§, Tien Yin Wong, MD, PhD¶,
Chui Ming Gemmy Cheung, FRCOphth¶, Andrew Chang, MBBS, PhD¶¶¶,
and Adrian Koh, MBBS, MMed||||||

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Building Strategic Partnerships and Enabling Translational Research

- Phenotypic variations and management implications

- Develop novel therapies targeting functional alterations

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Translational Asian Age-related macular degeneration Programme

Drug development platform

Preclinical validation

Target identified from genetics or metabolomics studies	In vitro	Ex vivo	Small animal model	Mechanistic study	*STDR Pilot grant awarded in July 2022	Manuscript and patent application

TAAP 002

TAAP 003

TAAP 004

TAAP 005

TAAP 006

A/Prof Wang Xiaomeng

Developing novel anti-Fibrotic therapy (TAAP 001)

Asian AMD phenotyping cohort

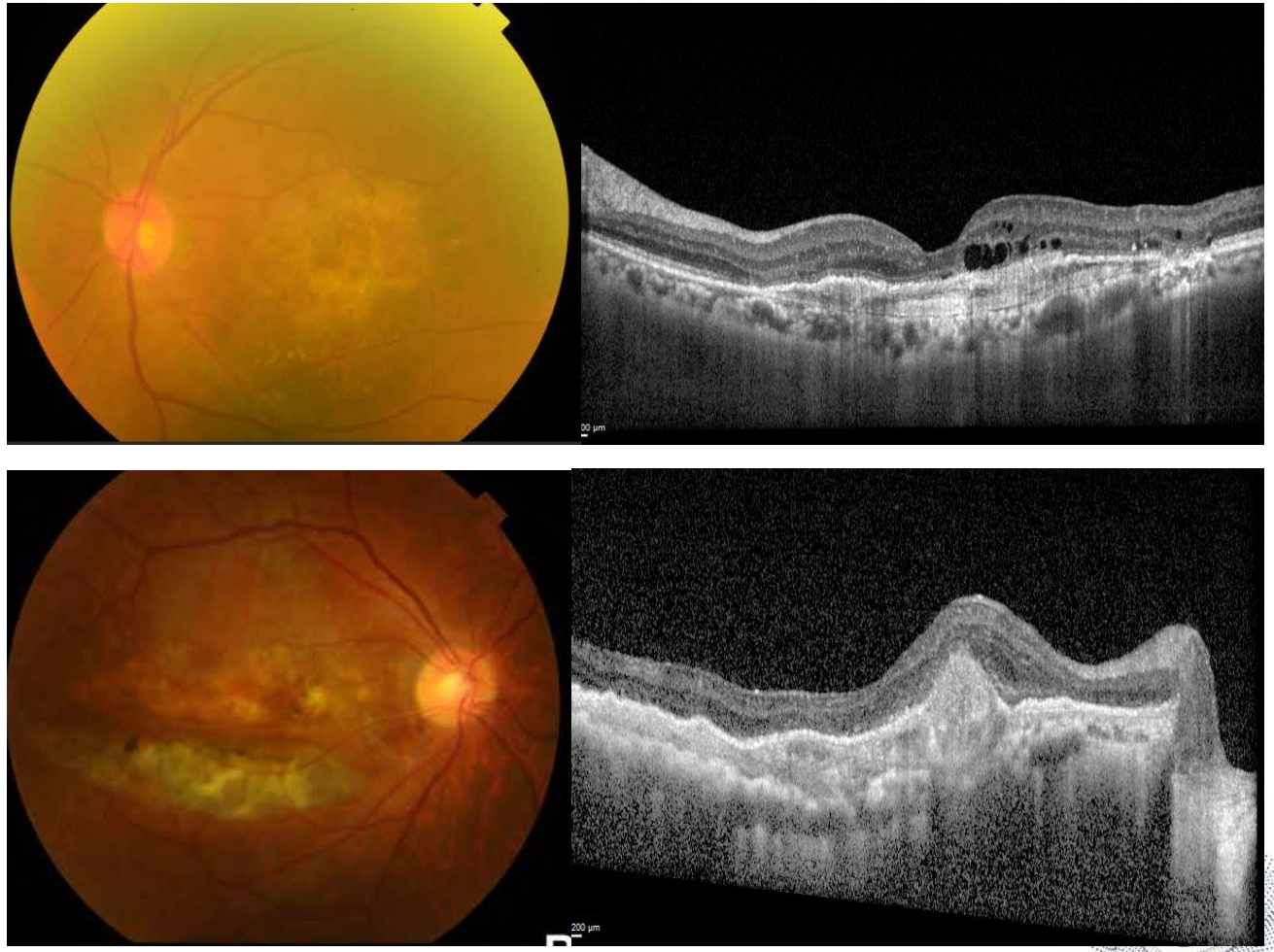
Serum biomarkers

Characterized in-vitro, ex-vivo

Validation in mouse model

Collaboration with EDDC to generate neutralizing antibodies for NHP studies

Commercialization pathway



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Translational Asian Age-related macular degeneration Programme

Building Strategic Partnerships and Enabling Translational Research

- Phenotypic variations and management implications

- Develop novel therapies targeting functional alterations
  - Complement activation, inflammation
  - Choroidal vascular insufficiency and ischemia
  - Oxidative stress
  - Lipid metabolism
  - Endothelial dysfunction

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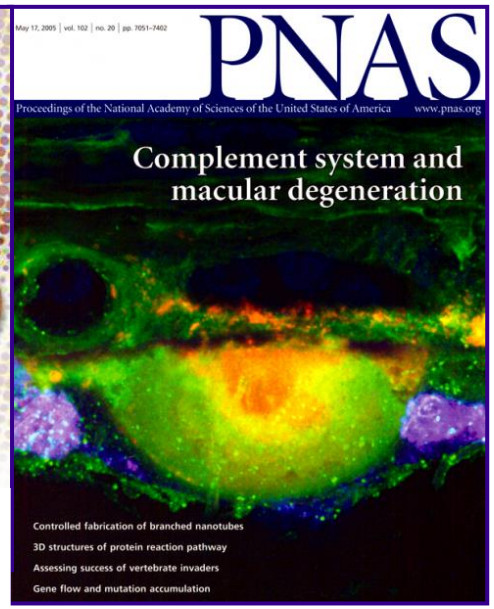
Genetics of AMD

