MEDIA RELEASE

22 MARCH 2021

SINGAPORE SCIENTISTS IDENTIFY GENETIC MUTATION ASSOCIATED WITH EXFOLIATIVE SYNDROME, THE MOST COMMON CAUSE OF GLAUCOMA

Eye of a patient with exfoliation syndrome. The typical white exfoliation material deposits on the surface of the lens are visible (red arrows) with the aid of a slit lamp at 16x magnification under white light. Exfoliation material may not be visible on unaided exam.

SINGAPORE – A team of researchers from the Agency for Science, Technology and Research’s (A*STAR) Genome Institute of Singapore (GIS) and Bioprocessing Technology Institute (BTI), as well as Singapore Eye Research Institute (SERI), have identified a genetic mutation (functionally defective CYP39A1 gene) associated with exfoliation syndrome, the most common cause of glaucoma. The findings could pave the way for future research on the cause of exfoliation syndrome and potential cures. Their research was published in Journal of the American Medical Association (JAMA) on 24 February 2021.

Genome Institute of Singapore
60 Biopolis Street #02-01 Genome Singapore 138672
T + 6808 8000 W www.a-star.edu.sg/gis

CREATING GROWTH, ENHANCING LIVES
Exfoliation syndrome is a systemic disorder characterised by abnormal protein material that progressively accumulates in the front of the eye. This disorder is the most common cause of glaucoma, and a major cause of irreversible blindness.

In this study, the scientists sequenced all protein encoding genes of more than 20,000 participants from 14 countries across Asia, Europe, and Africa, including more than 1,200 Singaporeans. They observed that people with exfoliation syndrome are twice as likely to carry damaging mutations in the gene encoding for the CYP39A1 protein, an enzyme which plays an important role in the processing of cholesterol. Further extended analyses suggest that defective CYP39A1 function is strongly associated with increased risk of exfoliation syndrome.

Although exfoliation syndrome is the most common cause of glaucoma, its origin is shrouded in mystery because it is not known where the abnormal protein deposits (exfoliative material) originate, and how the disease comes about. Answers to these questions could provide approaches to design and develop an effective treatment. The current findings point to the important role of cholesterol processing in the exfoliation syndrome disease process. As cholesterol is found abundantly in all cells, disruption to how cholesterol is processed due to defective CYP39A1 activity could adversely impact their normal functions. In particular, this study discovered that epithelial cells in the front of the eye responsible for filtering the blood supply to produce the clear fluid known as aqueous humour that bathes and nourishes other cells in the eye, were most affected by the CYP39A1 gene mutation. Disruption to the gene function can compromise the filtering function of epithelial cells and lead to leakage of exfoliative material from the blood into the eye.

Prof Patrick Tan, Executive Director of GIS, said, “This is a ground-breaking study that could facilitate future research efforts aimed at restoring defective CYP39A1 function and inhibiting the formation of exfoliation material in the eye as treatments for exfoliation syndrome and glaucoma.”

Prof Aung Tin, Director of SERI and Deputy Medical Director of SNEC, said, “This is a major eye disease, affecting over 70 million people worldwide, which causes a lot of visual morbidity and blindness, not only from glaucoma but also due to complications related to cataract surgery. This study was notable for involving many centres from many different countries around the world, but led from Singapore. The study findings are very exciting as we found a new pathway for the disease which opens up possibilities for new treatments.”

Prof David Friedman, the Albert and Diane Kaneb Chair in Ophthalmology at Harvard University and Director of the Glaucoma Service at the Massachusetts Eye and Ear Infirmary, Boston, commented, “Very exciting work. The researchers have identified rare gene variants that results in disrupted cholesterol homeostasis and transport that will open the door to novel therapeutics. Having studied over 20,000 individuals, the study demonstrates the power of studying rare variants to detect disease-causing genes in complex conditions.” Prof Friedman was not involved in the study.

– END –
Enclosed:

ANNEX A – Notes to Editor

For media queries and clarifications, please contact:

Lyn Lai
Officer, Office of Corporate Communications
Genome Institute of Singapore, A*STAR
Tel: +65 6808 8258
HP: +65 8755 8759
Email: laiy@gis.a-star.edu.sg

Ravi Chandran
Corporate Communications
Singapore National Eye Centre
Tel: +65 8121 8569
Email: ravi.chandran@snec.com.sg

About A*STAR’s Genome Institute of Singapore (GIS)

The Genome Institute of Singapore (GIS) is an institute of the Agency for Science, Technology and Research (A*STAR). It has a global vision that seeks to use genomic sciences to achieve extraordinary improvements in human health and public prosperity. Established in 2000 as a centre for genomic discovery, the GIS pursues the integration of technology, genetics and biology towards academic, economic and societal impact, with a mission to "read, reveal and write DNA for a better Singapore and world".

