

The Sankara Nethralaya ONGC Department of Genetics and Molecular Biology was inaugurated on the 6th September 1993. The Molecular Biology lab was established in 1997. The department members have made significant contributions to genetics of eye diseases. The department offers clinical support through cytogenetic studies for chromosomal eye disorders and molecular studies for retinitis pigmentosa. Considerable amount of work has been done in genetics of retinoblastoma, retinitis pigmentosa, glaucoma, diabetic retinopathy. These work have been published in high-indexed journals. The department currently runs 5 projects funded by government and private funding agencies. The lab is equipped with Affymetrix Genechip facility and sophisticated instruments which include genetic analyzer and fluorescent in situ hybridization (FISH) microscope. The new arrivals are advanced equipments with which research work on par with international standards can be accomplished.

Head of the Department

Prof. G. Kumaramanickavel, M.D

Reader

Dr. V S Sankaranand, PhD

Senior Scientists

Dr. J. Madhavan, MBBS, DO

Research Fellows

Ms. S. Uthra, MS (MLT)

Ms. Vinita Kumari, MS (MLT)

Mr. K. Ramprabhu, MSc

Ms. M. Aarthi, MSc

Dr. V.L.Ramprasad, PhD

Dr. S. Sripriya, PhD

Dr. N Soumittra, PhD

Secretary

Ms. T. Jayasri, B.Com, M.A, D.L.L

Medical Social Worker

Mr. T Arokiasamy, MSW

Technical Group

Ms. G. Salomi S S, BSc, PGDMLT

Ms. S. Srilekha, BSc, PGDMLT

Mr. M. Rajesh, BSc, CMLT

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Ms. L. Praveena, BSc, PGDMLT





Genetic counseling - to patients with inherited eye disorders

Diagnosis – cytogenetic analysis for chromosomal disorders and molecular diagnosis of retinitis pigmentosa

Teaching – genetics and molecular biology for students of B.S.Optomety, M.S. Medical Laboratory Technology, M.Phil Optometry, DO/DNB and FRCS (Ed)

Research – molecular genetics of retinoblastoma, age related cataract, glaucoma, retinitis pigmentosa, diabetic retinopathy, congenital cataract, corneal dystrophies, etc.

Collaborations - with international universities

What is genetic counseling?

Genetic counseling is the process of evaluating family history and medical records, ordering genetic tests, evaluating the results of this investigation, and helping parents understand and reach decisions about what to do next.

Whom do we counsel here?

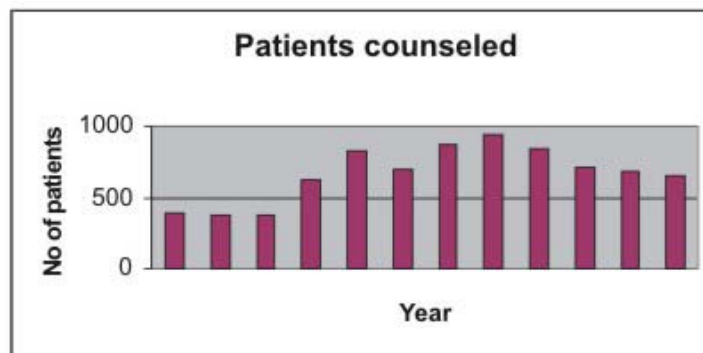
We counsel patients with hereditary ocular disorders referred by the consultants. We educate the patients and/or parents about the disease and offer suggestions regarding their future and rehabilitation program.



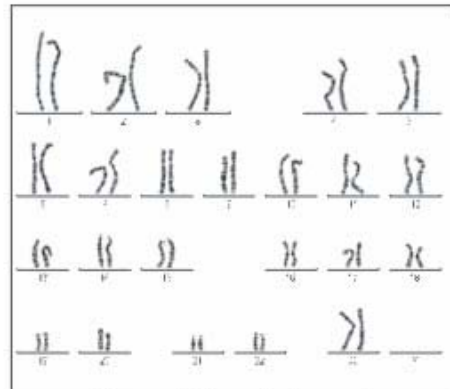
Which are the common disorders for which genetic counseling is sought?

