ABCA4 Heterozygosity

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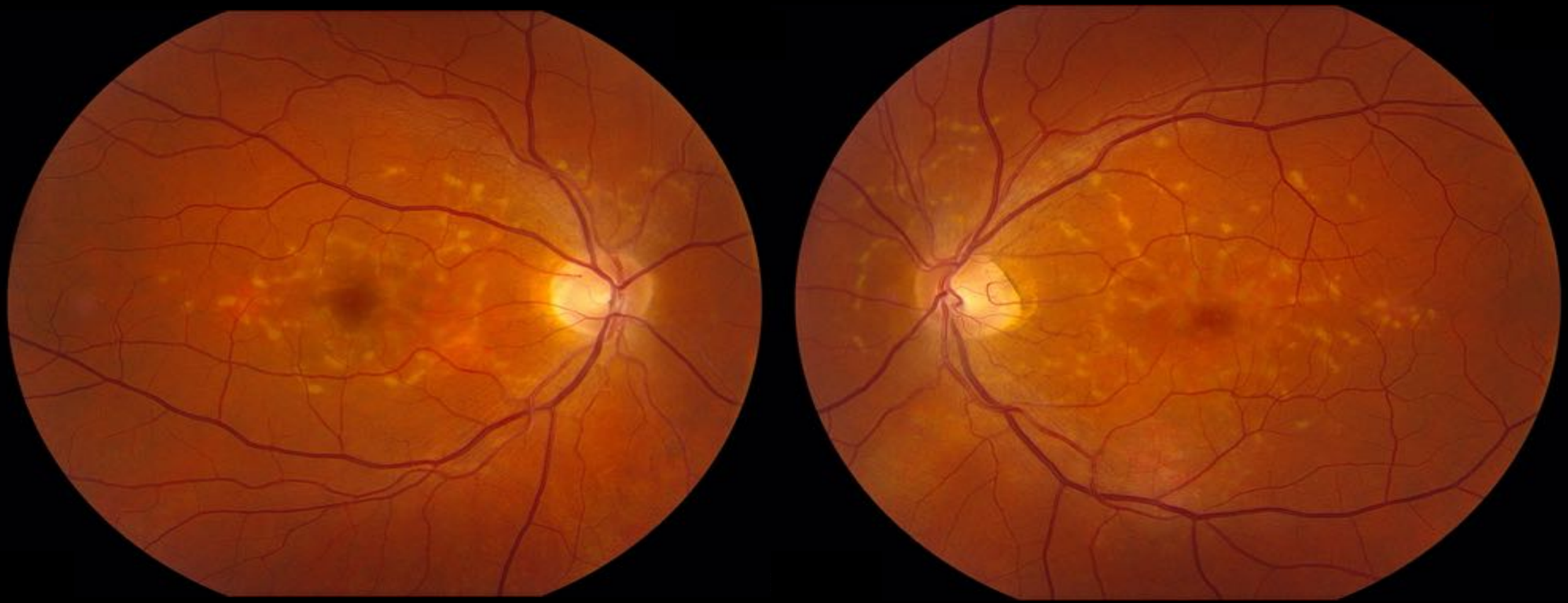
Summary

- In a small group of patients heterozygous for *ABCA4* mutations, there was a trend towards mutations in critical motifs
- 2 novel mutations and 2 un-described mutations are characterized
- Similarities with late-onset Stargardt’s disease
- Possible mechanisms discussed