- Two principal genes
  - CFH
  - ARMS2-HTRA-1

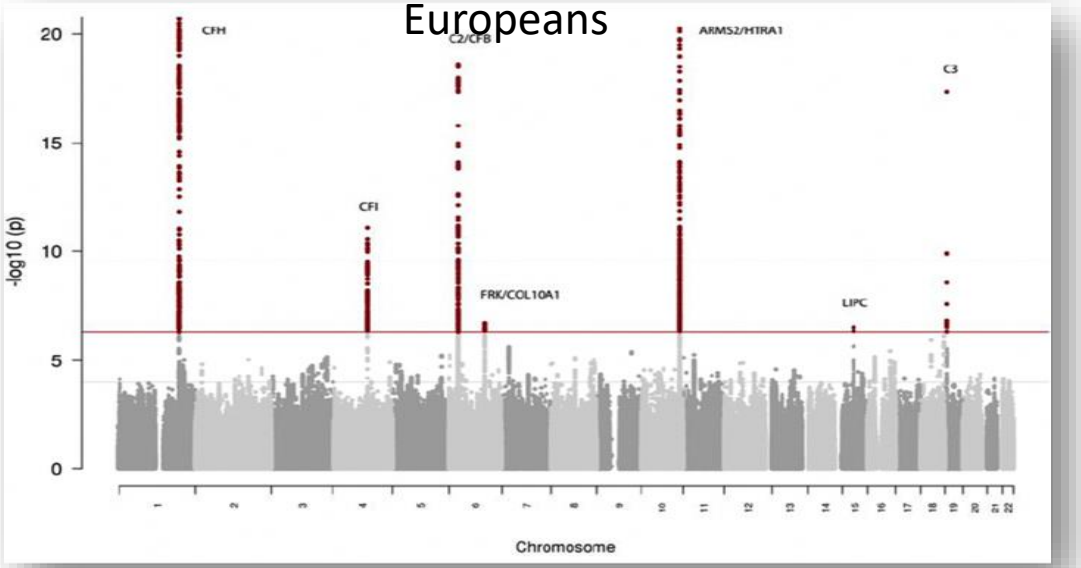
Complement Factor H Polymorphism in Age-Related Macular Degeneration

Robert J. Klein,[1] Caroline Zeiss,[2]* Emily Y. Chew,[3]* Jen-Yue Tsai,[4]* Richard S. Sackler,[1] Chad Haynes,[1] Alice K. Henning,[5] John Paul SanGiovanni,[3] Shrikant M. Mane,[6] Susan T. Mayne,[7] Michael B. Bracken,[7] Frederick L. Ferris,[3] Jurg Ott,[1] Colin Barnstable,[2] Josephine Hoh[7]†

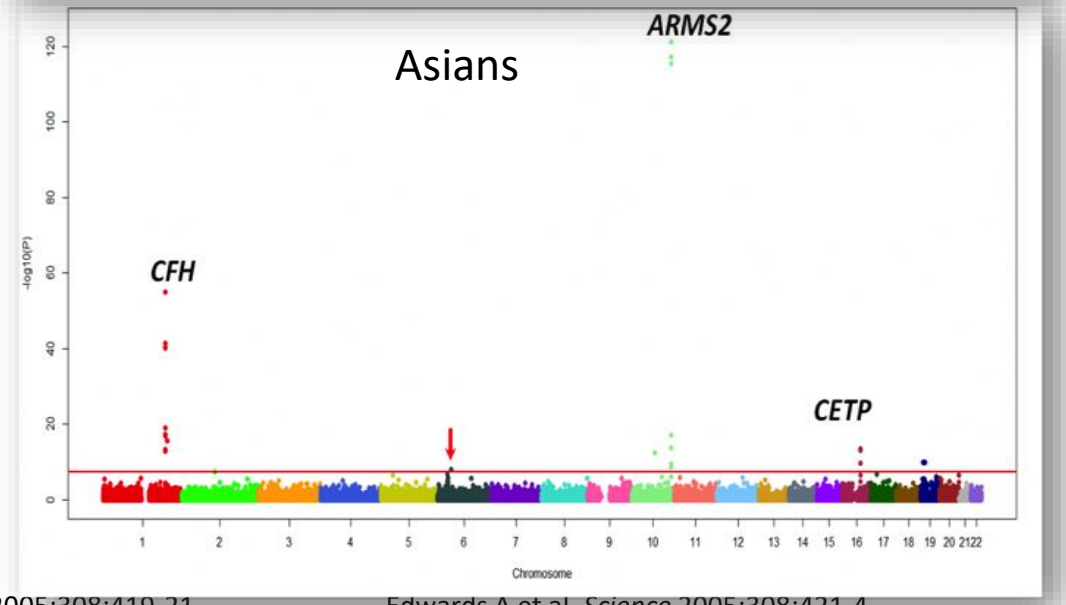
Age-related macular degeneration (AMD) is a major cause of blindness in the elderly. We report a genome-wide screen of 96 cases and 50 controls for polymorphisms associated with AMD. Among 116,204 single-nucleotide polymorphisms genotyped, an intronic and common variant in the complement factor H gene (*CFH*) is strongly associated with AMD (nominal *P* value $<10^{-7}$). In individuals homozygous for the risk allele, the likelihood of AMD is increased by a factor of 7.4 (95% confidence interval 2.9 to 19). Resequencing revealed a polymorphism in linkage disequilibrium with the risk allele representing a tyrosine-histidine change at amino acid 402. This polymorphism is in a region of CFH that binds heparin and C-reactive protein. The *CFH* gene is located on chromosome 1 in a region repeatedly linked to AMD in family-based studies.



Europeans



Asians



Haines JL et al. *Science* 2005;308:419-21 Edwards A et al. *Science* 2005;308:421-4
Klein RJ et al. *Science* 2005;308:385-9 Hageman G et al , PNAS, 2005

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Article

HTRA1 Regulates Subclinical Inflammation and Activates Proangiogenic Response in the Retina and Choroid

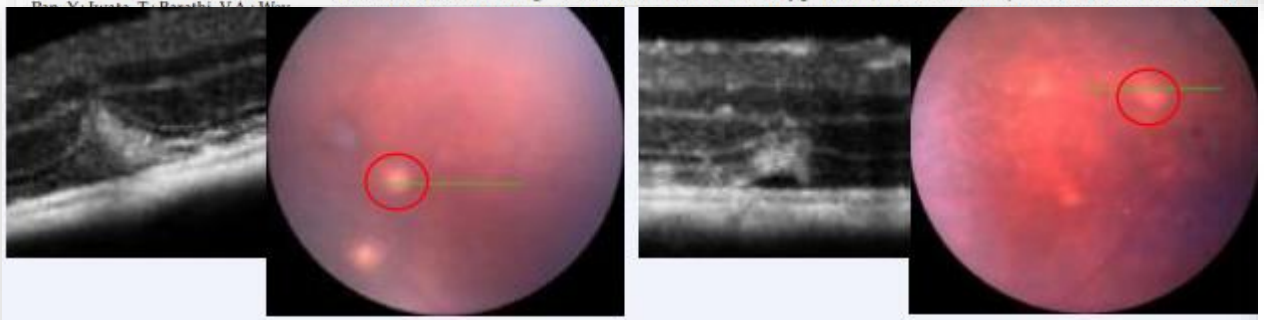
Waseem Ahamed [1,†], Richard Ming Chuan Yu [1,†], Yang Pan [2], Takeshi Iwata [2], Veluchamy Amutha Barathi [1,3], Yeo Sia Wey [1], Sai Bo Bo Tun [1], Beiying Qiu [1,3], Alison Tan [1,3], Xiaomeng Wang [1,3,4], Chui Ming Gemmy Cheung [1,3], Tien Yin Wong [1,3] and Yasuo Yanagi [1,3,*]

1 Singapore National Eye Centre, Singapore Eye Research Institute, 11 Third Hospital Ave, Singapore 168751, Singapore
2 Molecular and Cellular Biology Division, National Institute of Sensory Organs, National Hospital Organization Tokyo Medical Center, Tokyo 152-8902, Japan
3 Academic Clinical Program, Duke-NUS Medical School, National University of Singapore, Singapore 169857, Singapore
4 Institute of Molecular and Cell Biology, Agency for Science, Technology and Research (A*STAR), Singapore 138673, Singapore
* Correspondence: yasuo.yanagi@snec.com.sg; Tel.: +81-45-253-5372
† These authors contributed equally to this work.

