AGLAIA system architecture for Glaucoma Diagnosis

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***Abstract*— The AGLAIA (Automatic GLaucoma Diagnosis and Its Genetic Association Study through Medical Image InformAtics) system architecture is proposed to address the automatic diagnosis of Glaucoma. Instead of using single image feature, AGLAIA measures the characteristics of peripapillary and optic nerve head related to glaucomatous changes based on digital non-stereo retinal (fundus) images and combines those multiple measures of optic nerve damage into a single holistic system. Medical Image Informatics principle is innovatively used to analyze the patient's genetic information and find the possible association between the image features and the glaucoma disease. Innovative medical image processing and understanding algorithms (including medical image segmentation, pattern recognition, filtering, statistical learning etc.) are applied for early detection and monitoring of glaucoma.**

I. INTRODUCTION

Glaucoma is a chronic and irreversible neurodegenerative disease in which the nerve that connects the eye to the brain (optic nerve) is progressively damaged and patients suffer from vision loss and blindness. Patients with early glaucoma do not usually have any signs or symptoms. Progression of the disease results in loss of peripheral vision, so and patients may complain of "tunnel vision" (being only able to see centrally). Advanced glaucoma is associated with total blindness.

Two large surveys have been studied on this condition in Singapore.[1, 2] The Tanjong Pagar Study and the Singapore Malay Eye Study showed that the prevalence of glaucoma is 3-4% in Singaporean adults 40 years and above, with more than 90% of the patients unaware that they have this condition [1, 2]. Worldwide, it is the second leading cause of blindness, affecting 60 million people by 2010,[3] and responsible for approximately 5.2 million cases of blindness (15% of the total burden of world blindness).[4] The problem is even more significant in Asia, as Asians account for approximately half of the world's glaucoma cases.[3] Finally, because it is a condition of aging, it will affect more people in Singapore and Asia with population aging.

Treatment (e.g., lowering the intraocular or eye pressure) can prevent progression of the disease in early cases, so early detection is critical to prevent blindness. While routine screening for glaucoma in the whole population may not be cost effective and is limited by poor sensitivity of current tests, screening may be useful for high risk individuals, such as older people (e.g., 60 years and older), certain racial/ethnic group (e.g., Chinese patients who have a higher risk of glaucoma) and those with a family history of glaucoma (e.g., first degree relatives of a glaucoma patient) [5]. Currently, there is no systematic way to detect and manage early glaucoma in Singapore. Glaucoma patients are often unaware they have the condition, and present late to the ophthalmologist (eye doctors), usually only when severe visual loss is already present. Treatment at this stage is limited to surgery, is expensive, requires skill personnel, and does not restore vision.

Recent years' development in the understanding of the genetics of glaucoma allows for the first time a molecular insight into the pathogenesis glaucoma. Genetic analysis is highly suited for glaucoma because, firstly, ophthalmologists have long recognized the presence of a subgroup of glaucoma that follows a mendelian form of inheritance (recessive or dominant). With large enough families, linkage analysis is a very powerful technique that can quickly identify the culprit genes in these families. Secondly, even the more common forms of glaucoma that don't typically follow a clear mendelian pattern of inheritance are known to cluster in families. Just as has been shown with other common diseases in medicine, this clearly indicates the existence of "genetic predisposition" that may differ between various populations. The current high throughput genetic platforms make it possible now to dissect the underpinning of such predisposition.

Two genes (MYOC and OPTN) have been shown to account for a small fraction of open-angle glaucoma cases. Moreover, the CYP1B1 gene has been found to be responsible for more than half of cases of congenital glaucoma in some populations studied. Many more regions around the genome have been identified as genetic risk factors for glaucoma but the actual genes involved have not been found. Future studies are expected to examine the roles of more glaucoma genes in populations.

Genome wide association studies (GWAS) look for associations between DNA sequence variants and phenotypes of interest. They do so by studying individuals with different phenotypes and determining their genotype at the positions of hundreds of thousands of single nucleotide polymorphisms (SNPs). To date, more than 300 replicated associations have now been reported for more than 70 common diseases, conditions and biological measurements as a result of GWA studies (http://www.genome.gov/gwastudies). To our best knowledge, no large scale GWAS has been conducted for Glaucoma disease. In AGLAIA, we plan to identify the genetic factors that underlie glaucoma from genomic data

acquired in the Singapore Malay Eye Study (SiMES), the Singapore Indian Chinese Cohort Eye Study (SICC) and the Blue Mountains Eye Study (BMES), Australia.