In our department the highest number of patients have come with retinitis pigmentosa followed by retinoblastoma. The data given below is for the year 2007

Retinitis pigmentosa	290
Retinoblastoma	10
Cone dystrophy	51
Stargardts	35
Glaucoma	26
Ushers	11
Coloboma	5
Microphthalmos	4
Cataract	3
Others	224
Total No of cases	659



Cytogenetic studies are being carried out for disorders caused by chromosomal abnormalities. Karyotyping is done and chromosomes are observed for the presence of numerical or structural abnormalities.



Normal female karyotype

Some of the disorders for which cytogenetic studies are done include:

Aniridia

Down syndrome

Blepharophimosis

Turner syndrome

Cri-du-chat

Klinefelter syndrome

Retinoblastoma

Anterior segment anomalies



Fluorescent in situ hybridization (FISH) workstation for rapid and precise analysis of chromosomes

and precise analysis of

COMPLETED PROJECTS

Developing DNA based diagnostic methods for Retinoblastoma and its phenotype genotype correlation. Funded by the Dept of Biotechnology, Govt of India, New Delhi

Proposal for Upgrading Research and Diagnostic Activities. Funded by Oil and Natural Gas Corporation Ltd.

Mutational screening of the Rhodopsin gene in patients of autosomal dominant retinitis pigmentosa and RPE65 gene in patients of childhood onset autosomal recessive retinitis pigmentosa and Lebers Congenital Amaurosis. Funded by the Indian Council of Medical Research.

Gene Mapping Complex diseases: Adult Onset Cataract in India. Funded by the Department of Science & Technology.

Novel molecular diagnostics for eye diseases and low vision enhancement devices. Funded by the Centre for Scientific Industrial Research.

Epidemiological & Genetic Studies of Diabetic Retinopathy in Urban Chennai. Funded by the R.D. Tata Trust, Mumbai.

Sankara Nethralaya Glaucoma Study & the Molecular Genetics of Glaucoma in the South Indian Population. Funded by the Chennai Willingdon Corporate Foundation, India.

ONGOING PROJECTS

Gene mapping for Myopia and identification of environmental risk factors for myopia progression in subjects with genetic susceptibility. Funded by the Department of Science & Technology.

Genetic association studies & fine mapping of critical genomic regions that harbor age related macular degeneration (AMD) susceptibility loci/genes. Funded by the Dept of Biotechnology, Govt of India, New Delhi

Sankara Nethralaya diabetic retinopathy epidemiology and molecular genetic studies (SNDREAMS II urban and SNDREAMS III rural). Funded by Jamshedji TATA Trust, Mumbai.

Molecular genetics of Corneal Dystrophy - Mutational Screening of SLC4A11 and COL8A2 gene in Fuch's Corneal Dystrophy (FCD) and Linkage analysis in FCD affected Families. Funded by Indian Council of Medical Research, New Delhi.



- -20 ° C, -80 ° C deep freezers
- Agarose gel tanks
- Autoclave
- Centrifuge
- CO₂ incubator, Incubator
- Cyclomixer
- DNA Thermal cyclers
- Electronic weighing balance
- FISH microscope.
- Gel documentation system
- ABI PRISM 3100 AVANT genetic analyzer
- ABI PRISM 7300 Real time PCR system
- Gel dryer
- HbA_{1c} auto analyzer

- Hot air oven
- Laminar flow hood
- Light Microscope
- Magnetic stirrer with heater
- Microfuge
- Microwave Oven
- Polyacrylamide electrophoresis units
- Sequencing gel systems
- Vacuum pump
- Water bath with shaker
- ABI PRISM 6100 Nucleic acid preparation station
- Affymetrix GeneChip 3000 7G targeted genotyping system (DNA microarray).