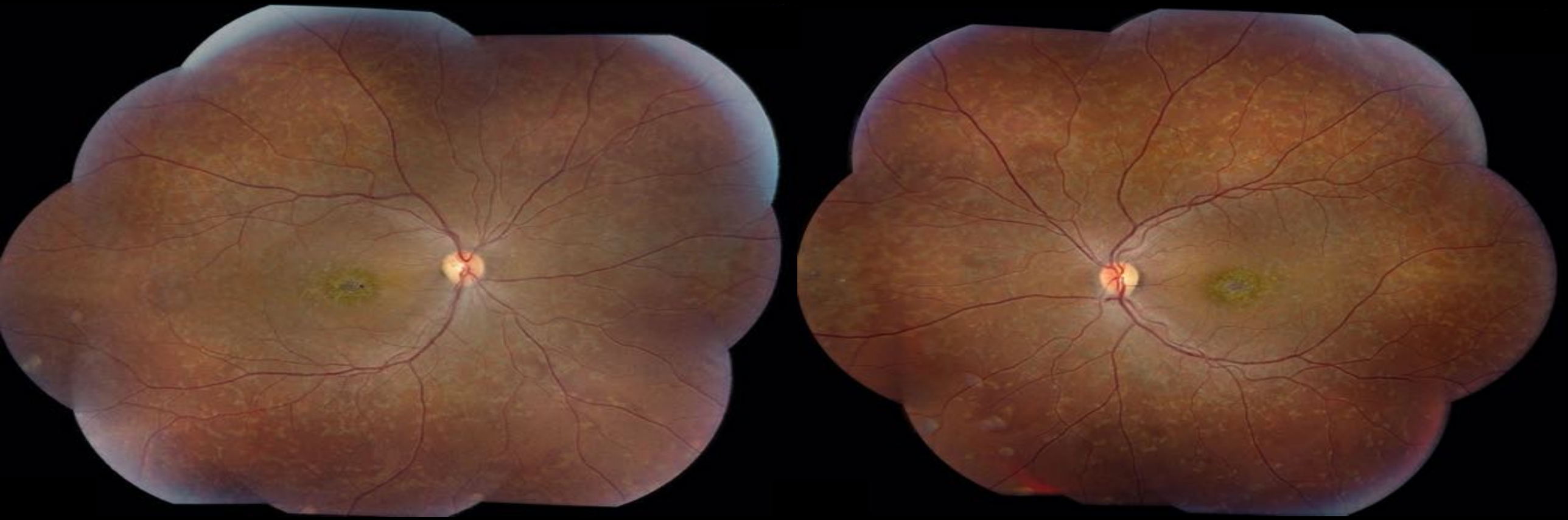
ABCA4

- One of the most common genetic mutations in inherited retinal dystrophies
- Associated with several disorders