We have developed the ARGALI [6,7] (an Automatic cup-to-disc Ratio measurement system for Glaucoma AnaLlysIs) software system, an inter-disciplinary collaboration between the Institute for Infocomm (I2R), the Singapore Eye Research Institute (SERI), and the Singapore National Eye Centre (SNEC). Comparing with other works [8,9,10], ARGALI is a preliminary diagnostic system for glaucoma detection that first time automatically measures optic nerve damage by calculating the cup-to disc ratio (CDR) from retinal photographs. ARGALI suggest that is possible to develop a fast, objective and consistent measurement of optic nerve damage with potential for early glaucoma screening. AGLAIA expands the scope of ARGALI.

II. METHOD

AGLAIA aims to provide a multi-modality system that captures globally a range of parameter that is indicative of early glaucoma damage. AGLAIA (Figure) automatically measures and assesses the following features objectively and quantitatively, features which are currently evaluated subjectively by glaucoma specialist in clinical practice:

- Cup-to-disc ratio (CDR) – further refinement is made based on initial algorithms developed in ARGALI
- Disc hemorrhage (DH)
- Thinning of the NRR (NeuroRetinal Rim)
- Notching of the NRR
- Compliance of NRR width by 'ISNT Rule' (inferior≥superior≥nasal≥temporal)
- Inter-eye asymmetry
- Parapapillary atrophy (PPA)
- Blood vessel pattern analysis
- Blood vessel kink analysis
- Tilted Disc - quantify the degree of tilting based on the disc contour
- Disc Size - automatically classify disc size to "large, medium or small" categories based on automatic disc measurement
- Gradeability – analyze the image and determine gradeability
- Check the presence of RNFL (Retinal Nerve Fiber Layer) defect.

AGLAIA system is developed using medical image informatics technology. Medical informatics is an emerging discipline that has been defined as the study, invention, and implementation of structures and algorithms to improve communication, understanding and management of medical image and information. The end objective of medical image informatics is the coalescing of image, data, knowledge, and the tools necessary to apply that data and knowledge in the clinical decision-making process, at the time and place that a decision needs to be made.

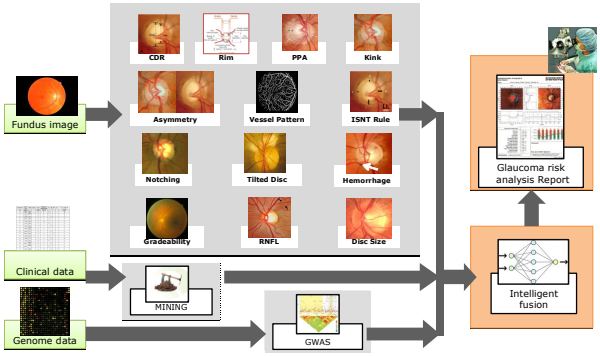

Fig. 1 AGLAIA Diagram

AGLAIA utilizes medical image processing, data mining, bioinformatics, pattern recognition, statistical learning, and neural network technologies.

AGLAIA system (as shown in Fig. 1) consists of following modules: It can be checked from Document Properties/Fonts in File menu of Adobe Acrobat.

A. *Cup-to-disc ratio (CDR)*

Optic disc cupping [11] is one of the most important features in the diagnosis of glaucoma. For the optic disc, a variational level-set approach, which is based on global optimization concepts, is used to segment the disc boundary and extract the optic disc region from the retinal image. Segmentation of the optic cup is more challenging than the optic disc due to the optic cup's interweavement with blood vessel and surrounding tissues. An innovative technique to extract the cup is developed, in which a multi-modal approach is employed. A color histogram analysis of the image is first carried out, and is subsequently followed by the application of level-set algorithms to segment the cup boundary. The segmented cup is then smoothened in two separate instances, one making use of ellipse fitting and another in which a maximum inscribed fitted circle is used. Finally, a neural network is trained to fuse the cup-to-disc calculation results from the level-set algorithms as well as the results after different smoothing processes. This neural network learning mechanism integrates the knowledge embedded in the clinical practice and provides an optimal CDR for the glaucoma screening, diagnosis and analysis.