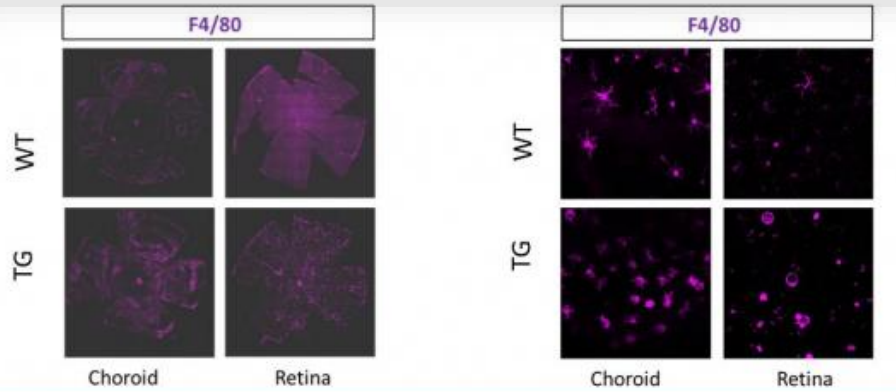
Abstract: High-temperature requirement A1 (HtrA1) has been identified as a disease-susceptib
gene for age-related macular degeneration (AMD) including polypoidal choroidal neovasculop
(PCV). We characterized the underlying phenotypic changes of transgenic (Tg) mice expres
ubiquitous CAG promoter (CAG-HtrA1 Tg). In vivo imaging modalities and histopathology v
performed to investigate the possible neovascularization, drusen formation, and infiltratio
macrophages. Subretinal white material deposition and scattered white-yellowish retinal foci v
detected on CFP [(Tg—33% (20/60) and wild-type (WT)—7% (1/15), $p < 0.05$]. In 40% (4/10) o

Citation: Ahamed, W.; Yu, R.M.C.;

Taken together, drusen-like deposits which have corresponding RPE elevation might be the representation of immune cells which have been migrated into the subretinal space. Moreover, detailed phenotypic investigations through in-vivo imaging and immunostaining form a robust method in proceeding forward to explore the epigenetic changes in the Htra1 mice model.



Subretinal like deposits in OCT corresponding to the white lesions on the fundus photography.



i) Increase macrophage infiltration and activation in subretinal area and retina.

Genetic Variability of Complement Factor H Has Ethnicity-Specific Associations With Choroidal Thickness

Beau J. Fenner,[1,2] Hengtong Li,[2] Alfred T. L. Gan,[2] Young Seok Song,[2,3] Yi Chung Tham,[2] Jost B. Jonas,[4] Ya Xing Wang,[5] Ching Yu Cheng,[2] Tien Yin Wong,[6] Kelvin Y. C. Teo,[1,2] Anna C. S. Tan,[1,2] Qiao Fan,[2,7] and Chui Ming Gemmy Cheung[1,2]

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[2]Singapore Eye Research Institute, Singapore
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Received: August 16, 2022
Accepted: January 3, 2023
Published: XXXXX XX, 2023

Citation: Fenner BJ, Li H, Gan ATL, et al. Genetic variability of complement factor H has ethnicity-specific associations with choroidal thickness. *Invest Ophthalmol Vis Sci.* 2023;0(0):35947. https://doi.org/10.1167/iovs.0.0.35947

Purpose. To identify ger
(CT) in a population-bas

Methods. A population-l
subjected to spectral-dom
ARMS2, and *CETP*. Subfo
OCT, and associations wi

Results. A total of 1045 h
were prospectively enrol
rs1329428) were associa
0.001–0.038) and margin
µm; $P = 0.014$–0.022). I
SFCT among races, with
in SFCT in the Chinese c
cohort ($P < 0.001$). Finall
between the *CFH* risk all
(−20.2 to −25.8 µm; $P =$

Conclusions. *CFH* varian
This has broad implicatio
macular degeneration ar
associated with CT.

SNP Name	Chromosomal Location	Gene	Consequence	Effect Allele*	Other Allele	Reported Associations for Effect Allele				References
						AMD†	PCV	CSC	SFCT	
rs800292	chr1:196642233	*CFH*	Missense variant	G	A	+(G)	+(G)	+(A)	+(A)	Hosoda et al.,[12] Hageman et al.,[37] Liu et al.,[38] Cipriani et al.,[39] Kondo et al.[40]
rs1061170	chr1:196659237	*CFH*	Missense variant	C	T	+(C)	+(C)	+(T)	+(T)	Ryoo et al.,[15] Kondo et al.,[40] Haines et al.,[41] Edwards et al.,[42] Lima et al.,[43] Mohabati et al.[44]
rs1329428	chr1:196702810	*CFH*	Intron variant	C	T	+(C)	—	+(T)	+(T)	Yoneyama et al.,[13] Cipriani et al.,[39] Klein et al.,[45] Kiraly et al.[46]
rs61818925	chr1:196815450	*CFH*	No consequence	G	T	+(G)	—	—	—	Cipriani et al.,[39] Pappas et al.[47]
rs3793217	chr7:158848821	*VIPR2*	Intron variant	G	A	—	—	+(G)	+(G)	Hosoda et al.[12]
rs7782658	chr7:158858007	*VIPR2*	Intron variant	A	G	—	—	—	+(A)	Hosoda et al.[12]
rs10490924	chr10:124214448	*ARMS2*	Missense variant	T	G	+(T)	+(T)	+(G)	+(G)	Yoneyama et al.,[13] Kondo et al.,[40] Klein et al.,[45] Jakobsdottir et al.[48]
rs3764261	chr16:56993324	*CETP*	No consequence	A	C	+(A)	+(A)	—	—	Liu et al.,[38] Chen et al.[49]

