An Eye on Research

Clinical Vision Science Program and Eye Care Team Newsletter, Issue 2, January 2006

Table of Content

Research Feature

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Determination of Phenotype Using Genetic Analysis in Hereditary Conditions with Incomplete Penetrance and Variable Expressivity: The Autosomal Dominant Optic Atrophy (ADOA) Story.

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Purpose

Autosomal dominant optic atrophy (ADOA), or Kjer type optic atrophy, is a hereditary disorder associated with variable loss of vision, anomalous color vision and contrast sensitivity, and visual field defects. The penetrance is incomplete and the expressivity variable. One gene and one additional locus have been described for the uncomplicated form of ADOA: *OPA1* maps to chromosome 3q28-29,1,2 and a second locus maps to chromosome 18q12.2 to 12.3.3 We describe a family of British ancestry with 6 affected individuals. Electroretinogram (ERG) abnormalities were noted in some family members, some of which also had optic atrophy. The purpose of the study is to identify the causative gene in this family, and to characterize the phenotype in affected members, including determining whether the ERG abnormalities are part of the

ADOA phenotype or a coincidental, unassociated finding.

Methods

•Collection of pedigree information and clinical data (including psychophysical and electrodiagnostic testing) from Maritime Canada family (33 family members)

•Scoring of affectation status based on following 6 tests: visual acuity, color vision, contrast sensitivity, Goldmann visual field, optic nerve appearance, and visually evoked potential. For each abnormal finding a score of 0.5 is added for each eye: if the score is 2 or greater (maximum score of 6), i.e. 4 abnormal tests OD + OS, then the person is thought to be affected.

•Blood sample collection and DNA extraction

•Mutation screening of OPA1 gene by direct sequencing analysis (using previously published markers)1,2

Results

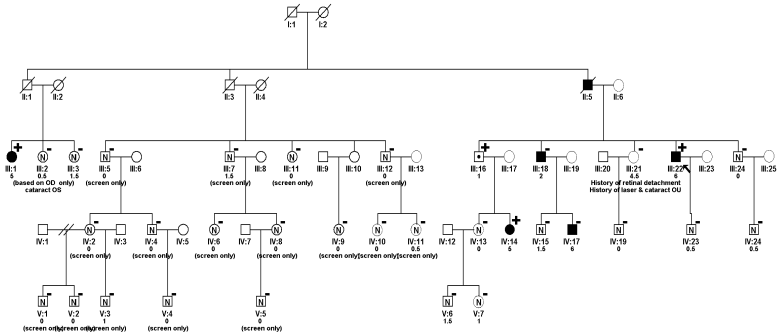


Figure 1: Pedigree Symbols: Circles are females, squares are males; Clear = unexamined; Solid = Examined and affected; N = Unaffected (examined); ? = Unclear status (examined); dot in center of symbol = carrier status; "+" = presence of Q217X mutation; "-" =absence of Q217X mutation. Number below each participant indicates optic nerve function score as described in methods and summarized in table.

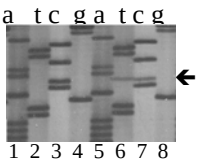


Figure 2. DNA sequencing autoradiography. Lanes 1-4 are an unaffected family member and lanes 5-8 are an affected family member. The c > t missense mutation in the affected is seen in lane 6 and not in the unaffected (lane 2); this changing caa (Gln) > taa (term): Q217X.

ID	Age	Optic Nerve Function score (0-6)	Q217X mutation +/-	ERG Scotopic Abnormality		ERG Photopic Abnormality	
V6	11	1.5	-				
V7	9	1	-				
IV13	35	0	-				
III24	43	0	-				
IV24	10	0.5	-				
III16	59	1	+				
11122	52	**6**	+				
1V17	28	**6**	-				
IV15	35	1.5	-				
IV23	25	0.5	-				
IV14	32	**5**	+				
III18	54	**2**	-				
IV19	34	0	-				
III1	73	**5**	+				
III2	70	1	-				
III3	66	1.5	-				

Table 1:medium shade = Normal scotopic ERG; light shade=Subnormal scotopic ERG; dark shade=Abnormal scotopic ERG

Shaded optic nerve function cells indicate individuals with a score compatible with ADOA (i.e. phenotype considered affected). ERG abnormalities are light gray and dark gray if mildly and severely reduced in amplitude, respectively, and medium gray is used for normal ERG results (white background only indicates test was not done). Individual III:21 is not included in this table because of the questionable status.