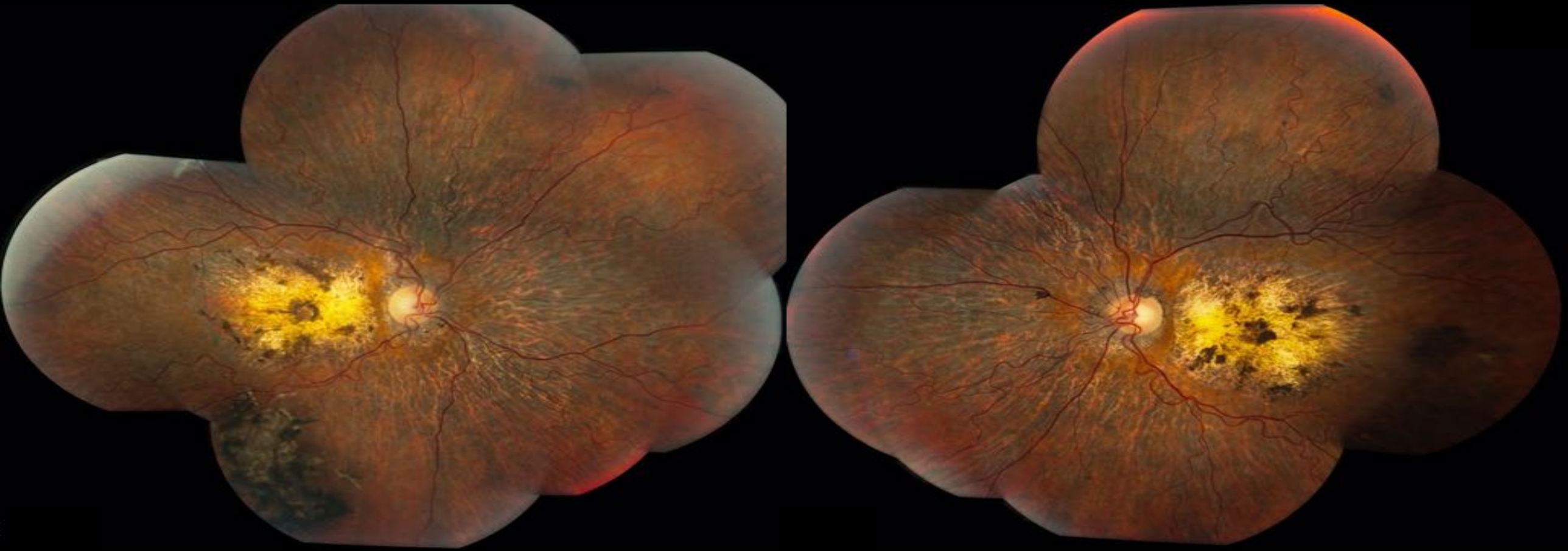
Stargardt’s Disease



Fundus Flavimaculatus

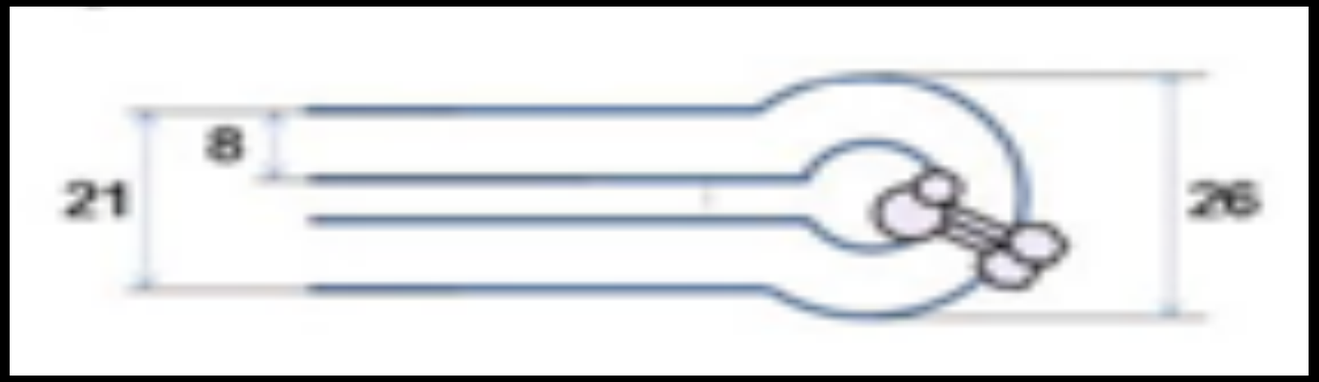


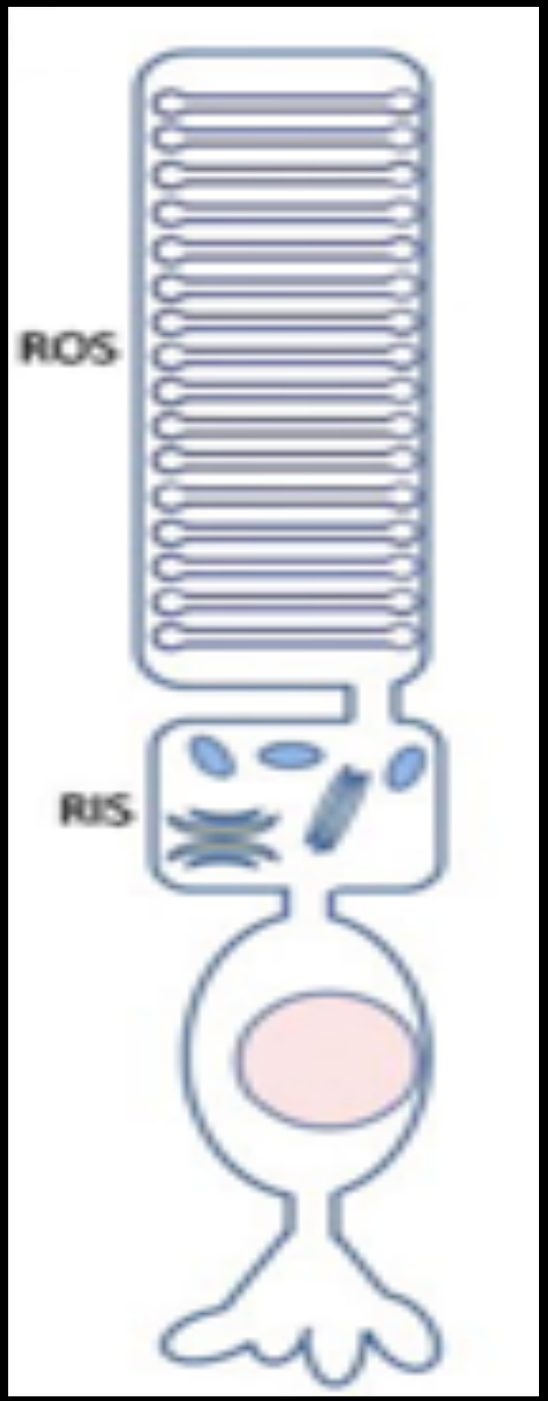
Generalized Choriocapillaris Dystrophy



ABCA4

Retinoid transport within ROS

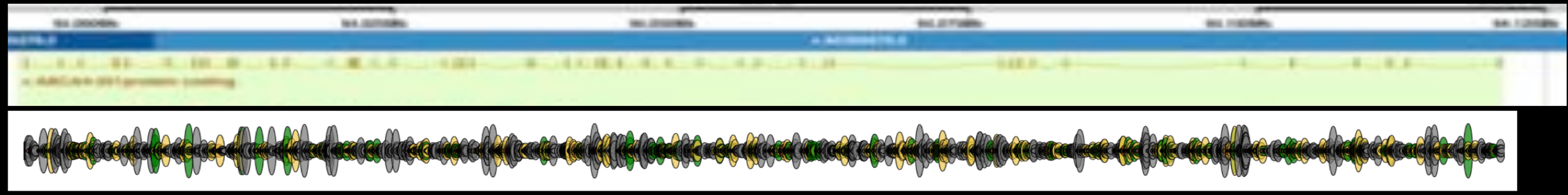




Illustrations adapted from Tsybovsky *et al*. The ATP-binding cassette transporter ABCA4: structural and functional properties and role in retinal disease. *Adv Exp Med Biol*. 2010;703:105-125.

ABCA4

- 50 exons over 6,800 base pairs
- Over 1000 known variants



Illustrations adapted from Ensembl and GnomAD

ABCA4

- High carrier rates of ABCA4 allelic variation, 5-6% in some populations
- Some patients carry only a single mutation even when tested with advanced sequencing methods

Purpose

- To identify and describe genotypic and phenotypic characteristics of ABCA4 heterozygotes

Methods

- Retrospective study
- Queried all records that had undergone genetic testing at a single, large vitreo-retinal practice from 2007-2020.
- Records selected which carried a single variation in ABCA4 with no other potentially causative variants in other genes

Methods

- Patients underwent either Sanger sequencing or Next Generation Sequencing
- hg build GRCH37 hg19
- reference sequences for ABCA4 (RefSeq NG_009073.1 for gDNA, NM_000350 for mRNA)
- Public databases: ClinVar, LOVD, EVS, GnomAD
- *In silico:* Polyphen-2, SIFT, Mutation Taster