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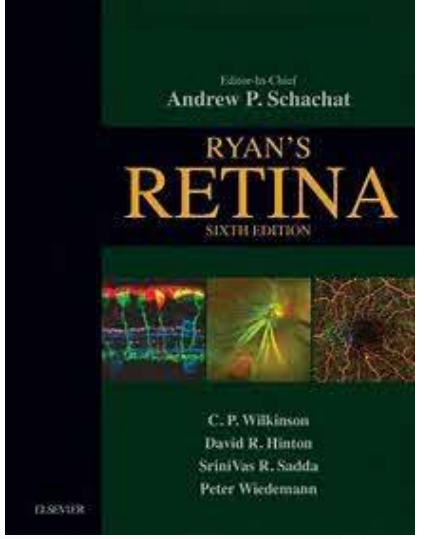
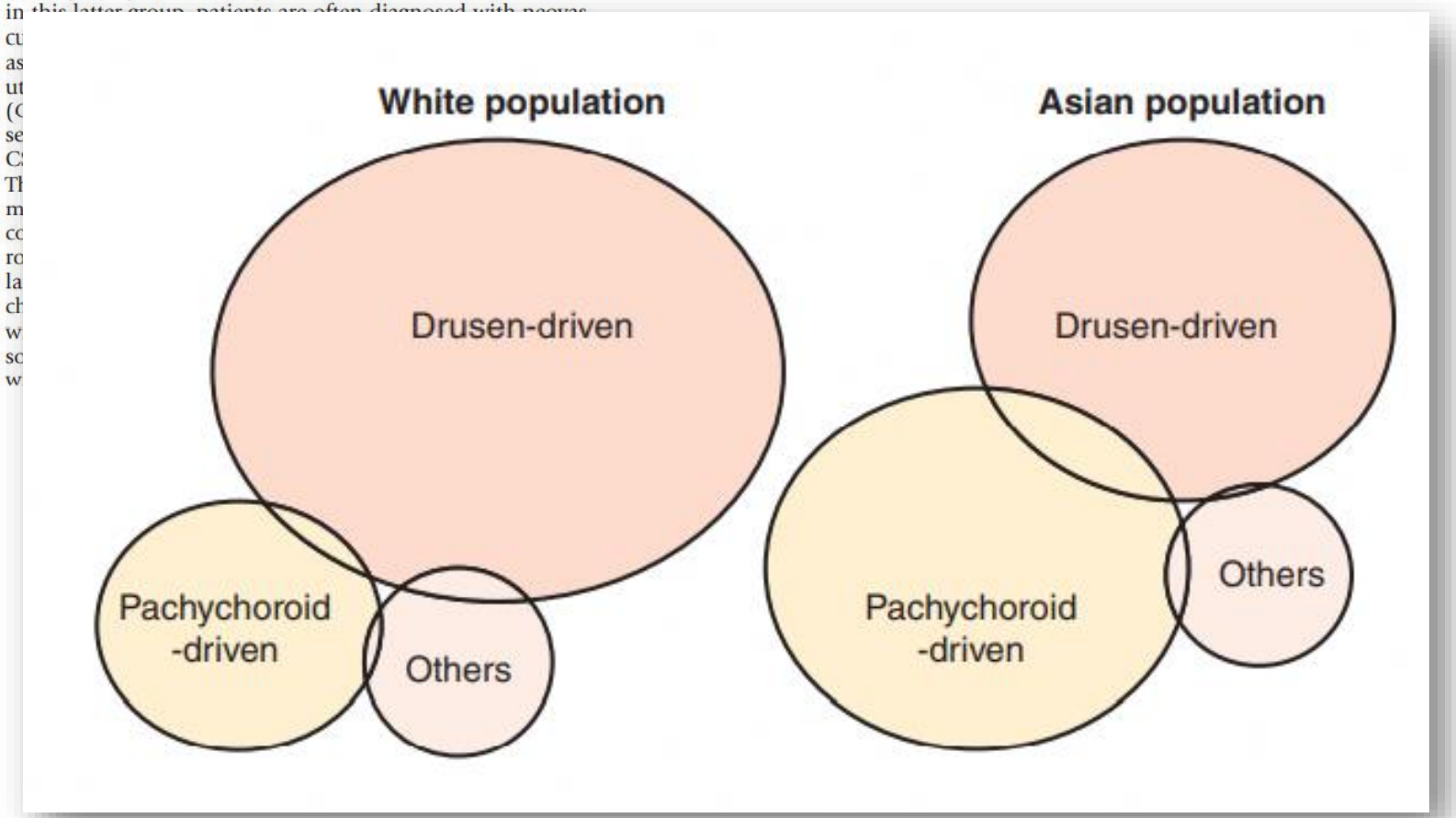
72 Pachychoroid Disease and Its Association With Polypoidal Choroidal Vasculopathy

