

Age-related Macular Degeneration in Greenland - A Pilot Project

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Overview

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Background

- Age-related Macular Degeneration (AMD) is a chronic progressive disease of the central part of the retina (macula).
- It is the leading cause of blindness in the industrialized world (including Greenland since 1981; Blinde registret)
- 10-15 % of the population worldwide have (any) AMD
- 10 % of the population above 80 years have advanced AMD (neovascularization (wet), geographic atrophy (dry) or combination of both)

Normal fundus



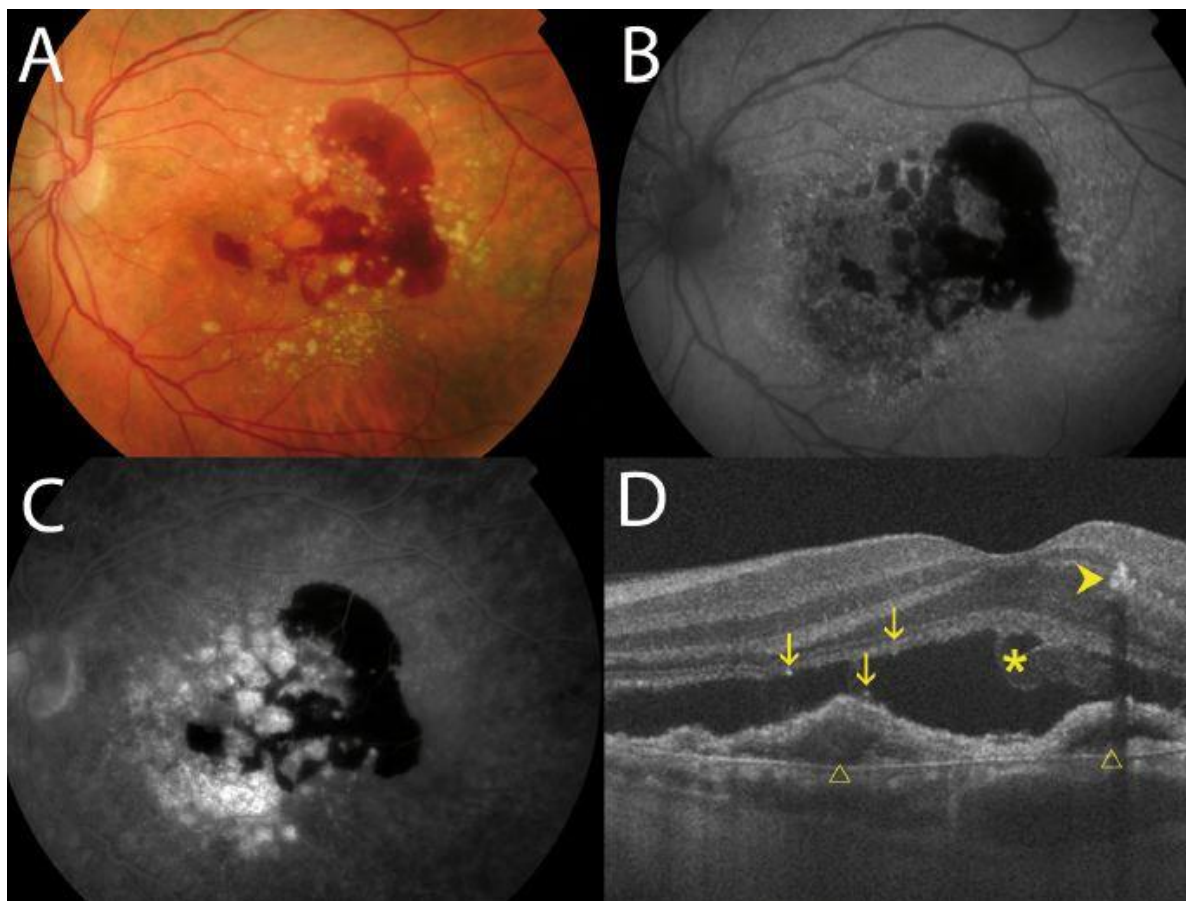
Drusen



Geographic Atrophy (Dry AMD)



Neovascularization (Wet AMD)



Pathogenesis

- Is multifactorial
- Smoking and increasing age are the significant riskfactors
- Environmental factors, like sunlight exposure, and genetic factors are greater focus

Greenland Inuit Eye Study (2008)

Prevalence of Age-Related Maculopathy and Age-Related Macular Degeneration among the Inuit in Greenland

The Greenland Inuit Eye Study

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Greenland Inuit Eye Study (2008)

