High-resolution analysis of DNA copy number alterations in patients with primary open-angle glaucoma.

Khaled K Abu-Amero  
*King Saud University, Riyadh, Saudi Arabia*

Ali Hellani  
*PGD Laboratory, Saad Specialist Hospital, Al-Khobar, Saudi Arabia*

Patrick Bender  
*National Institutes of Mental Health, Rochville, MD*

George L. Spaeth  
*Wills Eye Institute/Jefferson Medical College*

Jonathan Myers  
*Wills Eye Hospital, Thomas Jefferson University*

Follow this and additional works at: https://jdc.jefferson.edu/willsfp

Let us know how access to this document benefits you

See next page for additional authors

**Recommended Citation**  
Abu-Amero, Khaled K; Hellani, Ali; Bender, Patrick; Spaeth, George L.; Myers, Jonathan; Katz, L Jay; Moster, Marlene; and Bosley, Thomas M, "High-resolution analysis of DNA copy number alterations in patients with primary open-angle glaucoma." (2009). *Wills Eye Hospital Papers*. Paper 27.  
https://jdc.jefferson.edu/willsfp/27
High-resolution analysis of DNA copy number alterations in patients with primary open-angle glaucoma

Khaled K. Abu-Amero,1 Ali Hellani,2 Patrick Bender,3 George L. Spaeth,4 Jonathan Myers,4 L. Jay Katz,4 Marlene Moster,4 Thomas M. Bosley1,5

1Ophthimal Genetics Laboratory, Department of Ophthalmology, College of Medicine, King Saud University, Riyadh, Saudi Arabia; 2PGD Laboratory, Saad Specialist Hospital, Al-Khobar, Saudi Arabia; 3National Institutes of Mental Health, Rockville, MD; 4William and Anna Goldberg Glaucoma Service, Wills Eye Hospital, Thomas Jefferson University Hospital, Philadelphia, PA; 5Division of Neurology, Cooper University Hospital, Camden, NJ

Purpose: To determine whether patients with isolated primary open-angle glaucoma (POAG) have evidence of chromosomal copy number alterations.

Methods: Twenty-seven Caucasian and African-American POAG patients and 12 ethnically matched controls were carefully screened for possible glaucoma and tested for chromosomal copy number alterations using high resolution array comparative genomic hybridization.

Results: No POAG patient had evidence of chromosomal copy number alterations when compared to normal ethnically matched controls. Additionally, there was no evidence of somatic mosaicism in any tested POAG patient.

Conclusions: Chromosomal deletions and/or duplications were not detected in POAG patients as compared to controls. Other chromosomal imbalances such as translocations, inversions, and some ploidies cannot be detected by current array comparative genomic hybridization technology, and other nuclear genetic, mitochondrial abnormalities, or epigenetic factors cannot be excluded as a possible contributing factor to POAG pathogenesis.

Glaucoma is one of the leading causes of blindness worldwide [1] with a prevalence of over 2% in individuals older than 40 years [2]. Primary open-angle glaucoma (POAG) is the most common type of glaucoma in Western countries and has risk factors that include elevated intraocular pressure (IOP) and age [3], but these factors do not predict the presence or degree of visual loss [4]. Up to half of all patients with POAG have a positive family history, and the risk of POAG is increased three to nine times in first-degree relatives of POAG patients [2,5]. These observations suggest that genetic factors contribute to POAG [1,6,7].

Currently, 14 chromosomal loci are linked to POAG by the Human Genome Organization. Thus far, only three genes associated with POAG have been identified within these loci including myocilin [8], optineurin [9], and WD repeat domain 36 (WDR36) [10]. However, mutations in these three genes are present in less than 5% of POAG patients [11]. Over 20 other gene variants have been associated with the disorder, but in general, these loci have been identified from linkage analysis of family data sets often without corroboration by other investigators or in other populations. Therefore, the cause of the genetic risk for the occurrence of POAG remains largely unknown.

Several chromosomal aberrations have been reported to cause glaucoma, but in general, glaucoma has been associated with an obvious genetic syndrome in these patients [12,13]. To our knowledge, no study has investigated chromosomal copy number variations in patients with isolated POAG. Therefore, we examined possible chromosomal copy number changes in POAG patients using high resolution array comparative genomic hybridization (array CGH) technology.