Key research areas at the GIS include Precision Medicine & Population Genomics, Genome Informatics, Spatial & Single Cell Systems, Epigenetic & Epitranscriptomic Regulation, Genome Architecture & Design, and Sequencing Platforms. The genomics infrastructure at the GIS is also utilised to train new scientific talent, to function as a bridge for academic and industrial research, and to explore scientific questions of high impact.

For more information about GIS, please visit www.a-star.edu.sg/gis.

About the Agency for Science, Technology and Research (A*STAR)

A*STAR is Singapore's lead public sector R&D agency. Through open innovation, we collaborate with our partners in both the public and private sectors to benefit the economy and society. As a Science and Technology Organisation, A*STAR bridges the gap between
academia and industry. Our research creates economic growth and jobs for Singapore, and enhances lives by improving societal outcomes in healthcare, urban living, and sustainability. A*STAR plays a key role in nurturing scientific talent and leaders for the wider research community and industry. A*STAR’s R&D activities span biomedical sciences to physical sciences and engineering, with research entities primarily located in Biopolis and Fusionopolis. For ongoing news, visit www.a-star.edu.sg.

Follow us on
Facebook | LinkedIn | Instagram | YouTube

About Singapore Eye Research Institute (SERI)

SERI is Singapore’s national research institute for ophthalmic and vision research. SERI has grown from a founding team of five in 1997 to a faculty of more than 250 staff, encompassing clinician scientists, scientists, research fellows, PhD students and support staff. SERI has also over 240 adjunct faculties from various eye departments, biomedical institutes and tertiary centres in Singapore. This makes SERI one of the largest research institutes in Singapore, as well as the largest eye research institute in the Asia Pacific region.

SERI’s mission is to conduct high-impact eye research that prevents blindness, low vision and major eye diseases common to Singaporeans and Asians. Over the last decade, SERI has conducted landmark research projects that have led to tangible outcomes, patient benefits, and success stories. It has paved the way for significant improvements in how eye diseases are treated and prevented, not just for Singaporeans or Asians, but on a global scale.

For more information about SERI, please visit www.seri.com.sg

ANNEX A – NOTES TO EDITOR

The research findings described in this media release can be found in the scientific journal JAMA, under the title, “Association of rare CYP39A1 variants with exfoliation syndrome involving the anterior chamber of the eye” by the following authors:

---

Genome Institute of Singapore
60 Biopolis Street #02-01 Genome Singapore 138672
T + 6808 8000 W www.a-star.edu.sg/gis

CREATING GROWTH, ENHANCING LIVES
Authors of the Genetics of Exfoliation Syndrome (GenES) Partnership

Zheng Li, MD, PhD; Zhenxun Wang, PhD; Mei Chin Lee, PhD; Matthias Zenkel, PhD; Esther Peh, BS; Mineo Ozaki, MD, PhD; Fotis Topouzis, MD, PhD; Satoko Nakano, MD; Anita Chan, MD; Shuwen Chen, BS; Susan E.I. Williams, MD, PhD; Andrew Orr, MD; Masakazu Nakano, PhD; Nino Kobakhidze, MD; Tomasz Zarnowski, MD, PhD; Alina Popa-Cherecheanu, MD, PhD; Takanori Mizoguchi, MD; Shin-ichi Manabe, MD; Ken Hayashi, MD, PhD; Shigeyasu Kazama, MD; Kenji Inoue, MD; Yosai Mori, MD, PhD; Kazunori Miyata, MD, PhD; Kazuhiisa Sugiyama, MD, PhD; Tomomi Higashide, MD, PhD; Etsuko Chihara, MD, PhD; Ryuichi Ideta, MD, PhD; Satoshi Ishiko, MD, PhD; Akitoshi Yoshida, MD, PhD; Kana Tokumo, MD; Yoshiaki Kiuchi, MD, PhD; Tsutomu Ohashi, MD, PhD; Toshiya Sakurai, MD, PhD; Takako Sugimoto, MD; Hideki Chuman, MD, PhD; Makoto Aihara, MD, PhD; Masaru Inatani, MD, PhD; Kazuhiko Mori, MD, PhD; Yoko Ikeda, MD, PhD; Morio Ueno, MD, PhD; Daniel Gaston, PhD; Paul Rafuse MD, PhD; Lesya Shuba, MD, PhD; Joseph Saunders, BS; Marcello Nicolela, MD; George Chichua, MD; Sergio Tabagari, MD, PhD; Panayiotis Founti, MD, PhD; Kar Seng Sim, BS; Wee Yang Meah, BS; Hui Meng Soo, BS; Xiao Yin Chen, BS; Anthi Chatzikyriakidou, PhD; Christina Keskini, MD; Theofanis Pappas, MD; Eleftherios Anastasopoulos, MD; Alexandros Lambropoulos, PhD; Evangelia S. Panagiotou, MD, PhD; Dimitrios G. Mikropoulos, MD, PhD; Ewa Kosior-Jarecka, MD; Augustine Cheong, BS; Yuanhan Li, MS; Urszula Lukasik, MD, PhD; Monisha E Nongpiur, MD, PhD; Rahat Husain, MD; Shamira A. Perera, MD; Lydia Alvarez, PhD; Montserrat Garcia, PhD; Hector Gonazalez-Iglesias, PhD; Andres Fernandez-Vega Cueto, MD, PhD; Luis Fernandez-Vega Cueto, MD, PhD; Federico Martinon-Torres, MD, PhD; Antonio Salas, PhD; Celiling Onguz, PhD; Nevbahar Tamcelik, MD; Eray Atalay, MD; Bilge Batu, MD; Murat Irtek, MD; Diltek Aktas, MD, PhD; Burcu Kasmis, MD; Yury S. Astakhov, MD; Sergei Y. Astakhov, MD, PhD; Eugeny L. Akopov, MD, PhD; Andreas Giessl, PhD; Christian Mardin, MD; Claus Hellerbrand, MD; Jessica N. Cooke Bailey, PhD; Robert P. Igo, Jr., PhD; Jonathan L. Haines, PhD; Deepak P. Edward, MD; Steffen Heegaard, MD; Sonia Davila, PhD; Patrick Tan,
Affiliations of the Genetics of Exfoliation Syndrome (GenES) Partnership members.