Chui Ming Gemmy Cheung, Won Ki Lee, Xiaoxin Li, and K. Bailey Freund

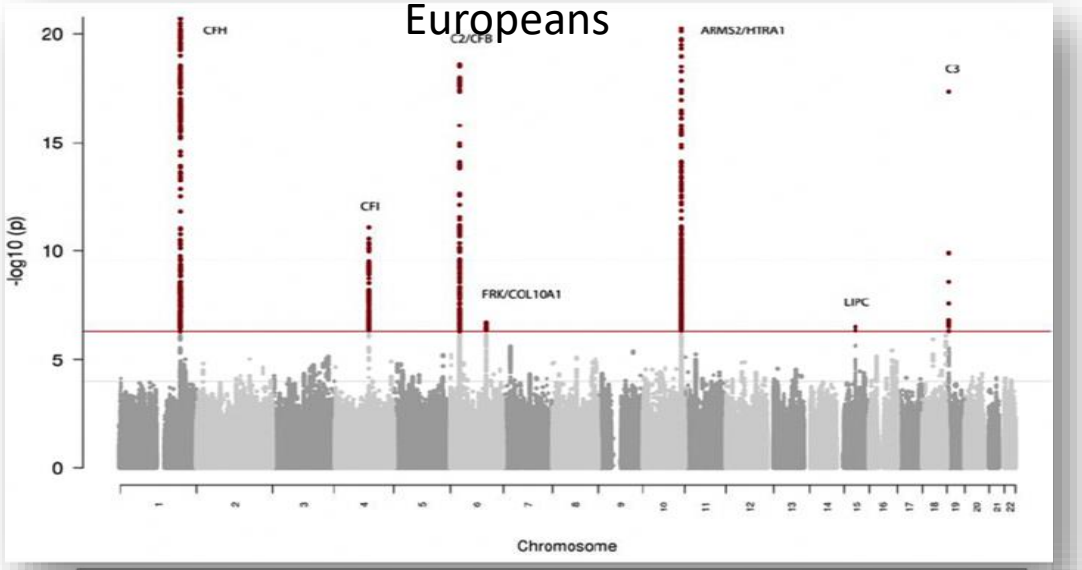


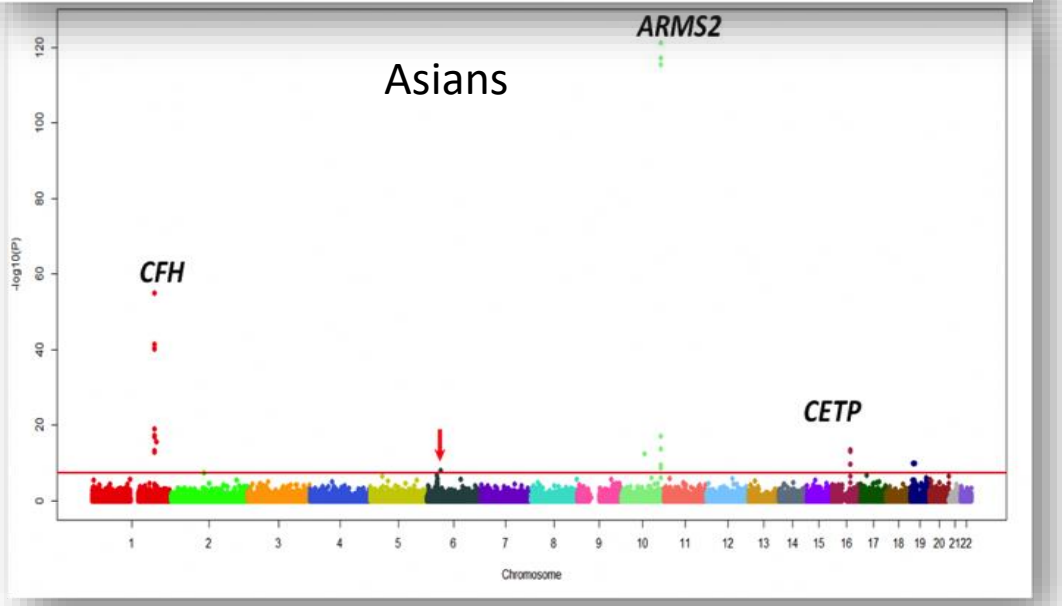
OUTLINE

Polypoidal structures, from type 1 MNV, became apparent in all three eyes, an observation supporting the hypothesis of Warrow et al. that PNV could precede the development of PCV. In a series of 27 eyes of 22 patients, Fung et al. demonstrated that although some patients with CSC are observed to develop type 1 MNV over the course of follow-up, in some patients, findings of prior CSC are noted when they are seen initially for symptomatic type 1 MNV. The authors noted that



Genetics of AMD





Complement Pathway

- Complement factor H (CFHl chr 1)
- Complement factor B (CFB; chr 6)
- Complement component 2 (C2; chr 6)
- Complement component 3 (C3; chr 19)
- Complement factor 1 (CF1; chr 4)

Oxidative damage

- HtrA-serinepeptidase 1 (ARMS/HTRA1; chr 10)
- Paraoxonase 1 (PON1; chr 7)

Lipid pathway

- Apolipoprotein E (APOE; chr 19)
- Hepatic lipase (LIPC; chr 15)
- Cholesterylester transfer protein (CETP; chr 16)

Haines JL et al. *Science* 2005;308:419-21 Edwards A et al. *Science* 2005;308:421-4
Klein RJ et al. *Science* 2005;308:385-9 Hageman G et al , PNAS, 2005

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JOURNAL OF LIPID RESEARCH ASBMB

Plasma lipoprotein subfraction concentrations are associated with lipid metabolism and age-related macular degeneration

Chui Ming Gemmy Cheung,[1,*,†,***] Alfred Gan,* Qiao Fan,[§] Miao Ling Chee,* Rajendra S. Apte,** Chiea Chuen Khor,[††] Ian Yeo,*[,***] Ranjana Mathur,*[,***] Ching-Yu Cheng,*[,***] Tien Y and E. Shyong Tai[§§]

Singapore Eye Research Institute,* Singapore National Eye Centre, Singapore; Department of Yong Loo Lin School of Medicine,[†] and Department of Medicine, Cardiovascular and Metabol Programme,[§§] National University of Singapore, Singapore; Centre for Quantitative Medicine, Ophthalmology and Visual Sciences Program,*** Duke-NUS Medical School, National Univer Singapore, Singapore; Ophthalmology and Visual Sciences,** Developmental Biology and Me Washington University School of Medicine, St. Louis, MO; and Genome Institute of Singapore

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Abstract **Disturbance in lipid metabolism has been suggested as a major pathogenic factor for age-related macular degeneration (AMD). Conventional lipid measures have been inconsistently associated with AMD. Other factors that can alter lipid metabolism include lipoprotein phenotype and genetic mutations. We performed a case-control study to examine the association between lipoprotein profile and neovascular AMD (nAMD) and whether the cholesterylester transfer protein (*CETP*) D442G mutation modulates these associations. Patients with nAMD had significantly higher concentrations of HDL and IDL compared with controls. The increase in HDL particles in nAMD patients was driven by an excess of medium-sized particles. Concurrently, patients with nAMD also had lower Apo A-1, lower VLDL and chylomicron lipoprotein. Many of these associations showed a dose-dependent association between controls, early AMD cases, and nAMD cases. Adjustment for the presence of the D442G mutation at the *CETP* locus did not significantly alter the increased AMD risk associated with HDL particle concentration. AMD is associated with va lipoprotein subclasses, including increased particles and decreased Apo A-1, VLDL, a particles. These data suggest widesprea turbance in lipid metabolism in the pathog including possible alterations in lipoprotei ity.—Cheung, C. M. G., A. Gan, Q. Fan, M. L. C. C. Khor, I. Yeo, R. Mathur, C–Y. Cheng, E. S. Tai. **Plasma lipoprotein subfraction co associated with lipid metabolism and age- degeneration.** ***J. Lipid Res.*** **2017.** 58: **1785–1**

Supplementary key words high density lipoprotein terylester transfer protein

Age-related macular degeneration (AMD major causes of blindness worldwide (1, 2).

Human Plasma Metabolomics Study across All Stages of Age-Related Macular Degeneration Identifies Potential Lipid Biomarkers

Inês Laíns, MD, MSc,[1,2,3,4] Rachel S. Kelly, PhD,[5] John B. Miller, MD,[1] Rufino Silva, MD, PhD,[2,3,4] Demetrios G. Vavvas, MD, PhD,[1] Ivana K. Kim, MD,[1] Joaquim N. Murta, MD, PhD,[2,3,4] Jessica Lasky-Su, PhD,[5] Joan W. Miller, MD,[1,] Deeba Husain, MD[1,*]*

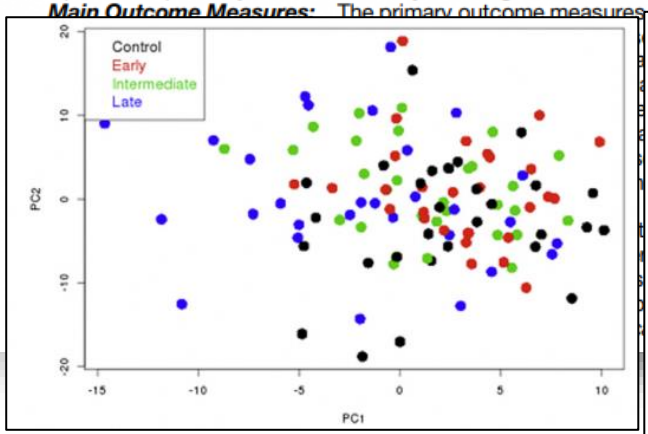
Purpose: To characterize the plasma metabolomic profile of patients with age-related macular degeneration (AMD) using mass spectrometry (MS).