Results

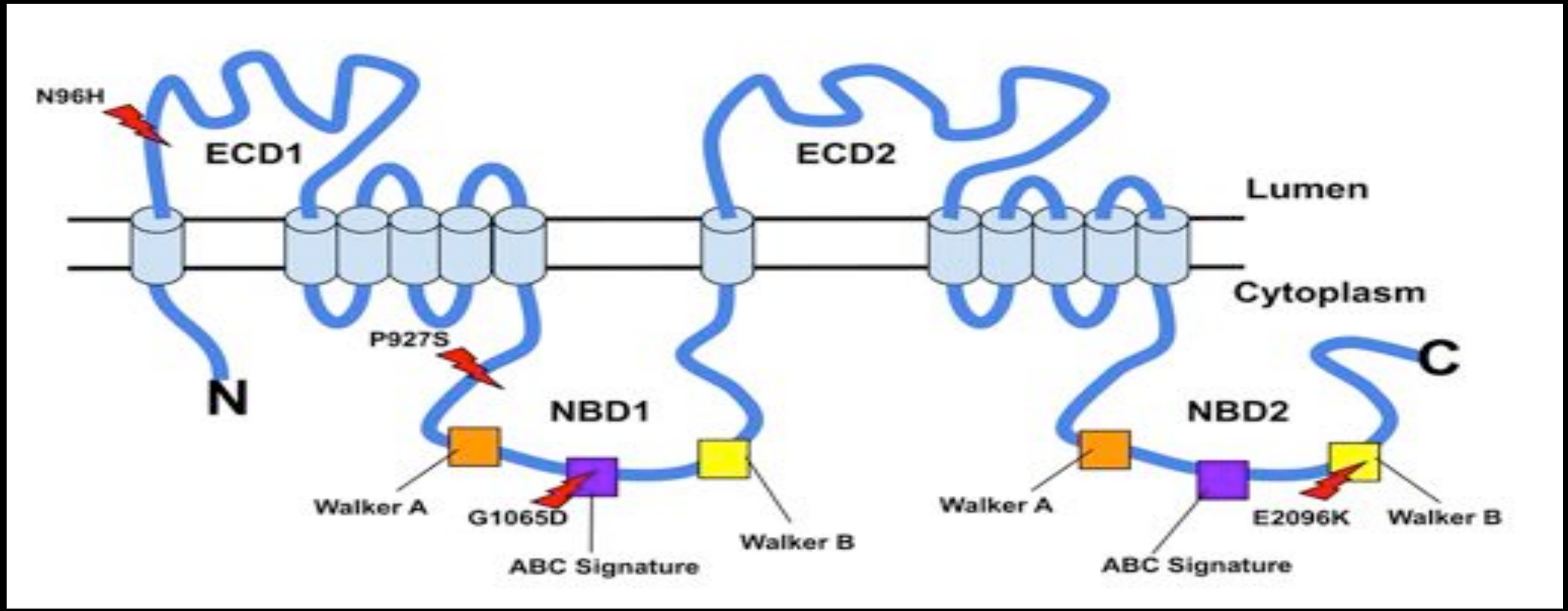
- Reviewed records for 37 patients with ABCA4 mutations

- N = 6 heterozygous patients
  - 1 large deletion of exons 10-11
  - 4 missense
  - 1 splice variant