METHODS

Patients and controls: Patients were selected from the Glaucoma Clinic at Wills Eye Hospital (Philadelphia, PA) after examination by a glaucoma specialist and after obtaining informed consent approved by the Wills Institutional Review Board. This research adhered to the tenets of the Declaration of Helsinki, and all patients and controls signed an informed consent approved by the Wills Eye Hospital Institutional Review Board.

Patients were eligible for inclusion in this study if they met standard clinical criteria for POAG [14-16] including age greater than 40 years, IOP greater than or equal to 21 mmHg in at least one eye before treatment, normal-appearing anterior chamber angles bilaterally on gonioscopy, and optic nerve injury characteristic of POAG (with narrowed or absent rim, asymmetric cupping of the optic discs, and static visual fields compatible with optic disc appearance and with glaucoma). Exclusion criteria included historical, neuroimaging, or biochemical evidence of another possible optic neuropathic process affecting either eye, significant visual loss in both
eyes not associated with glaucoma, or choosing not to participate.

All control subjects had full ophthalmologic examinations and static perimetry. Each had IOPs below 21 mmHg and symmetry in the two eyes, normal anterior chambers, optic discs that were normal and symmetric in appearance, entirely normal static perimetry (both eyes), and no prior history of glaucoma. All patients and controls had Humphrey Swedish interactive threshold algorithm (SITA) achromatic static perimetry, stimulus III, 24–2 (Humphrey Field Analyzer II; Carl Zeiss Meditec Inc., Dublin, CA).

Array CGH technique: Blood was collected in acid-citrate-dextrose (ACD) tubes, and DNA was extracted using a Qiagen Autopure LS instrument (Qiagen, Valencia, CA) following the manufacturer’s recommended procedure. To detect chromosomal rearrangements, 2 μg of POAG patient genomic DNA was competitively hybridized with 2 μg of ethnically matched control DNA (as a reference sample) on an Agilent Human Genome CGH 244A Oligo Microarray Kit (Agilent Technologies Inc., Santa Clara, CA), which has an average probe spacing across the human genome of 6.4 Kb. Briefly, 50 μl of DNA from POAG patients and controls was digested using 50 units of Alu1 (Roche, Mannheim, Germany) and 50 units of Rsa1 (Roche) restriction enzymes in a 100 μl volume with 10 μl of 10X Promega Buffer C. Digestions were performed for 2 h at 37 ºC. Digested samples were purified using QIAprep Spin Miniprep columns (Qiagen) and eluted according to the manufacturer’s instructions. Samples were then analyzed using the Agilent 2100 Bioanalyzer with the DNA 7500 LabChip Kit and DNA 7500 Software Script (Agilent) as per the manufacturer’s instructions. Alu1/Rsa1 digested DNA samples were labeled using the BioPrime Array CGH Labeling Kit (Invitrogen, Carlsbad, CA) according to the manufacturer’s protocol. POAG patient and control DNA samples were systematically labeled with Alexa Fluor 555 and 647, respectively.

Labeled products of each sample and control DNA were purified using QIAprep Spin Miniprep columns (Qiagen), mixed together, and checked on the Agilent 2100 Bioanalyzer (Agilent) to evaluate the Alexa Fluor 555 integration into the DNA samples. The following hybridization blocking reagents were added to the purified Alexa Fluor 555 and 647 labeled samples: 50 μg Cot-1 DNA (Invitrogen) and 50 μl of 10X control targets (Agilent). The volume was brought to 250 μl with double-distilled H2O, and 250 μl of 2X hybridization buffer (Agilent) was added. The hybridization mixture was then denatured at 100 ºC for 3 min in a water bath. Samples were immediately transferred to a 37 ºC water bath for 30 min to allow pre-annealing of the blocking agents to the labeled sample. Samples were centrifuged for 5 min at 16,000x g and immediately applied to the Agilent Human Genome CGH 244A Oligo Microarray Kit as per the manufacturer’s recommendations. Hybridizations were performed at 65 ºC for 42 h.

Microarrays were disassembled in Agilent wash buffer-1 at room temperature (RT), transferred to a slide holder, and incubated for 5 min with stirring in the Agilent wash buffer-1 at RT. The second washing step was performed for 1 min in

Figure 1. Array CGH result for internal control. As an internal quality control for the array CGH procedure, control DNA was hybridized against POAG DNA of the opposite sex (ratio of +1 with regard to chromosome X for XX POAG and XY control).
wash buffer-2 at 37 °C. The third and fourth washing steps were done with acetonitrile (Fisher Scientific, Fair Lawn, NJ) and stabilization solutions (Agilent) for 1 min and 30 s at RT, respectively. Microarray slides were immediately scanned in the Agilent DNA Microarray Scanner using the default settings.