- Cross-sectional study of the population aged 60+ in Nuuk and Sisimiut
- 951 potential participants. 685 included in the study.
- Only 8 of the 685 did not have drusen

Greenland Inuit Eye Study (2008)

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Table 4. Age-Related Maculopathy (ARM) and Age-Related Macular Degeneration (AMD), by Worse Eye

	ARM			AMD		
	Gradable at Risk	With Lesion	%	Gradable	With Lesion	%
Males						
60-69	178	86	48.3	181	7	3.9
70-79	75	40	53.3	79	13	16.5
≥80	12	5	41.7	12	6	50.0
All ages	265	131	49.4	272	26	9.6
Females						
60-69	224	115	51.3	226	9	4.0
70-79	112	70	62.5	119	16	13.4
≥80	26	12	46.2	25	10	40.0
All ages	362	197	54.4	370	35	9.5
Total						
60-69	402	201	50.0	407	16	3.9
70-79	187	110	58.8	198	29	14.6
≥80	38	17	44.7	37	16	43.2
All ages	627	328	52.3	642	61	9.5

Greenland Inuit Eye Study (2008)

- Is AMD more common in Greenland than other industrialized countries?
- Coincidence?
- Environmental?
- Smoking?
- Genetical?

Aims

- 1) To investigate, using exome sequencing, whether there is a correlation between frequent variations / mutations in selected genes and AMD among Greenlanders.
- 2) Determine whether there are similar variations / mutations in the same selected genes in Greenlandic patients with AMD compared to Danish patients with AMD.

Selection of Candidate Genes

- Genome Wide Association Studies (GWAS) has identified frequent AMD-associated genetic variants in Caucasians (single nucleotide polymorphism SNP's)
- These can explain 15-65 % of the observed heritability of AMD (moderate risk of development of AMD)
- Other studies have identified genetic variations in the complement system which are associated with a high risk of developing AMD

Gener indeholdende SNPs positive i mindst to GWASs	Complement pathway ⁶²	Samlet
APOE	C1QA	APOE
ARMS2	C1QB	ARMS2
C2	C1QC	C1QA
C3	C1R	C1QB
CFB	C1S	C1QC
CFH	C2	C1R
CFI	C3	C1S
HTRA1	C3AR1	C2
LIPC	C4A	C3
PLEKHA1	C4B	C3AR1
SYN3	C5	C4A
TIMP3	C5AR1	C4B
VEGFA	C6	C5
	C7	C5AR1
	C8A	C6
	C8B	C7
	C8G	C8A
	C9	C8B
	CD46	C8G
	CD59	C9
	CFB	CD46
	CFD	CD59
	CFH	CFB
	CFHR1	CFD
	CFHR2	CFH
	CFHR3	CFHR1
	CFHR4	CFHR2
	CFHR5	CFHR3
	CFI	CFHR4
	CFP	CFHR5
	CR1	CFI
	CR1L	CFP
	CR2	CR1
	ITGAM	CR1L
	ITGAX	CR2
	ITGB2	ITGAM
		ITGAX
		ITGB2
		HTRA1
		LIPC
		PLEKHA1
		SYN3
		TIMP3
		VEGFA
I alt: 13 gener	I alt: 36 gener	I alt: 44 gener

Methods

- 25 patients with wet AMD and 25 patient with dry AMD, all from Greenland, will undergo sequencing of the selected 44 genes (through targeted exome sequencing)
- The results will be analysed to find any variations in patients with AMD (part 1)
- The same analysis will be compared to danish patients with AMD, who will undergo same genetic analysis, to determine whether the same variations exist both in greenlandic and in danish patients with AMD (part 2)

Ethical considerations

- Exome sequencing: Risk of accidental findings of pathogenic mutations associated with other hereditary diseases.
- The risk of carrier state for a hereditary disease with recessive inheritance is higher than dominant inheritance (elderly patients)
- Could cause anxiety etc.
- Or is it an advantage? (earlier diagnosis/frequent consultations or when planning pregnancy)

Ethical considerations

- So why chose exome sequencing?
 - This project will take about 1-2 years to complete (recruiting, analysis etc.)
 - During this time new genes could be relevant
 - (When finding no frequent variations analysis of the entire exome in few patients could be relevant (to compare with danish))

Conclusion

- There are indications of the fact that the incidence of AMD is higher in Greenland than in and other countries
- It is therefore particularly interesting to know whether variations in the genome in Greenlandic patients with AMD in Greenland differs from the situation elsewhere in the world, including in Denmark
- If this study detects frequently occurring variations / mutations in Greenlanders with AMD it will probably require a larger project with more Greenlandic participants to verify these findings

Qujanaq