Of 33 family members recruited and examined, 16 underwent only the screening exam (vision, color vision and fundus exam) due to

limitations from traveling distances, and 17 had the full testing.

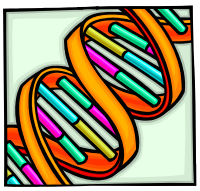
A Q217X mutation in the *OPA1* gene was identified in 4 of the 6 affected individuals with unambiguous optic atrophy or carrier status. The mutation did not segregate with the ERG abnormalities in this family. Individuals III:18 and IV:17 represent phenocopies of the disease.

Discussion

ADOA in this family is due to an OPA1 mutation that does not segregate with the ERG abnormalities, suggesting that these abnormalities are not associated with ADOA and were inherited separately.

In conditions demonstrating incomplete penetrance and variable expressivity, the determination of associated features can be difficult, especially if these features are rare occurences. Examination of unaffected members and identification of gene mutations are critical parameters to accurately describe the phenotype of hereditary conditions. This is essential in making proper diagnoses and counseling of family members. We suspect that the previously reported cases (approximately 10 individuals from 5 pedigrees) of ADOA in association with ERG anomalies4-8 were also coincidental findings.

Text taken from Dr J Robitaille presentation poster



Clinical Research Practice Feature

The Consent Process

Most researchers think that obtaining the consent for participation in a particular study entails signing a consent form. Informed consent is more than just a signature on a form; it is a process of information exchange. The exchange of information begins at the initial contact, which could be a discussion, a letter or even an ad, and continues until the study is complete.

The consent process include the following steps:

- Present the study to a potential participant. This may be initiated by one of your colleagues mentioning to his/her patients that someone in the department is recruiting for a study. Take in consideration the location of the discussion; a busy waiting area may compromise the participant's privacy.
- Give all information in relation to the study to the potential participant and his/her family if applicable by explaining the information contained in the consent form.
- Explain the study in a comprehensive manner. This include measuring their understanding and explaining the

study to minor with partial or full decisional capacity

- Give ample time for the potential participant and/or a family member to read the information provided in the information and consent/authorization form.
- Assess the level of comprehension. You can even ask them questions to ascertain that they understand.
- Allow them to ask questions and provide answers.
- Provide name and contact information of principal investigator and/or research coordinator for future communication
- Sign the consent form and treat it as a legal document
- Give a copy of the information and consent form to the participant
- Throughout the study, provide any information that may influence their willingness to participate.

In addition, to signing the consent form, the participant or caregiver authorizing participation must indicate the date and time to ensure the consent was obtained prior to participation. The investigator or coordinator should also indicate in the clinic notes the consent process and that consent was obtained prior to participation in the particular study.
It always seems easier to recruit friends, colleagues and family members for participation in a study, especially if you need a control population. However, we don't always think about cohersion and undue influence. Thus, it is important that all potential participants are treated the same, are given the same information, and sign a consent form.

This covers the main elements of the consent process. To learn more, the IWK Research Services will be offering Good Clinical Practices workshops starting in mid-January. The consent process will by the discussion of two of these workshops. Please refer to the Meeting and conference section.

Meetings and Conferences

The IWK Research Services presents: "The Basics of Good Clinical Practices for Researchers" a series of six workshops (held during lunch) with topics such as informed consent process and research study records. The first workshop is scheduled for January 18, 2006. To register, please contact Becky Merritt at 470- 7879. (no fee)

The Nova Scotia Health Research Foundation will be offering weekly presentation on the application process. These will take place at their office, located at 1660 Hollis Street, 9th floor, suite 905, every Thursday from 1-2pm during the months of February and March. Please RSVP at 424-4043.

Congratulations!!

★Congratulations to Heather Gunn for obtaining the best research award at the 2005 Annual COS meeting held this past June for her research project entitled: *The Interocular Effects of Luminance Attenuation and Optical Blur on Visual Function*

★Congratulations to Dr Johane Robitaille for obtaining the best poster award at the Annual COS meeting held this past June for her poster entitled: *Determination of Phenotype Using Genetic Analysis in Hereditary Conditions with Incomplete Penetrance and Variable Expressivity: The Autosomal Dominant Optic Atrophy (ADOA) Story*
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Grants

Here are a few upcoming grants that might be of interest, especially for students that may be interested in initiating their research project this summer. For the IWK grant opportunities, details can be found on Pulse, select research under departments/services.