FISH Workstation



ABI PRISM 3100 AVANT genetic analyzer



ABI PRISM 6100 Nucleic acid preparation station



ABI PRISM 7300 Real time PCR system



Affymetrix GeneChip 3000 7G targeted genotyping system (DNA microarray).

PhD Passed:

Dr. VL Ramprasad* (Genome Wide Linkage & Candidate Gene Analyses: Molecular Genetic Studies In Mendelian And Complex Ophthalmic Diseases)

Dr. Biju Joseph* (Cytogenetic, Mutation Detection, Methylation Status, Fragment Analysis of RB1 Gene and Phenotype Correlation in Retinoblastoma Patients from India)

Dr S. Sripriya* (Genetic Association Studies, Genome Wide Linkage Analysis and Mutation Screening in Primary Open Angle and Closed Angle Glaucomas)

Submitted:

Dr. J Madhavan** (Molecular genetic profile of ophthalmic disorders and its phenotypic correlation)

Ms. S Uthra* (Diabetic Retinopathy: Genetic Association Studies of Candidate Genes in a South Indian Population-Based Cohort)

Pursuing:

Ms. G Mamatha* (Genetics of retinitis pigmentosa)

Ms. Vinita Kumari* (Molecular Genetics of Diabetic retinopathy)

* Birla Institute of Technology, Pilani, Rajasthan

** Co guide. The Tamil Nadu Dr. MGR Medical University, Chennai

Dr. G. Kumaramanickavel

- 2001 Swarnalatha Punshi Award (Best Research Worker, Sankara Nethralaya)
- 2000 Mr. YT Cheng Visiting Scholar Award, The Chinese University of Hong Kong
- 2000 Asian Cataract Research Conference Travel Fellowship
- 1997 Visiting Associate - Ophthalmic Genetics and Clinical Services Branch, National Eye Institute, National Institute of Health, Bethesda, MD, United States of America.

Dr. V. Swami Sankaranand

- 2000 *Distinguished Abstract Award (American Gastroenterology Association), USA,*
- 96–98 *Postdoctoral Fellowship, Department of Biotechnology, Govt. of India.*

Dr. S. Sripriya

- 2006 Young scientist award, ISHG conference, New Delhi.
- 2004 Best poster, Indian Society for Human Genetics (ISHG) conference, India.
- 2001 Best Paper, 3rd Singapore National Eye Research Meeting

Dr. V.L. Ramprasad

- 2007 AMJAD RAHI prize for best poster. IERG meeting, July 28 – 29, 2007.
- 2005 Bausch & Lomb travel fellowship - SERI-ARVO meeting, Singapore
- 2004 Swarnalatha Punshi Award (Best Research worker, Sankara Nethralaya)
- 2003 Bausch & Lomb travel fellowship - SERI-ARVO meeting, Singapore
- 2002 Best paper, ISHG conference, Trivandrum, India
- 2002 Young scientist travel fellowship from CSIR

Dr. J Madhavan

- 2006 E Balakrishnan Memorial Award. XXVI Annual Conference of Indian Association of Biomedical Scientist held at Thiruvananthapuram, Nov 25 – 27 2006
- 2007 Swarnalatha Punshi Award (Best Research worker, Sankara Nethralaya)

Ms. G Mamatha

- 2005 Best paper, ISHG Conference, Hyderabad, India.
- 2005 Travel fellowship – IERG meeting, Hyderabad.
- 2005 E Balakrishnan Memorial Award. XXVI Annual Conference of Indian Association of Biomedical Scientist held at Kolkata, Nov 25 - 27, 2005.