B. *Disc haemorrhage*

Disc haemorrhage (DH) is a clinical sign which is often associated with glaucomatous optic nerve damage. Medical image processing technology is used to detect disc haemorrhage. Rarely found in normal eyes, disc haemorrhages are detected in about 4% to 7% of eyes with glaucoma [12]. These are usually dot-shaped when within the NRR and flame-shaped (splinter) when on, or adjacent to, the disk margin.[12,13] Flame-shaped haemorrhages within the RNFL that cross the scleral ring in the absence of disk edema (ie, Drance haemorrhages), are highly suggestive of progressive optic nerve damage.[15] Disc haemorrhages are more common in the early stages of glaucoma. They are

usually located in the infero- or supero-temporal disk regions and are more frequent in normal tension glaucoma. Depending on their original size, they are visible for about 1 to 12 weeks after the initial bleed. A localized retinal nerve fiber layer (RNFL) defect and/or NRR notch may be detected, corresponding to a visual field defect.[12]

We developed a method to detect DH by first identifying a ring-shaped region of interest (ROI) encompassing the optic disc boundary. Two dilated images are then generated. The first dilated image is formed by applying edge detection methods on the green and grey channels of the fundus image to detect and remove the retinal blood vessels. Edge detection is then applied on the red channel of the retinal fundus image to obtain an outline of an optic disc region to construct the second dilated image. The two dilated images are then fitted together to create a summed image. The identified region of interest (ROI) is then masked on the summed image to extract blood vessels. Colour-based analysis is performed to detect disc haemorrhages from the extracted blood vessels regions in the identified region of interest to pinpoint the candidate disc haemorrhages. Lastly, knowledge-based contraints are applied in post-processing to screen and identify the true disc haemorrhages.

C. *Thinning of neuroretinal rim (NRR)*

Neuroretinal rim loss is preferentially located at the

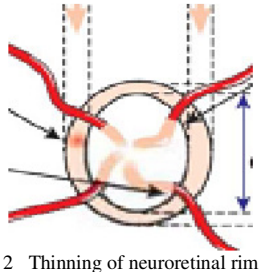

Fig. 2 Thinning of neuroretinal rim (NRR).

inferotemporal and supertemporal in early glaucoma [14]. Therefore, assessment of neuroretinal rim (NRR) thinning is very important for the detection of glaucoma. The measurement of the neuroretinal rim loss would also complement the Parapapillary atrophy (PPA) detection, as the site of the largest area of atrophy tends to correspond with the part of the disk with most NRR loss (Kotecha A, 2002).[17] An example of thinning of neuroretinal rim (NRR) at superior & inferior regions is shown in Fig.2.

D. *Compliance of NRR width by 'ISNT Rule'*

The neuroretinal rim (NRR) is usually broadest inferiorly, followed by superiorly, then nasally, and finally temporally (Jonas ISN'T rule).[14] In large optic discs, the 'ISNT' rule is less apparent, with the NRR appearing to have equal thickness all around the disc. In glaucoma, NRR loss can be diffuse, in all sectors of the optic disc, or localized, forming a "notch".

Adherence to ISNT rule is an important indicator for non-glaucoma, thus, any variation from this rule may help to detect glaucomatous damage. Medical image processing technology and statistical learning models is used to identify and detect whether the optic rim follows ISNT rule.

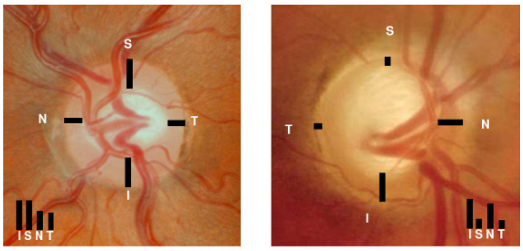

Fig. 3 Application of the ISNT rule. Disk on the left adheres to the ISNT rule; and disk on the right does not.

E. *Inter-eye asymmetry*

Inter-eye asymmetry of cupping (difference 0.2 or greater) may useful to identify glaucoma because one eye is frequently more advanced than the fellow eye in glaucoma patients.