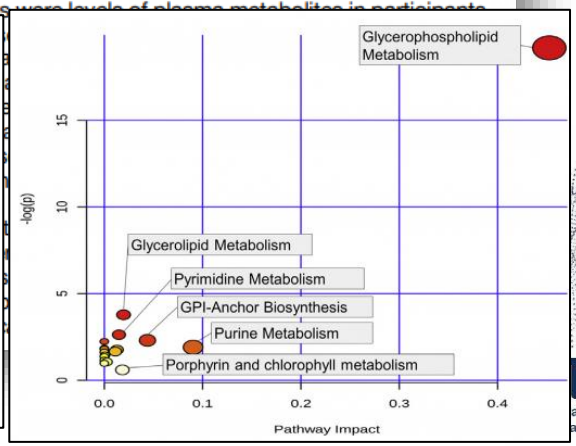
Design: Cross-sectional observational study.

Participants: We prospectively recruited participants with a diagnosis of AMD and a control group (>50 years of age) without any vitreoretinal disease.

Methods: All participants underwent color fundus photography, used for AMD diagnosis and staging, according to the Age-Related Eye Disease Study classification scheme. Fasting blood samples were collected and plasma was analyzed by Metabolon, Inc. (Durham, NC), using ultrahigh-performance liquid chromatography (UPLC) and high-resolution MS. Metabolon's hardware and software were used to identify peaks and control quality. Principal component analysis and multivariate regression were performed to assess differences in the metabolomic profiles of AMD patients versus controls, while controlling for potential confounders. For biological interpretation, pathway enrichment analysis of significant metabolites was performed using MetaboAnalyst.

Main Outcome Measures: The primary outcome measures were levels of plasma metabolites in participants





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Serum Cholesterol Efflux Capacity in Age-Related Macular Degeneration and Polypoidal Choroidal Vasculopathy

Yasuo Yanagi, MD, PhD,[1,2] Richard M.C. Yu, PhD,[1] Waseem Ahamed, MS,[1] Marco Yu, PhD,[1,2] Kelvin Yi Chong Teo, MBBS, MMed (Ophth),[1,2] Anna C.S. Tan, MBBS,[1,2] Ching-Yu Cheng, MD, PhD,[1,2] Tien Yin Wong, MD, PhD,[1,2] Rajendra S. Apte, MD, PhD,[3,4,5] Chui Ming Gemmy Cheung, FRCOphth[1,2]

Purpose: To investigate serum cholesterol efflux capacity (the ability of the serum to accept cholesterol) and factors that regulate it using nuclear magnetic resonance-quantified measures of lipoprotein particle composition and size and apolipoproteins metrics in patients with age-related macular degeneration (AMD).

Design: Case-control study.

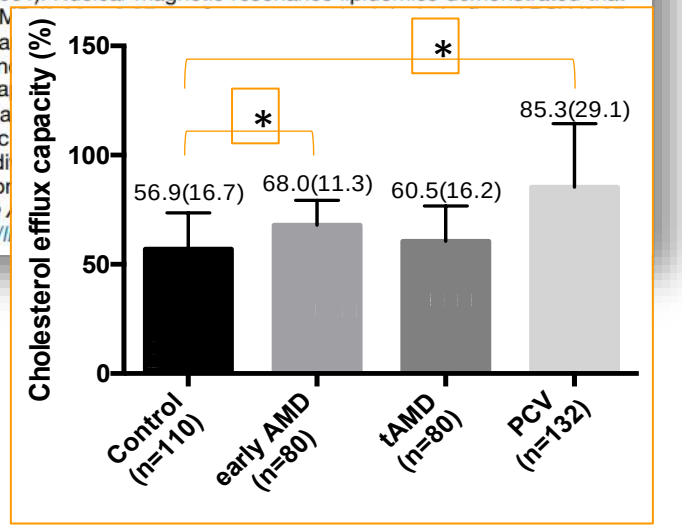
Participants: Four hundred two serum samples from 80 patients with early AMD (eAMD), and 212 patients with neovascular AMD (nAMD), including 80 with typical nAMD (tAMD) and 132 with polypoidal choroidal vasculopathy (PCV), and 110 age- and gender matched control participants.

Methods: Serum from participants showed cholesterol efflux capacity measured using in vitro cell assays and lipoprotein subfractions measured using nuclear magnetic resonance (Nightingale, Ltd). Associations between cholesterol efflux capacity (measured in percentage) and lipid subfractions were investigated in the patients and control participants.

Main Outcome Measures: Cholesterol efflux capacity and lipid subfractions in control, eAMD, and nAMD. Associations between HDL subfractions and cholesterol efflux capacity.

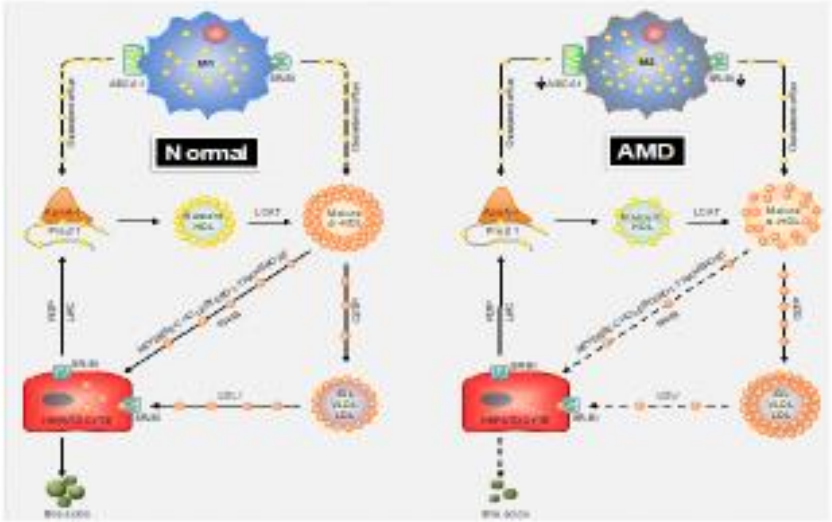
Results: Cholesterol efflux capacity was higher in patients with eAMD (68.0 ± 11.3% [mean ± standard deviation]) and nAMD (75.9 ± 27.7%) than in the control participants (56.9 ± 16.7%) after adjusting for age, gender, and use of lipid-lowering drug ($P < 0.0001$). Nuclear magnetic resonance lipidomics demonstrated that the mean diameter of HDL was larger both in eAM
± 0.23 mm) compared with that of the control pa
HDL subfractions, most of the small, medium, an
associated moderately with cholesterol efflux ca

Conclusions: Serum cholesterol efflux capa
reflecting differential underlying pathophysiologic
should be directed toward investigating the di
pigment transport, regulation of inflammatio



HDL metabolism

DUKE NUS GRADUATE MEDICAL SCHOOL SINGAPORE



Hypothesis: HDL lipoproteins in AMD patients are less efficient in supporting cholesterol transport

- Accumulation of cholesterol in macrophages and tissues
- These dysfunctional HDL lipoproteins display a distinct phenotype