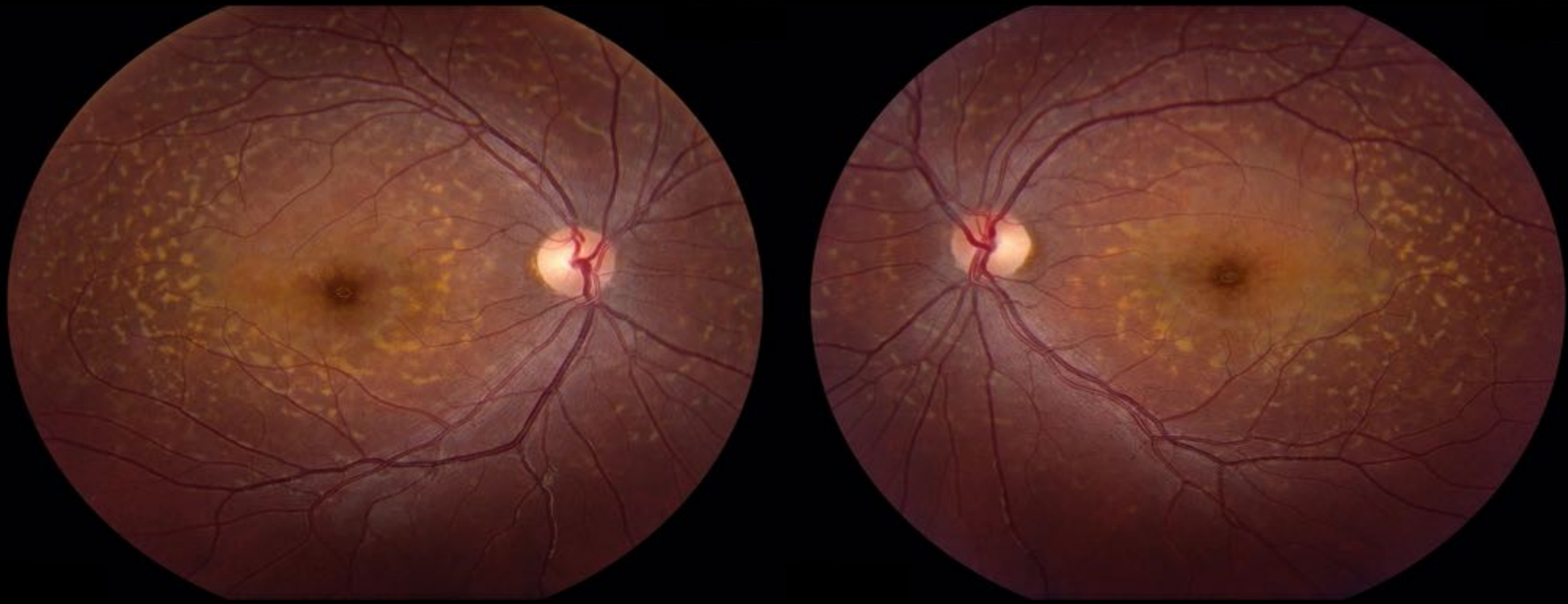
Results

- Several phenotypes observed
  - Stargardt's – 3 of 6
  - ABCA4 disease – 1 of 6
  - Pattern Dystrophy - 2 (initial diagnosis)
- No patients had a prior family history
- Mean age at diagnosis 40.2 years (range 19-67)
- Final BCVA ranged from 20/25 to 20/250