Ms. S Uthra

- 2007 Travel Fellowship grant – Asia ARVO meeting, Singapore

Ms. S Srilekha

- 2003 Outstanding employee (Laboratory)



UNIVERSITY OF OTAGO
NEW ZEALAND



NATIONAL EYE INSTITUTE
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CHINESE UNIVERSITY
OF HONG KONG



SINGAPORE NATIONAL
EYE CENTRE



THE UNIVERSITY OF
TORONTO, CANADA



MARSHFIELD
CLINIC, USA



Uthra S, Raman R., Mukesh BN, Rajkumar SA., Kumari RP, Agarwal S, Paul PG, Lakshmi pathy P, Gnanamoorthy P, Sharma T, McCarty CA, Kumaramanickavel G. Association of VEGF gene polymorphisms with Diabetic Retinopathy in a south Indian cohort. *Ophthalmic Genet.* (in press).

Vithana EN, Morgan PE, Ramprasad V, Tan DTH, Yong VHK, Venkataraman D, Venkatraman A, Yam GHF, Soumitra N, Law RWK, Rajagopal R, Pang CP, Kumaramanickavel G, Casey JR, Tin A. *SLC4A11* Mutations in Fuchs Endothelial Corneal Dystrophy (FECD). *Human Molecular Genetics*. *Human Molecular Genetics*, 2008, Vol. 17, No. 5 656 –666. (Impact Factor: 8.10)

Madhavan J, Ganesh A, Roy J, Biswas J, Kumaramanickavel G. Retinoblastoma: Early onset of the disease shows association to well-differentiated tumor. *J Pediatric Ophthalmology & Strabismus* 2008;45:22-25.

Madhavan J, Coral K, Mallikarjuna K, Corson TW, Amit N, Khetan V, George R, Biswas J, Gallie BL, Kumaramanickavel G. High expression of KIF14 in retinoblastoma: association with older age at diagnosis. *Invest Ophthalmol Vis Sci*. 2007 Nov;48(11):4901-6. PMID: 17962437 [PubMed - in process] (Impact Factor: 3.77)

Uthra S, Raman R, Mukesh BN, Rajkumar SA, Kumari R P, Agarwal S, Paul PG, Lakshmi pathy P, Gnanamoorthy P, Sharma T, McCarty CA, Kumaramanickavel G. Diabetic retinopathy and IGF -1 gene polymorphic cytosine -adenine repeats in a Southern Indian cohort. *Ophthalmic Res*. 2007;39(5):294-9. Epub 2007 Sep 12. PMID: 17851271 [PubMed - indexed for MEDLINE]

Sripriya S, George R, Arvind H, Baskaran M, Raju P, Ramesh SV, Karthiyayini T, Vijaya L, Kumaramanickavel G. Transforming growth factor beta -1 -509C>T polymorphism in Indian patients with primary open angle glaucoma. *Mol Diagn Ther*. 2007;11(3):151-4. PMID: 17570736 [PubMed - indexed for MEDLINE]

Uthra S, Raman R, Mukesh BN, Kumari RP, Paul PG, Praveena L, Gnanamoorthy P, Sharma T, McCarty CA, Kumaramanickavel G. Intron 4 VNTR Of Endothelial Nitric Oxide Synthase (eNOS) Gene And Diabetic Retinopathy In Type 2 Patients In Southern India. *Ophthalmic Genetics* 2007, 28 (2) 77-81.

Ramprasad VL, Ebenezer ND, Aung T, Rajagopal R, Yong VHK, Tuft SJ, Viswanathan D, El-Ashry MF, Liskova P, Tan DTH, Bhattacharya SS, Kumaramanickavel G, Vithana EN. Novel *SLC4A11* Mutations in Patients with Recessive Congenital Hereditary Endothelial Dystrophy (CHED2). *Hum Mutat*. 2007 May;28(5):522-3.

Ramprasad VL, George R, Sripriya S, Nirmaladevi J, Vijaya L, Kumaramanickavel G. Molecular genetic analysis of a consanguineous South Indian family with congenital glaucoma: Relevance of genetic testing and counseling. *Ophthalmic Genetics* 2007 Jan-Mar;28(1):17-24.