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Endothelial cell dysfunction

Hyaluronidase-1-mediated glycocalyx impairment underlies endothelial abnormalities in polypoidal choroidal vasculopathy

Kan Xing Wu[1], Natalie Jia Ying Yeo[1], Chun Yi Ng[1], Florence Wen Jing Chioh[1], Qiao Fan[2,3], Xianfeng Tian[1,2], Binxia Yang[4], Gunaseelan Narayanan[5], Hui Min Tay[6], Han Wei Hou[1,6], N. Ray Dunn[1,7,8], Xinyi Su[4,9,10,11], Chui Ming Gemmy Cheung[2,10] and Christine Cheung[1,4*]

Abstract

Background: Polypoidal choroidal vasculopathy (PCV), a subtype of age-related macular degeneration (AMD), is a global leading cause of vision loss in older populations. Distinct from typical AMD, PCV is characterized by polyp-like dilatation of blood vessels and turbulent blood flow in the choroid of the eye. Gold standard anti-vascular endothelial growth factor (anti-VEGF) therapy often fails to regress polypoidal lesions in patients. Current animal models have also been hampered by their inability to recapitulate such vascular lesions. These underscore the need to identify VEGF-independent pathways in PCV pathogenesis.

Results: We cultivated blood outgrowth endothelial cells (BOECs) from PCV patients and normal controls to serve as our experimental disease models. When BOECs were exposed to heterogeneous flow, single-cell transcriptomic analysis revealed that PCV BOECs preferentially adopted migratory-angiogenic cell state, while normal BOECs undertook proinflammatory cell state. PCV BOECs also had a repressed protective response to flow stress by demonstrating lower mitochondrial functions. We uncovered that elevated hyaluronidase-1 in PCV BOECs led to increased degradation of hyaluronan, a major component of glycocalyx that interfaces between flow stress and vascular endothelium. Notably, knockdown of hyaluronidase-1 in PCV BOEC improved mechanosensitivity, as demonstrated by a significant 1.5-fold upregulation of Krüppel-like factor 2 (*KLF2*) expression, a flow-responsive transcription factor. Activation of *KLF2* might in turn modulate PCV BOEC migration. Barrier permeability due to glycocalyx impairment in PCV BOECs was also reversed by hyaluronidase-1 knockdown. Correspondingly, hyaluronidase-1 was detected in PCV patient vitreous humor and plasma samples.

Conclusions: Hyaluronidase-1 inhibition could be a potential therapeutic modality in preserving glycocalyx integrity and endothelial stability in ocular diseases with vascular origin.

International Journal of *Molecular Sciences*

MDPI

Article

Single-Cell Transcriptome of Wet AMD Patient-Derived Endothelial Cells in Angiogenic Sprouting

Natalie Jia Ying Yeo [1,†], Vanessa Wazny [1,†], Nhi Le Uyen Nguyen [1], Chun-Yi Ng [1], Kan Xing Wu [1], Qiao Fan [2,3], Chui Ming Gemmy Cheung [2,4,*] and Christine Cheung [1,5,*]

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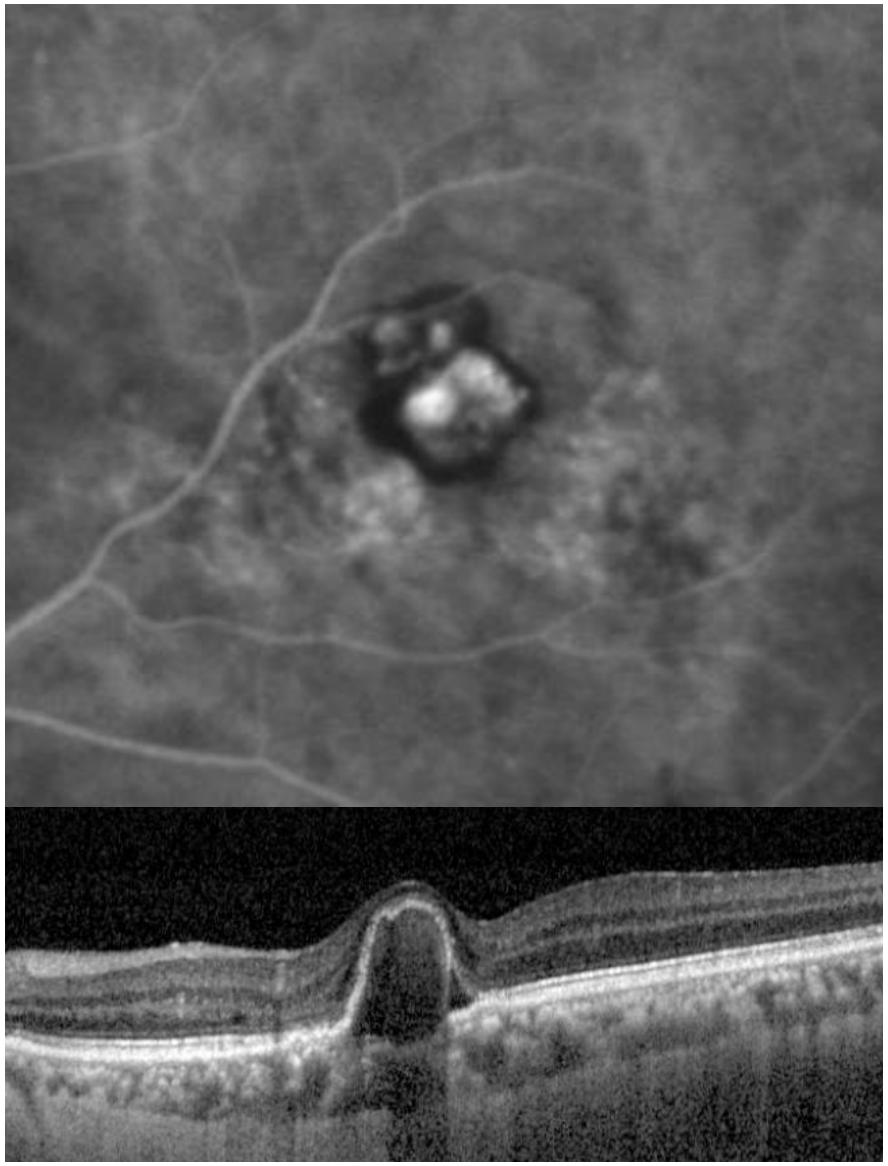
* Correspondence: gemmy.cheung.c.m@singhealth.com.sg (C.M.G.C.); ccheung@ntu.edu.sg (C.C.)
† These authors contributed equally to this work.