Summary of Missense Mutations



1.p22.1(94542998_94544254)x1
Deletes portion of ECD1



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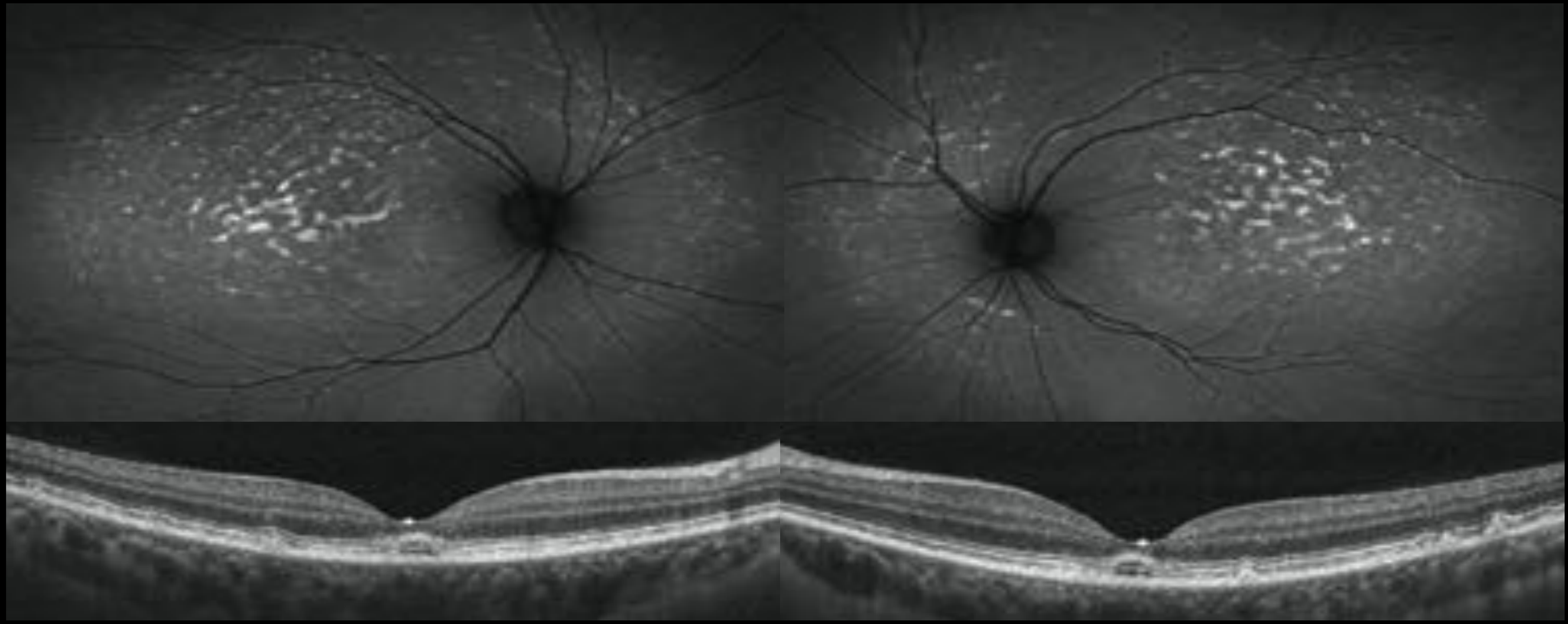
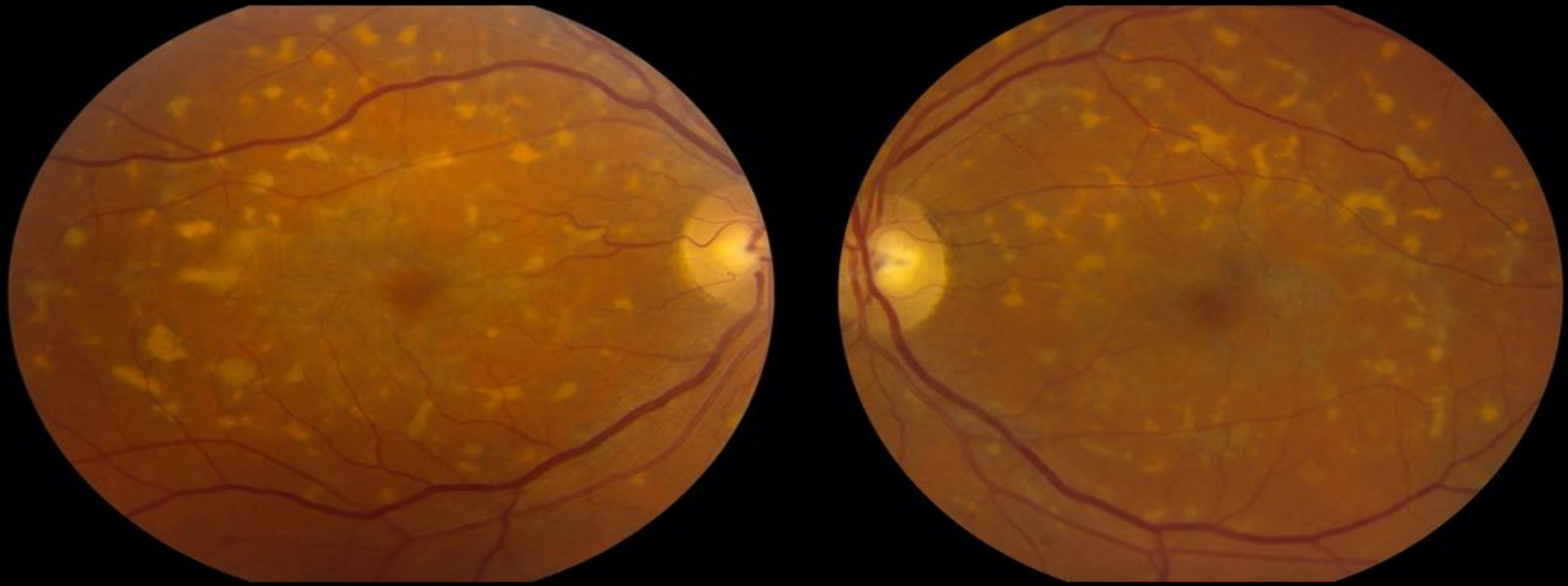