Data analysis was performed by Agilent Feature Extraction 9.1 and CGH Analytics 3.4 (Agilent). Log₂ expression ratios were computed and normalized using CGH Analytics 3.4 software. Putative chromosome copy number changes were defined by intervals of three or more adjacent probes with log₂ ratios suggestive of a deletion or duplication when compared with the log₂ ratios of adjacent probes. The quality-weighted interval score algorithm (ADM2) was used to compute and assist in the identification of aberrations for a given sample.

As an internal quality control measure, DNA from Caucasian patients were mixed with DNA from Caucasian controls of the same and opposite sex and co-hybridized to the 244K chip (Figure 1). The same was done for POAG patients and controls of African American ethnicity.

RESULTS
Clinical characteristics of the 27 POAG patients included in this study are detailed in Table 1. Patient sex (15 males and 12 females) and ethnicity (14 Caucasian and 13 African-American) were similar to that of the 12 controls, which were carefully screened for presence of POAG or other optic neuropathies (5 males and 7 females; 9 Caucasian and 3 African-American). The mean age of patients (70.7±10.8 years) was somewhat greater than that of controls (61.1±10.8 years).

The signal ratio of each patient compared to a simultaneously tested control (patient-cy3/control-cy5) documented the absence of chromosomal copy number variations in any patient. No POAG patient had evidence of somatic mosaicism. Representative images of array CGH results are shown in Figure 2.

DISCUSSION
The 27 patients reported here met rigorous clinical criteria for definite POAG [14-16] with elevated IOP, normal anterior chamber, and evidence on the fundoscopic exam and visual fields of glaucomatous optic nerve damage. By clinical criteria, they did not have evidence of other types of glaucoma or alternative causes of optic nerve injury. None had dysmorphism or an obvious genetic syndrome. They were compared to 12 controls in which POAG and other evidence of optic nerve damage were carefully excluded.

High resolution array CGH used here provides quantitative information about the level of chromosome gain or loss such as regions with a high level amplification or high magnitude deletion and will recognize a chromosomal duplication or deletion of a size greater than or equal to 6 Kb. This technique did not detect any chromosomal copy number variations of this size in POAG patients or controls. These results indicate that it is very unlikely that chromosomal deletions or duplications are universally responsible for isolated POAG. Because of the relatively small sample size, it remains possible that chromosomal aberrations might be present in a portion of patients with isolated POAG. More patients from multiple centers and various ethnicities would need to be examined to make a general statement about the absolute absence of chromosomal copy number variations in the setting of POAG. No comment can be made about other chromosomal imbalances such as translocations, inversions, and some ploidies because these cannot be detected by current array CGH technology.

These negative results stand in contrast to reports of chromosomal anomalies causing glaucoma in association with a variety of genetic syndromes and abnormalities of globe development. For example, several chromosomal anomalies have been reported to cause the Axenfeld-Rieger syndrome (OMIM 602482) with variable ocular dysgenesis associated with short height, stunted development of midfacial features, and mental deficiencies. These anomalies include distal deletions of chromosome 6p [12], duplications [17], balanced translocations [18], and unbalanced translocations [19], but they are all associated with abnormal development of the anterior segment and early onset glaucoma [20,21]. Similarly, one reported patient was documented to have partial trisomy of 7q and partial

Figure 2. Array CGH results for POAG patients versus controls. Chromosomes shown were chosen randomly as representative of all chromosomes and in all POAG patients tested. In the image, A indicates Chromosome 1; B indicates Chromosome 13; C indicates Chromosome 15; and D indicates Chromosome 18. When control DNA was hybridized against POAG DNA, a signal ratio of zero (0) was obtained, indicating the absence of chromosomal copy number alterations.
monosomy of 15q, and the Silver-Russell phenotype (OMIM 180860; low birth weight, delayed maturation, facial dysmorphism, clinodactyly, ivory epiphyses, etc.) with congenital glaucoma [13] while another had a balanced translocation t(9/17)(q34.1;q25) and the Nail-Patella Syndrome (OMIM 161200; dysplasia of the nails, absent or hypoplastic patellae, and a low frequency of glaucoma and ocular hypertension) [22]. Several reported patients with early onset glaucoma and genetic syndromes lack a firm genetic diagnosis [23,24], and micro-anomalies of chromosomes remain possible in some of these patients. The cohort reported here had isolated POAG beginning in late adult life without ocular malformations, dysmorphic features, or other evidence of genetic syndromes, and to date, no such patient has been reported to have an associated chromosome aberration.