Ramprasad VL, Madhavan J, Murugan S, Sujatha J, Suresh S, Sharma T, Kumaramanickavel G. Retinoblastoma in India. Microsatellite Analysis and its Application in Genetic Counseling. *Journal Mol. Diagn. Ther* 2007;11(1): 63-70.

Joseph B, Raman R, Uthra S, Jagadeesan M, Ganesh A, Paul PG, Sharma T, Kumaramanickavel G. Genotype-phenotype correlation analysis in retinoblastoma patients from India. *Asian Pac J Cancer Prev*. 2006 Oct-Dec; (4):619-22.

Joseph B, Madhavan J, Mamatha G, Ramprasad VL, Gopal L, Kumaramanickavel G. Retinoblastoma: A Diagnostic Model for India. *Asian Pacific J Cancer Prev*, 7, 465-468: 2006.

Mamatha G, Joseph B, Shanmugam MP, Kumaramanickavel G. CGA codons multiplex PCR in rapid diagnosis of retinoblastoma. *Indian J Hum Genet* 2006;12:34-38

Sripriya S, Nirmaladevi J, George R, Hemamalini A, Baskaran M, Prema R, Ramesh S Ve, Karthiyayini T, Amali J, Job S, Vijaya L., Kumaramanickavel G. *OPTN* gene: Profile of Patients with glaucoma from India. *Molecular Vision* 2006 12: 816-20.

Joseph B, Paul PG, Anuradha E, Roy J, Vidhya A, Shanmugam MP, Kumaramanickavel G. Karyotyping in Retinoblastoma. *Asian Pacific Journal of Cancer Prevention*. Vol 6, 2005; 468-471.

Ramprasad VL, Sripriya S, Ronnie G, Nancarrow D, Saxena S, Hemamalini A, Kumar D, Vijaya L, Kumaramanickavel G. Genetic homogeneity for inherited congenital microcoria loci in an Asian Indian pedigree. *Molecular Vision* 2005; 11:934 - 40.

Ramprasad VL, Alka T, Sakthivel M, Derek N, Prateep V, Rao SK, Vidhya A, Ravishankar K, Kumaramanickavel G. Truncating mutation in NHS gene: Phenotypic heterogeneity of Nan ce-Horan syndrome in an Asian Indian family. *IOVS*. January 2005; 46:17-23

Joseph B, Narayana KS, Mamatha G, Gayathree R, Kumaramanickavel G. Mutational scanning of RB1 gene by multiplex PCR. *Indian Journal of Biotechnology*. Vol 4, April 2005, pp. 194 – 200.

Joseph B, Shanmugam MP, Srinivasan MK, Kumaramanickavel G. Retinoblastoma: Genetic testing is cheaper than conventional clinical screening in India. *Molecular Diagnosis*. 2004;8(4): 237-43.

Joseph B, Mamatha G, Raman G, Shanmugam MP, Kumaramanickavel G. Methylation status of RB1 promoter in Indian Retinoblastoma patients. *Cancer Biology & Therapy* 3:2, 1-4 February 2004.

Sripriya S, Uthra S, Sangeetha R, George RJ, Hemamalini A, Paul PG, Amali J, Vijaya L, Kumaramanickavel G. Low frequency of Myocilin mutations in Indian POAG patients. *Clinical genetics* Apr 2004 (4) 333 – 337.

Sripriya S, Kumaramanickavel G. Development gene and eye. *Insight* Nov 2003; 69 – 73.

Ramprasad VL, Rao SK, Ravishankar K, Kumaramanickavel G. Genetic studies in age related cataract : Problems encountered (9 Oct 2003) E letters to the editor: *Investigative ophthalmology and visual science*.