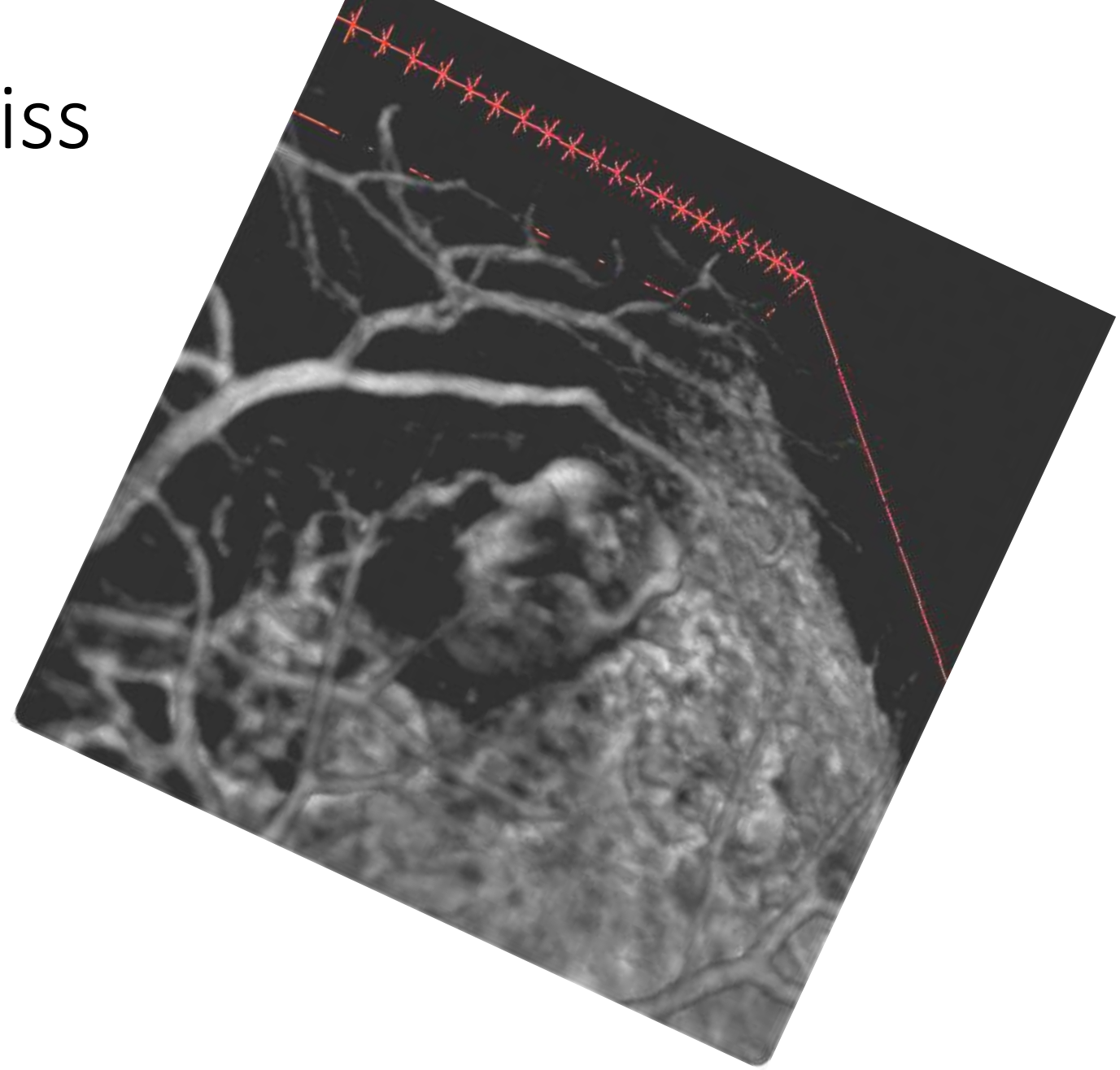
Abstract: Age-related macular degeneration (AMD) is a global leading cause of visual impairment in older populations. 'Wet' AMD, the most common subtype of this disease, occurs when pathological angiogenesis infiltrates the subretinal space (choroidal neovascularization), causing hemorrhage and retinal damage. Gold standard anti-vascular endothelial growth factor (VEGF) treatment is an effective therapy, but the long-term prevention of visual decline has not been as successful. This warrants the need to elucidate potential VEGF-independent pathways. We generated blood out-growth endothelial cells (BOECs) from wet AMD and normal control subjects, then induced angiogenic sprouting of BOECs using a fibrin gel bead assay. To deconvolute endothelial heterogeneity, we performed single-cell transcriptomic analysis on the sprouting BOECs, revealing a spectrum of cell states. Our wet AMD BOECs share common pathways with choroidal neovascularization such as extracellular matrix remodeling that promoted proangiogenic phenotype, and our 'activated' BOEC subpopulation demonstrated proinflammatory hallmarks, resembling the tip-like cells in vivo. We uncovered new molecular insights that pathological angiogenesis in wet AMD BOECs could also be driven by interleukin signaling and amino acid metabolism. A web-based visualization of the sprouting BOEC single-cell transcriptome has been created to facilitate further discovery research.

check for updates

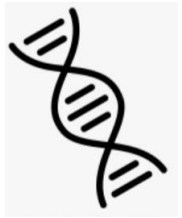
Citation: Yeo, N.J.Y.; Wazny, V.; Nguyen, N.L.U.; Ng, C.-Y.; Wu, K.X.; Fan, Q.; Cheung, C.M.G.; Cheung, C. Single-Cell Transcriptome of Wet AMD Patient-Derived Endothelial Cells in Angiogenic Sprouting. *Int. J. Mol. Sci.* **2022**, 23, 12549. https://

Collaboration with Zeiss





Achievements so far



6 novel gene targets discovered

>300 peer reviewed publications and clinical guidelines

5 invention disclosures

5 patents

2 electronic tools

3 international consortiums

Asian Eye Epidemiology Consortium (AEEC)
Asia Pacific Ocular Imaging Society (APOIS)
Fight Retinal Blindness! Registry

>10 PhD students and Clinical/Research Fellows

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Pathways to translation

Theme 1 **Improve population health and reduce global burden on disease**	**Theme 2** **Develop novel Therapeutic targets**	**Theme 3** **Biomarkers to identify high risk groups and guide better treatment**	**Theme 4** **Clinical trial of local relevance to Asian AMD to improve patient care in local context**	**Theme 5** **Assess impact of disease from patients' perspectives**
Pathways to achieving impact				
• Policy, • Guidelines, • Media Publicity • Public education	• Drug development through identifying novel molecular signatures and disease pathways	• Novel non-invasive devices & novel clinically relevant software • Novel techniques to study choriocapillaris, choroid and beta amyloid • Understand early disease mechanisms • Improve diagnostic capability	• Cost effective therapeutic approach • Develop Treatment guidelines in choosing multiple treatment options	• Improved estimates of burden of care from patient and societal perspectives • Data to inform government policy and provide justification to resource management and care delivery planning • Policy/guidelines to promote mental well-being and overall holistic care.

Thank you

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NMRC National Medical Research Council Singapore
OPEN FUND - LARGE COLLABORATIVE GRANT

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Singapore National Eye Centre
SingHealth

DukeNUS Medical School

Tan Tock Seng HOSPITAL
National Healthcare Group

NUHS National University Health System

NANYANG TECHNOLOGICAL UNIVERSITY

Agency for Science, Technology and Research
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