In summary, we used high resolution array CGH to evaluate a group of patients with isolated POAG and found no evidence of chromosomal copy number variations. Therefore, neither autosomal genetics [11] nor chromosomal deletions/duplications currently provide a complete explanation for the substantial familial association widely recognized in POAG [2,5]. Although unrecognized genetic or epigenetic factors remain possible, POAG patients do have a variety of mitochondrial [25] and metabolic [26] abnormalities that might put the optic nerve at risk. In this regard, POAG may have certain similarities to Leber hereditary optic neuropathy, another spontaneous optic neuropathy with no obvious autosomal or chromosomal [27] cause that also is associated with mitochondrial abnormalities [28-30].

ACKNOWLEDGMENTS

The authors thank Ahmed Mousa, Ph.D., for statistical assistance. K.K.A. and T.M.B. are supported by a grant from the Glaucoma Research Chair of the Department of Ophthalmology, College of Medicine, King Saud University (Riyadh, Saudi Arabia). This research was also supported by a grant from the Saad Specialist Hospital (Al-Khobar, Saudi Arabia).

REFERENCES

1. Quigley HA. Number of people with glaucoma worldwide. Br J Ophthalmol 1996; 80:389-93. [PMID: 8695555]
2. Tielsch JM, Sommer A, Katz J, Royall RM, Quigley HA, Javitt J. Racial variations in the prevalence of primary open-angle glaucoma. The Baltimore Eye Survey. JAMA 1991; 266:369-74. [PMID: 2056646]

Table 1. Clinical characteristics of POAG patients.

| Patient | Age | Sex | Race | VA OD | VA OS | Max IOP OD | Max IOP OS | Vertical C/D OD | Vertical C/D OS | HVF PSD OD | HVF PSD OS |
|---------|-----|-----|------|-------|-------|------------|------------|----------------|----------------|-------------|-------------|
| 1       | 54  | M   | C    | 20/100| 20/20 | 34         | 0.9        | 0.3            | 12.94          | 1.53        |
| 2       | 63  | F   | C    | 20/40 | 20/25 | 29         | 0.4        | 0.7            | 1.36           | 11.97       |
| 3       | 62  | M   | C    | 20/16 | 20/16 | 30         | 0.8        | 0.8            | 5.78           | 11.36       |
| 4       | 81  | M   | C    | 20/25 | 20/25 | 25         | 0.85       | 0.85           | 10.37          | 1.83        |
| 5       | 71  | F   | C    | 20/100| 20/25 | 27         | 0.9        | 0.9            | 7.38           | 12.33       |
| 6       | 60  | F   | C    | 20/30 | CF    | 35         | 0.9        | 0.9            | 12.37          | 5.37        |
| 7       | 79  | M   | C    | 20/20 | 20/20 | 28         | 0.85       | 0.65           | 2.18           | 1.89        |
| 8       | 97  | M   | C    | 20/25 | 20/25 | 40         | 0.99       | 0.99           | 1.86           | 11.38       |
| 9       | 90  | F   | C    | 20/70 | 20/30 | 20         | 0.9        | 0.8            | 8.83           | 8.84        |
| 10      | 63  | M   | AA   | 20/25 | 20/20 | 25         | 0.8        | 0.85           | 1.46           | 3.8         |
| 11      | 64  | F   | C    | 20/20 | 20/20 | 23         | 0.9        | 0.9            | 11.78          | 10.49       |
| 12      | 66  | M   | AA   | 20/25 | 20/25 | 32         | 0.9        | 0.9            | 10.03          | 8.28        |
| 13      | 68  | F   | AA   | 20/30 | 20/25 | 30         | 0.5        | 0.6            | 1.27           | 1.99        |
| 14      | 75  | F   | C    | 20/400| 20/30 | 25         | 0.95       | 0.8            | 10.63          | 3.73        |
| 15      | 81  | F   | C    | 20/70 | 20/25 | 30         | 0.8        | 0.65           | 4.62           | 1.91        |
| 16      | 76  | M   | AA   | 20/30 | 20/30 | 26         | 0.3        | 0.7            | 1.7            | 3.4         |
| 17      | 65  | M   | AA   | 20/30 | 20/50 | 29         | 0.85       | 0.8            | 1.81           | 1.98        |
| 18      | 84  | M   | C    | 20/20 | 20/20 | 31         | 0.5        | 0.5            | 3.75           | 4.02        |
| 19      | 57  | M   | AA   | 20/70 | 20/50 | 41         | 0.9        | 0.9            | 13.66          | 8.9         |
| 20      | 65  | M   | AA   | 20/200| CE    | 38         | 0.95       | 0.95           | 12.88          | 3.56        |
| 21      | 62  | M   | AA   | 20/20 | 20/20 | 27         | 0.8        | 0.8            | 9.31           | 9.43        |
| 22      | 56  | F   | AA   | 20/200| 20/40 | 30         | 0.9        | 0.3            | 4.81           | 1.77        |
| 23      | 69  | M   | AA   | 20/25 | 20/25 | 16         | 0.7        | 0.8            | 12.38          | 7.67        |
| 24      | 86  | F   | AA   | 20/20 | 20/40 | 29         | 0.3        | 0.3            | 4.09           | 6.51        |
| 25      | 73  | F   | C    | 20/25 | 20/100| 22         | 0.8        | 0.8            | 14.88          | 14.3        |
| 26      | 72  | M   | AA   | 20/25 | 20/25 | 24         | 0.2        | 0.8            | 3.29           | 11.76       |
| 27      | 69  | F   | AA   | 20/20 | 20/25 | 15         | 0.95       | 0.95           | 10.54          | 11.31       |