Kumaramanickavel G, Joseph B, Narayana K, Natesh S, Mamatha G, Shanmugam MP, Anuradha E, Biswas J. Molecular genetic analysis of two cases with retinoblastoma: benefits for disease management *Journal of Genetics* Vol 82, Nos 1 & 2, April & August 2003.

Hemamalini A, Paul PG, Prema R, Baskaran M, George R, Sukumar B, Sripriya S, Ramesh S. Ve, Mukesh BN, Vijaya L, Kumaramanickavel G, McCarty C. Methods and design of the Chennai Glaucoma Study. *Ophthalmic Epidemiology – 2003*, Vol. 10, No. 5.

Kumaramanickavel G, Vijaya L. Predictive Medicine and Glaucoma: The changing clinical scenario. *Vietnamese Pharmaceutical Jol* No. 4, 56 - 60.

Kumaramanickavel G, Joseph B, Vidhya A, Arokiasamy T, Shetty NS. Consanguinity and Ocular Genetic Diseases in South India: Analysis of a Five-Year Study. *Community Genet* 2002;5:182-185.

Kumaramanickavel G, Sripriya S, Ramprasad VL, Upadyay NK, Paul PG, Tarun S. Z -2 aldose reductase allele and diabetic retinopathy in India. *Ophthalmic Genetics*;2003;24:1: 41 – 48.

Association of *Gly82Ser* polymorphism in the RAGE gene with Diabetic Retinopathy in Type II diabetic Asian Indian patients. *J Diabetes and its complications*;2002;16:391 – 394.

Joseph B, Anuradha S, Soumitra N, Vidhya A, Shetty NS, Uthra S, Kumaramanickavel G. RPE 65 gene: Multiplex PCR and Mutation screening in patients from India having retinal degenerative diseases. *Journal of Genetics*; 2002;81:1.

Dollfus H, Biswas P, Kumaramanickavel G, Stoetzel C, Quillet R, Biswas J, Lajeunie L, Renier D, Perrin-Schmitt F. Saethre-Chozen Syndrome: Notable intrafamilial phenotypic variability in a large family with Q28X TWIST mutation. *Am J Med Genet*;2002;109:3:218-25.

Biju J, Anupama S, Kumaramanickavel G. Microarrays – 'Chipping' in Genomics. *Indian journal of Biotechnology*, 2002;1: 245-254.

Kumaramanickavel G, Sripriya S, Vellanki RN, Upadyay NK, Badrinath SS, Vinatha R, Sukumar B, Ramprasad VL, Sharma T. inducible Nitric Oxide Synthase gene and Diabetic Retinopathy in Asian Indian patients *Clinical Genetics*; 2002; 61:5:344-8.

Kumaramanickavel G, Sripriya S, Vellanki RN, Upadhyay NK, Badrinath SS, Arokiasamy T, Sukumar B, Vidhya A, Joseph B, Sharma T, Gopal L. Tumor necrosis factor allelic polymorphism with Diabetic Retinopathy in India. *Diabetes Research and Clinical Practice*;2001:54:89-94

Ramprasad VL, Paul PG, Sripriya S, Kumaramanickavel G. Databases and free softwares on the Net for DNA analyses. *Insight*;Nov 2001:19:3.

Dollfus H, Kumaramanickavel G, Biswas P, Stoetzel C, Quillet R, Denton M, Maw M, Perrin-Schmitt F. Identification of a new TWIST mutation (7p21) with variable eyelid manifestations supports locus homogeneity of BPES at 3q22. *J Med Genetics* ;2001:58:470-471.

Madhavan C, Bhende P, Lekha G, Vasanthi SB, Kumaramanickavel G. Retinitis Pigmentosa patients with Sickle Cell Disease and Dextrocardia and Situs Inversus Syndrome. *Indian Journal Of Ophthalmology*; 2001:49:193-95.

Kumaramanickavel G. Genetics & Ophthalmology The Changing Scenario in Clinical Practice. *Journal of Tamilnadu Ophthalmic Association*. 41:4: 2000:165-172.