IWK Summer Student Research Program: University students may gain salary support for a summer project supervised by an IWK researcher. Student reimbursement is cost shared with the researcher. DEADLINE Febuary 6th.

IWK Graduate Student Research Scholarship
The goals of the IWK graduate student scholarship are to foster the development of partnerships with IWK departments and universities, to encourage graduate student interest and research in women's and child health and to facilitate the recruitment of highly qualified graduate students for supervision by university program directors. DEADLINE: March 7th

Category A: IWK Research Operating Grant for proposals up to $4,000. Members of the IWK staff and trainees (residents, graduate students, etc) may apply. DEADLINE April 1st. This is a good opportunity for students and residents to recover some study costs .

Joint Commission of Allied Health Personnel in Ophthalmology is offering scholarships to clinical vision science students. DEADLINES March 24, 2006 and June 23, 2006
www.jcahpo.org

The Faculty of Graduate Studies Research Grant are available for graduate students when funding is not available through their supervisor, external funding, or awards.
www.dalgrad.dal.ca/forms/students/#research

The Faculty of Graduate Studies Conference Travel Grant are available to students presenting the results from their thesis at a national or international conference. DEADLINE: One month prior to the conference date
www.dalgrad.dal.ca/forms/students/#research

The Nova Scotia Health Research Foundation will be launching their 2006 competition on Feburary 1st 2006. Health Research Project Grants, Student Research Awards, and Capacity Building Program are available. Guidelines and application forms are available at www.nshrf.ca
DEADLINES:
Grants- pre-registration deadline is March 1st, 2006 and final deadline May 1st, 2006
Students- pre-registration deadline is April 4, 2006 and Final deadline is May 4, 2006

Last Word

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Research Update

Investigator	Title of Project	Status
Dr J Robitaille	The Genetic Study of Bardet Biedl Syndrome and other related disorders (collaborative study)	REB approval pending
Dr J. Robitaille	Genetic Analysis of Frizzled-4 (FZD4) and its influence on familial exudative vitreoretinopathy (ROP) and others associated retinal disorders	Active
Dr J Robitaille	Clinical and Genetic Analysis of Presumed Pericentral Retinal Degeneration	Active
Dr J. Robitaille	Genetic Analysis of Autosomal Dominant Optic Atrophy	Active
Dr J. Robitaille	Genetic Analysis and Mutation Effect on the Variation of Phenotype of Congenital Stationary Night Blindness	Active
Dr J. Robitaille	Genetic Analysis of Leber Congenital Amaurosis (PI at MCH, part of large collaborative study)	Active
Dr J. Robitaille	Genetic Analysis of FZD4 and Retinopathy of Prematurity	Preliminary Stage
Karen McMain	The eye in CHARGE	Active
Dr LE. Marcoux/ Dr GR.Laroche	Residual Action of the Inferior Oblique Muscle After Myectomy	Active
Dr LE. Marcoux/ Dr J. Robitaille	Incidence of Retinopathy of Prematurity in a Neonatal Intensive Care Unit in Nova Scotia	Active
Dr GR. Laroche	Inferior Oblique Histology-Surgical and Functional Implications	Active
Dr F. Tremblay	Retinal Ganglion Cell Functional Integrity; Non-Invasive In Vivo Eval'n After Injury and During Neuroprotective Therapy	Active
Dr F. Tremblay	Do Blueberries Improve Vision and Eye Health	REB approval pending
Lillian Aledejebi	Nature of Binocular Cortical Supression in Patients with Intermittent Exotropia	Preliminary Stage
Christina Brasset	Validation of contrast and sensitivity chart	Preliminary Stage
Jennifer Winberg	Abnormal versus Normal Early Visual Experience in Cats	Active
Heather Fennell	Anatomical changes occurring during the visual system development critical period in cats with strabismus	Active
Leah Walsh	The Recurrence of Amblyopia after the Cessation of Treatment	Active
Riannon Johnson	Development of the Visual Field Using Rarebit Perimetry	Preliminary Stage
Tara Fraser	Functional Implications of Non Stereoacuity in Reaching and Grasping	Preliminary Stage
Heather Gunn	Interocular Effects in Amblyopia: Effect of Occlusion Method on Visual Function Test	Active
Lesley MacSween	Form-from-Motion Processing in the Intact Dorsal Cortex	Active