Abbreviations in the table are: Age=age at enrollment; Race=C=Caucasian; AA=African-American; VA=visual acuity; OD=right eye; OS=left eye; Max IOP=maximum IOP measured at Wills Eye Hospital; C/D=vertical cup to disk ratio; HVF PSD=Humphrey visual field pattern standard deviation.
3. Gherghel D, Hosking SL, Orgul S. Autonomic nervous system, circadian rhythms, and primary open-angle glaucoma. Surv Ophthalmol 2004; 49:491-508. [PMID: 15325194]

4. Spaeth GL. A new classification of glaucoma including focal glaucoma. Surv Ophthalmol 1994; 38:59-17. [PMID: 7940153]

5. Wilson MR, Hertzmark E, Walker AM, Childs-Shaw K, Epstein DL. A case-control study of risk factors in open angle glaucoma. Arch Ophthalmol 1987; 105:1066-71. [PMID: 3632414]

6. Tielsch JM, Katz J, Sommer A, Quigley HA, Javitt JC. Family history and risk of primary open angle glaucoma. The Baltimore Eye Survey. Arch Ophthalmol 1994; 112:69-73. [PMID: 8285897]

7. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. Br J Ophthalmol 2006; 90:262-7. [PMID: 16488940]

8. Fingert JH, Héon E, Liebmann JM, Hockey RR, Williams-Lyn D, Trope G, Kitazawa Y, Ritch R, MacKay DA, Alward WL, Sheffield VC, Stone EM. Analysis of myocilin mutations in 1703 glaucoma patients from five different populations. Hum Mol Genet 1999; 8:899-905. [PMID: 10196380]

9. Alward WL, Kwon YH, Kawase K, Craig JE, Hayreh SS, Johnson AT, Khanna CL, Yamamoto T, Mackey DA, Utermann G. Nail patella syndrome in a cytogenetically balanced t(9;17) (q34.1;q25) carrier. Eur J Hum Genet 1998; 6:75-9. [PMID: 9781017]

10. Monemi S, Spaeth G, DaSilva A, Popinchalk S, Ilitchev E, Liebmann J, Ritch R, Héon E, Crick RP, Child A, Sarfarazi M. Identification of a novel adult-onset primary open-angle glaucoma (POAG) gene on 5q22.1. Hum Mol Genet 2005; 14:725-33. [PMID: 15677485]

11. Wu Dunn D. Genetic basis of glaucoma. Curr Opin Ophthalmol 2002; 13:55-60. [PMID: 11880716]

12. Maclean K, Smith J, St Heaps R, Chia N, Williams R, Peters GB, Onikul E, McCrossin T, Leornard OJ, Ades LC. Axenfeld-Rieger malformation and distinctive facial features: Clues to a recognizable 6p25 microdeletion syndrome. Am J Med Genet 2005; 132:381-5. [PMID: 15654696]

13. Kato R, Kishibayashi J, Shimokawa O, Harada N, Niiwaki N, Matsumoto N. Congenital glaucoma and Silver-Russell phenotype associated with partial trisomy 7q and monosomy 15q. Am J Med Genet 2001; 104:319-22. [PMID: 11754068]