Medical image processing technology such as color correction and euclidean geometry transformations is used to detect the asymmetry of cupping between patients eyes.

F. *Parapapillary atrophy (PPA)*

PPA is another clinical sign associated with glaucoma [15,16]. Medical image processing methods such as level-set, histogram-based segmentation, edge detection and region growing is explored to detect PPA.

PPA is the recession of the retinal pigment epithelium (RPE) into the choroid. PPA is divided into a central zone beta-PPA and peripheral zone alpha-PPA. Beta-PPA is characterised by visible sclera and choroidal vessels, extending from the sclera ring. Zone alpha-PPA is characterised by hyper- or hypo-pigmentation of the RPE. Only beta-PPA has significance in glaucoma, therefore, grading of PPA is purely based on the presence and extent of beta-PPA.

A temporal crescent of alpha-PPA may be is present in about 80% of the normal population, however, in glaucoma, the frequency and area of PPA increases. The site of the largest area of atrophy tends to correspond with the part of the disk with most NRR loss [17]. Beta-PPA should be graded on the severity or extent of its presence. The available grading codes are 'mild', 'moderate', and 'extensive'. The following examples serve as reference images:

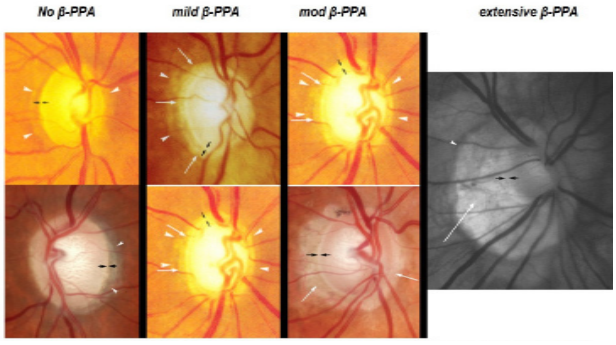

Fig. 4 Grading codes for PPA

G. *Notching of the NRR*

Neuroretinal rim notching [18] is focal thinning of the rim which is another glaucomatous structural damage at optic disc.

Disc haemorrhage or RNFL defect often develop at the edge of notch. Medical image processing technology is used to detect notching. Apply a red-free filter to enhance the cup margin and RNFL appearance. The presence of a 'notch' is recorded in relation to its location within the optic disc. Edge detection, shape models and variation of gradient changes is used to detect the notches.

H. Blood vessel pattern analysis

Retinal blood vessel [18] can provide very useful information for the analysis of ocular diseases, including glaucoma. Wavelet analysis is used to generate and analyze the blood vessel patterns.

I. Blood vessel "kink" analysis

Kinks are defined as the morphological bending of small blood vessels at the boundary between the optic cup and optic disc and are formed when small vessels cross over from the surrounding disc region into the depression formed by the optic cup. The locations of kinks are thus useful for the assessment of the border of the optic cup to determine the optic cup boundaries. [18]

J. Disc Size classification

Given that the NRR is made up the optic nerve fibres exiting the disc, a large disc may have a thinner relative NRR, or larger CDR than a smaller disc because the fibres are spread over a larger area. Therefore, a CDR of 0.7 in a large disc may be equivalent to a CDR of 0.4 in a small disc in Glaucoma diagnosis, as the same surface area of nerve fibres may be present on both discs. We'll automatically calculate the disc size and classify it into large/medium/small categories.

K. Disc Tilting analysis

Disc tilting (Fig. 5) angle is automatic measured in AGLAIA. With a tilted disc, the optic nerve inserts into the retina on an oblique angle. The disc may look distorted with a distinct crescent of exposed sclera. This disc often creates discrepancy among different graders. AGLAIA quantifies the degree of tilting based on the disc contour.

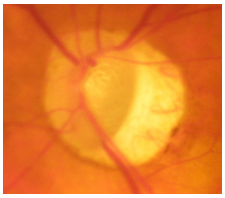

Fig. 5 A tilted disc

L. Gradeability

Based on both global and local analysis of the retinal image, AGLAIA determines the gradeability of the images. This helps to provide an objective and repeatable analysis to the image. The gradeability of the fundus images provides constraints and optimal parameters for the detection of the other image processing modules.