Harini R, Ata-ur-Rasheed M, Shanmugam MP, Amali J, Das D, Kumaramanickavel G. Genetics of retinoblastoma: A cytogenetic and segregation analyses profile of 81 patients from a referral hospital in southern India. *Indian Journal of Ophthalmology*;2001: 49:37-42.

Maw MA, Corbeil D, Koch J, Hellwig A, Wilson-Wheeler JC, Bridges RJ, Kumaramanickavel G, John S, Nancarrow D, Roper K, Weigmann A, Huttner WB, Denton MJ. A frameshift mutation in prominin (mouse)-like 1 causes human retinal degeneration. *Hum Mol Genet*;2000:1;9:27-34.

Gu S, Kumaramanickavel G, Srikumari CR, Denton MJ, Gal A. Autosomal recessive retinitis pigmentosa locus RP28 maps between D2S1337 and D2S286 on chromosome 2p11-p15 in an Indian family. *J Med Genet*;1999;36:9:705-7.

Klintworth GK, Sommer JR, Obrian G, Han L, Ahmed MN, Qumsiyeh MB, Lin PY, Basti S, Reddy MK, Kanai A, Hotta Y, Sugar J, Kumaramanickavel G, Munier F, Schorderet DF, El Matri L, Iwata F, Kaiser-Kupfer M, Nagata M, Nakayasu K, Hejtmancik JF, Teng CT. Familial subepithelial corneal amyloidosis (gelatinous drop-like corneal dystrophy): exclusion of linkage to lactoferrin gene. *Mol Vis*. 1998 ; 31;4:31.

Finckh U, Xu S, Kumaramanickavel G, Schurmann M, Mukkadan JK, Fernandez T, John S, Weber JL, Denton MJ, Gal A. Homozygosity mapping of autosomal recessive retinitis pigmentosa locus (RP22) on chromosome 16p12.1-p12.3. *Genomics*;1998 48:341-345.

Maw MA, Kumaramanickavel G, Kar B, John S, Bridges RJ, Denton MJ. Two Indian siblings with Oguchi disease are homozygous for an arrestin mutation encoding premature termination. *Human Mutations*;1998;1:S317-S319.

Gu SM, Thompson DA, Srikumari CR, Lorenz B, Finckh U, Nicoletti A, Murthy KR, Rathmann M, Kumaramanickavel G, Denton MJ, Gal A. Mutations in RPE65 cause autosomal recessive childhood-onset severe retinal dystrophy. *Nature Genetics*;1997: 17:194-197.

Vijaya R, Gupta R, Panda G, Ravishankar K, Kumaramanickavel G. Genetic analysis of adult-onset cataract in a city-based ophthalmic hospital. *Clinical Genetics*;1997:52:427-431.

Vijaya R, Kumaramanickavel G. Ophthalmic Genetic Clinic: A six month analysis of ocular disorders. *Insight XV*;1997::21-27.

Maw MA, Kar B, Biswas J, Biswas P, Nancarrow D, Bridges R, Kumaramanickavel G, Denton M, Badrinath SS. Linkage of Blepharophimosis syndrome in a large Indian pedigree to chromosome 7p. *Human Molecular Genetics*;1996: 5:2049-2054.

Maw MA, John S, Jablonka S, Muller B, Kumaramanickavel, Oehlmann R, Denton MJ, Gal A. Oguchi disease: suggestion of linkage to markers on chromosome 2q. *J Medical Genetics*;1995:32:396-398.

Kar B, John S, Kumaramanickavel G. Retinitis pigmentosa in India: a genetic and segregation analysis. *Clinical Genetics*;1995: 47: 75-79.

Kumaramanickavel G, Maw MA, Denton MJ, John S, Srikumari CRS, Orth U, Ralph O, Gal A. Missense rhodopsin mutation in a family with recessive RP. *Nature Genetics*; 1994:8: 10-11.