2. Singapore Eye Research Institute, Singapore National Eye Centre
3. Department of Ophthalmology, Universitätsklinikum Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany
5. Ozaki Eye Hospital, 1-15, Kamezaki, Hyuga, Miyazaki 883-0066 Japan
6. 1st Department of Ophthalmology, School of Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki, Greece.
7. iScreen Research Team, Center for Interdisciplinary Research and Innovation (CIIRI), Aristotle University of Thessaloniki, Thessaloniki, Greece
8. Department of Ophthalmology, Oita University Faculty of Medicine, 1-1 Idaigaoka, Hasama-machi, Yufu-City, Oita 879-5593, Japan
9. Duke-NUS Medical School, Singapore

10. Division of Ophthalmology, Department of Neurosciences, University of the Witwatersrand, Johannesburg, South Africa.


12. Department of Pathology, Dalhousie University, Halifax, Nova Scotia, Canada

13. Department of Genomic Medical Sciences, Kyoto Prefectural University of Medicine, Kyoto, Japan

14. Chichua Medical Center Mzera, Georgia.

15. Department of Diagnostics and Microsurgery of Glaucoma, Medical University, Lublin, Poland, Chmielna 1, 20-079 Lublin, Poland.

16. “Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania

17. University Emergency Hospital, Department of Ophthalmology, Bucharest, Romania

18. Mizoguchi Eye Hospital, Nagasaki, Japan, 6-13 Tawara-machi, Sasebo, Nagasaki, Japan 857-0016

19. Hayashi Eye Hospital, 4-23-35 Hakataekimae, Hakata-ku, Fukuoka 812-0011, Japan

20. Shinjo Eye Clinic, 889-1, Mego, Simokitatamachi, Miyazaki-shi, Miyazaki 880-0035, Japan

21. Inouye Eye Hospital, 4-3 Kanda-Surugadai, Chiyoda-ku, Tokyo 101-0062

22. Miyata Eye Hospital, 6-3, Kurahara, Miyakonojo, Miyazaki 885-0051 Japan

23. Department of Ophthalmology Kanazawa University Graduate School of Medical Science, 13-1 Takara-machi, Kanazawa, 920-8641, Japan

24. Sensho-kai Eye Institute, Minamiyama 50-1, Iseda, Uji, Kyoto 611-0043, Japan

25. Ideta Heisei retina consultants, Kumamoto, Japan.
26. Department of Medicine and Engineering Combined Research Institute, Asahikawa Medical University, Asahikawa, Japan.

27. Department of Ophthalmology, Asahikawa Medical University, Asahikawa, Japan.

28. Hiroshima University, Department of Ophthalmology and Visual Sciences, 1-2-3 Kasumi, Minami-ku, Hiroshima, 734-8551, Japan

29. Ohashi eye center, Kita1-1 Hondori6 Shiroishi-ku Sapporo 003-0027 Japan

30. Tane Memorial Eye Hospital, 1-1-39, Sakaigawa, Nishi-ku, Osaka, 550-0024, Japan

31. Department of Ophthalmology, Miyazaki Medical College Hospital, 5200 Kihara Kiyotake, Miyazaki.

32. Department of Ophthalmology, University of Tokyo, Bunkyo, Tokyo 113-8655, Japan

33. Department of Ophthalmology, Faculty of Medical Science, University of Fukui, 23-3 Shimoaizuki, Matsuoka, Eiheiji, Yoshida, Fukui, 910-1193, Japan