M. Retinal Nerve Fiber Layer (RNFL) defect presence detection

In normal eyes, the RNFL appears as grey fibre bundle striations, unevenly distributed. The fibre bundles are most obvious in the inferotemporal sector, followed by the supero-temporal area, the supero-nasal region and finally the infero-nasal sector. It's least visible horizontally in the temporal and nasal regions. Some Glaucoma patients RNFL layer is defected, AGLAIA automatically detect the presence or absence of RNFL detection based on image analysis. The medical image processing techniques include color and texture-based methods.

N. Medical report mining module

The module structures the input medical report (usually parsing, along with the addition of some derived linguistic features and the removal of others, and subsequent insertion into a database), deriving patterns within the structured data, and finally evaluation and interpretation of the output. 'High quality' in text mining usually refers to some combination of relevance, novelty, and interestingness. Typical text mining tasks include text categorization, text clustering, concept/entity extraction, production of granular taxonomies, sentiment analysis, document summarization, and entity relation modelling (i.e., learning relations between named entities). Data mining techniques such as pattern matching, data modelling, features selection, classifications and correlation is utilized.

O. GWAS module

The genome-wide association approach has been the most powerful and efficient study design thus far in identifying genetic variants that are associated with complex human diseases. This approach became feasible only recently as the result of several key advancements in genetic knowledge, genotyping technologies, statistical analysis algorithms and the availability of large collections of cases and controls. [19]

It is well known that the features of the eye which contribute to the clinical appearance of glaucoma are strongly genetically determined. To date, detection and risk stratification in glaucoma are crude. The three known genes (MYOC, OPTN, WDR36) implicated in primary open angle glaucoma (POAG) by classical linkage studies contribute to the pathogenesis of POAG in less than 5% of cases in the general population. Genes accounting for a more significant proportion of the known heritable component of glaucoma remain to be identified. The genetic markers found in this study hopefully can enable better risk assessment in glaucoma and the more appropriate distribution of clinical resources.

In this system, Genome-wide association studies are planned to find the genetic markers associated with the quantitative traits of glaucoma, some are known to be highly heritable. We link the genetic information with a comprehensive set of phenotypes, including various image cues detected by the above mentioned methods, such as CDR

and PPA. We formulate a case-control study population from various cohorts: the glaucoma cases and normal controls. We perform a single-stage GWAS and carry out the appropriate statistical analyses to identify correlation between genetic changes (SNPS) and the incidence of glaucoma. We further determine the Genetic Map position to locate the identified SNPs on exon, promoter or enhancer region.

Genotyping data from 3 population groups are used in this study, including 3K Singapore Malay population, 3K Singapore India and 5K Australia Caucasian population. All these unrelated individuals have been accurately phenotyped with genotyping data available. The results from 3 different populations are to be compared and consolidated. We aim to find replicable associations by multiple studies.

P. Intelligent fusion module

A multi-layer neural network is constructed in AGLAIA to fuse the various output from the previous modules. The output of the neural network is the optimal glaucoma risk assessment result of the system. The parameters of the neural network are to be trained using a large collection of retinal fundus images collected from the Singapore Eye Research Institute. In this way, this neural network learning mechanism integrates the knowledge embedded in the clinical practice. Other machine learning techniques that will be explored for use in this intelligent fusion module includes Support Vector Machines and AdaBoost.

Q. Glaucoma risk analysis report generator

A user friendly report is generated for easy reading and understanding for patients and doctors. The report also documents and consolidates the patient-specific's results and findings from the above 16 modules.

III. Experimental Results

Many experiments have been conducted to validate individual modules' effectiveness of the AGLAIA system. Initial validation of AGLAIA on data from Singapore National Eye Center Clinics Retinal Vessel and Glaucoma Subtype Study (RVGSS) Singapore Indian Chinese Cohort (SICC) databases gives a specificity of 0.88 and sensitivity of 0.95. Secondary validation on Origa-Light [20] data from population study is being conducted.

IV. Conclusions and Future Work

The system, the Automatic GLaucoma Diagnosis and Its Genetic Association Study through Medical Image InformAtics (AGLAIA), will develop, validate, test and evaluate a novel "global" automated glaucoma diagnostic system in Singapore, with the potential for translation into clinical usage and commercialization.

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