14. Spaeth GL. Prognostic factors for progression of visual field damage in patients with normal-tension glaucoma. Jpn J Ophthalmol 2007; 51:156. [PMID: 17401633]

15. Eisd TM, Spaeth GL, Bittman A, Steinmann WC. Rate and amount of visual loss in 102 patients with open-angle glaucoma followed up for at least 15 years. Ophthalmology 2003; 110:900-7. [PMID: 12750087]

16. Bayer A, Harasymowycz P, Henderer JD, Steinmann WG, Spaeth GL. Validity of a new disk grading scale for estimating glaucomatous damage: correlation with visual field damage. Am J Ophthalmol 2002; 133:758-63. [PMID: 12036666]

17. Lehmann OJ, Ebezezer ND, Jordan T, Fox M, Ocaha L, Payne A, Leroy BP, Clark BJ, Hitchings RA, Povey S, Khaw PT, Bhattacharya SS. Chromosomal duplication involving the forkhead transcription factor gene FOXC1 causes iris hypoplasia and glaucoma. Am J Hum Genet 2000; 67:1129-35. [PMID: 11007653]

18. Nishimura DY, Swiderski RE, Alward WL, Searby CC, Patel SR, Bennet SR, Kanis AB, Gastner JM, Stone EM, Sheffield VC. The forkhead transcription factor gene FKHL7 is responsible for glaucoma phenotypes which map to 6p25. Nat Genet 1998; 19:140-7. [PMID: 9620769]

19. Baruch AC, Erickson RP. Axenfeld-Rieger anomaly, hypertelorism, clinodactyly, and cardiac anomalies in sibs with an unbalanced translocation der(6)(6;6). Am J Med Genet 2001; 100:187-90. [PMID: 11343302]

20. Ekong R, Jeremiah S, Judah D, Lehmann O, Mirzayans F, Hung YC, Walter MA, Bhattacharya S, Gant TW, Povey S, Wolfe J. Chromosomal anomalies on 6p25 in iris hypoplasia and Axenfeld-Rieger syndrome patients defined on a purpose-built genomic microarray. Hum Mutat 2004; 24:76-85. [PMID: 15221791]

21. Gauld DB, John SW. Anterior segment dysgenesis and the developmental glaucomas are complex traits. Hum Mol Genet 2002; 11:1185-93. [PMID: 12015278]

22. Duba HC, Erdel M, Loffler J, Wirth J, Utermann B, Utermann G. Nail patella syndrome in a cytogenetically balanced t(9;17) (q34.1;q25) carrier. Eur J Hum Genet 1998; 6:75-9. [PMID: 9781017]

23. Ackerman JL, Ackerman AL, Ackerman AB. Taurodont, pyramidal and fused molar roots associated with other anomalies in a kindred. Am J Phys Anthropol 1973; 38:681-94. [PMID: 4349385]

24. Maroteaux P, Manouvrier S, Bonaventure J, Le Merrer M. Dyssegmental dysplasia with glaucoma. Am J Med Genet 1996; 63:46-9. [PMID: 8723085]

25. Abu-Amero KK, Morales J, Bosley TM. Mitochondrial abnormalities in patients with primary open-angle glaucoma. Invest Ophthalmol Vis Sci 2006; 47:2533-41. [PMID: 16723467]

26. Abu-Amero KK, Morales J, Mohamed GH, Osman MN, Bosley TM. Glutathione S-transferase M1 and T1 polymorphisms in Arab glaucoma patients. Mol Vis 2008; 14:425-30. [PMID: 18334963]

27. Yen MY, Chien YJ, Lin CH, Wang AG, Wei YH. Genetic analysis in Leber's hereditary optic neuropathy using the comparative genomic hybridization technique. Clin Experiment Ophthalmol 2003; 31:435-8. [PMID: 14516433]

28. Abu-Amero KK, Bosley TM. Mitochondrial abnormalities in patients with LHON-like optic neuropathies. Invest Ophthalmol Vis Sci 2006; 47:4211-20. [PMID: 17003408]

29. Newman NJ. Leber's hereditary optic neuropathy. New genetic considerations. Arch Neurol 1993; 50:540-8. [PMID: 8489411]

30. Carelli V, Ross-Cisneros FN, Sadun AA. Mitochondrial dysfunction as a cause of optic neuropathies. Prog Retin Eye Res 2004; 23:53-89. [PMID: 14766317]