34. Department of Ophthalmology, Kyoto Prefectural University of Medicine, Kyoto, Japan.

35. David Tvlidi Medical University, Tbilisi, Georgia.

36. Glaucoma Unit, Moorfields Eye Hospital NHS Foundation Trust, London, UK

37. Laboratory of Medical Biology - Genetics, School of Medicine, Aristotle University of Oviedo, Oviedo, Spain.

38. Fernández-Vega Ophthalmological Institute, Avda. Dres. Fernández-Vega, 34, Oviedo 33012, Spain
40. Translational Pediatrics and Infectious Diseases, Hospital Clínico Universitario de Santiago (SERGAS) and GENVIP Research Group, Instituto de Investigación Sanitaria (IDIS), University of Santiago de Compostela, Santiago de Compostela, Spain.

41. Unidade de Xenética, Instituto de Ciencias Forenses, Facultade de Medicina, Universidade de Santiago de Compostela, and GenPoB Research Group, Instituto de Investigación Sanitaria (IDIS), Hospital Clínico Universitario de Santiago (SERGAS), Travesa da Choupana s/n 15706 Galicia, Spain.

42. Department of Genetics, Eskisehir Osmangazi University, Meselik, Eskisehir, Turkey

43. Istanbul University Cerrahpasa Faculty of Medicine

44. Department of Ophthalmology, Eskisehir Osmangazi University, Meselik, Eskisehir, Turkey

45. Department of Ophthalmology, Hacettepe University, Faculty of Medicine, Ankara, Turkey

46. DAMAGEN Genetic Diagnostic Center, Ankara, Turkey

47. Department of Ophthalmology, Pavlov First Saint Petersburg State Medical University, St. Petersburg, Russia.


49. Department of Population and Quantitative Health Sciences, Institute for Computational Biology, Case Western Reserve University School of Medicine, Cleveland, OH, USA.

50. King Khaled Eye Specialist Hospital, Riyadh, Kingdom of Saudi Arabia.

51. Department of Ophthalmology and Visual Sciences, University of Illinois College of Medicine, Chicago, IL, USA

52. Department of Ophthalmology, Rigshospitalet, University of Copenhagen, Denmark
53. Department of Pathology, Rigshospitalet, Eye Pathology Section, University of Copenhagen, Denmark.

54. SingHealth Duke-NUS Institute of Precision Medicine, Singapore 169856, Singapore.

55. Cardiovascular and Metabolic Disorders Program, Duke-NUS Medical School, Singapore 169857, Singapore.


57. Channing Division of Network Medicine, Department of Medicine, Brigham and Women’s Hospital and Harvard Medical School, Boston, MA, USA

58. Department of Ophthalmology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

59. Institute of Human Genetics, University Hospital Erlangen, Friedrich-Alexander University Erlangen-Nuremberg, Erlangen, Germany

60. Department of Medicine, Duke University, Durham, NC, USA

61. Department of Ophthalmology, Duke University, Durham, NC, USA

62. Sydney Brenner Institute for Molecular Bioscience, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

63. Department of Ophthalmology, Medical University Graz, Graz, Austria

64. 1st and 3rd Departments of Ophthalmology, School of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece.

65. Department of Ophthalmology and Visual Science, Yale University School of Medicine, 300 George St, 8100A, New Haven, CT 06510, USA

66. Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore.

67. Department of Frontier Medical Science and Technology for Ophthalmology, Kyoto Prefectural University of Medicine, Kyoto, Japan.

68. State Research Institute of Highly Pure Biopreparations FMBA Russia, St. Petersburg, Russia.
69. Einhorn Clinical Research Center, New York Eye and Ear Infirmary of Mount Sinai, 310 East 14th Street, New York, NY 10003.

70. Department of Ophthalmology, Harvard Medical School, Massachusetts Eye and Ear Infirmary, Boston, Massachusetts.

71. Department of Ophthalmology, Yong Loo Lin School of Medicine, National University of Singapore.

72. Cancer Science Institute of Singapore, National University of Singapore, Singapore.

73. School of Biological Sciences, Nanyang Technological University, Singapore, Singapore.

74. Department of Biochemistry, Yong Loo Lin School of Medicine, National University of Singapore, Singapore.

Contact details of scientists:
Genome Institute of Singapore, 60 Biopolis Street, #02-01 Genome Building, Singapore 138672. Chiea Chuen Khor, M.D., PhD, (khorcc@gis.a-star.edu.sg), Wai Leong Tam, PhD (tamwl@gis.a-star.edu.sg).

Author Contributions: Dr Khor had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs. Z Li, Wang, Lee, Zenkel, Pasutto, Schlötzer-Schrehardt, Ho, Aung, Tam, and Khor contributed to the work equally.