c.2779C>T, p.P927S

Occurs within NBD1 domain

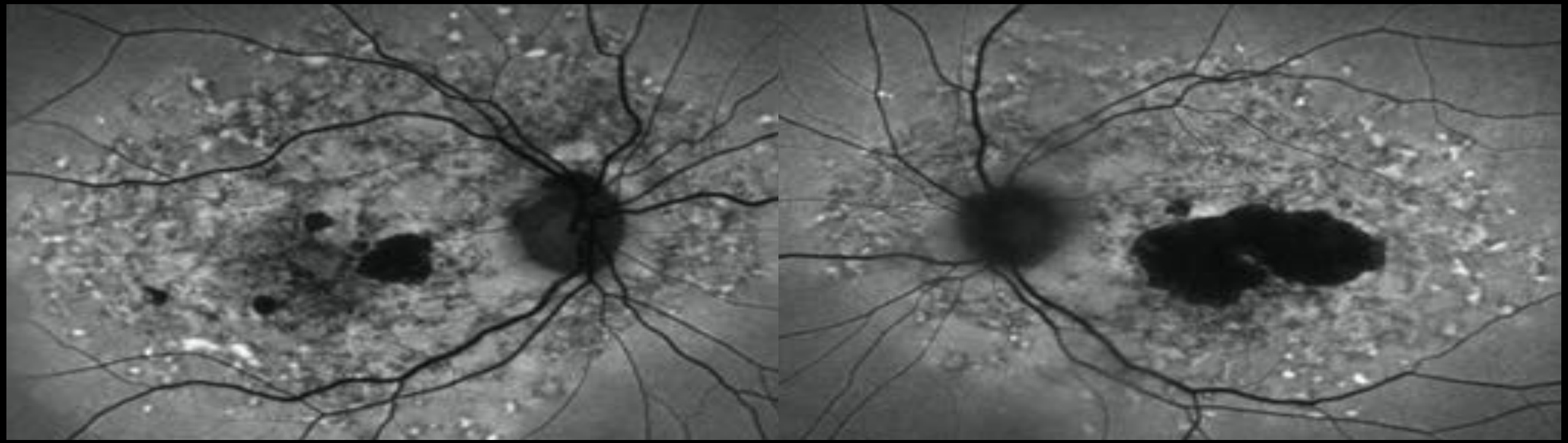
c.3194G>A p.G1065D

Occurs within ABC signature motif



c.3194G>A p.G1065D

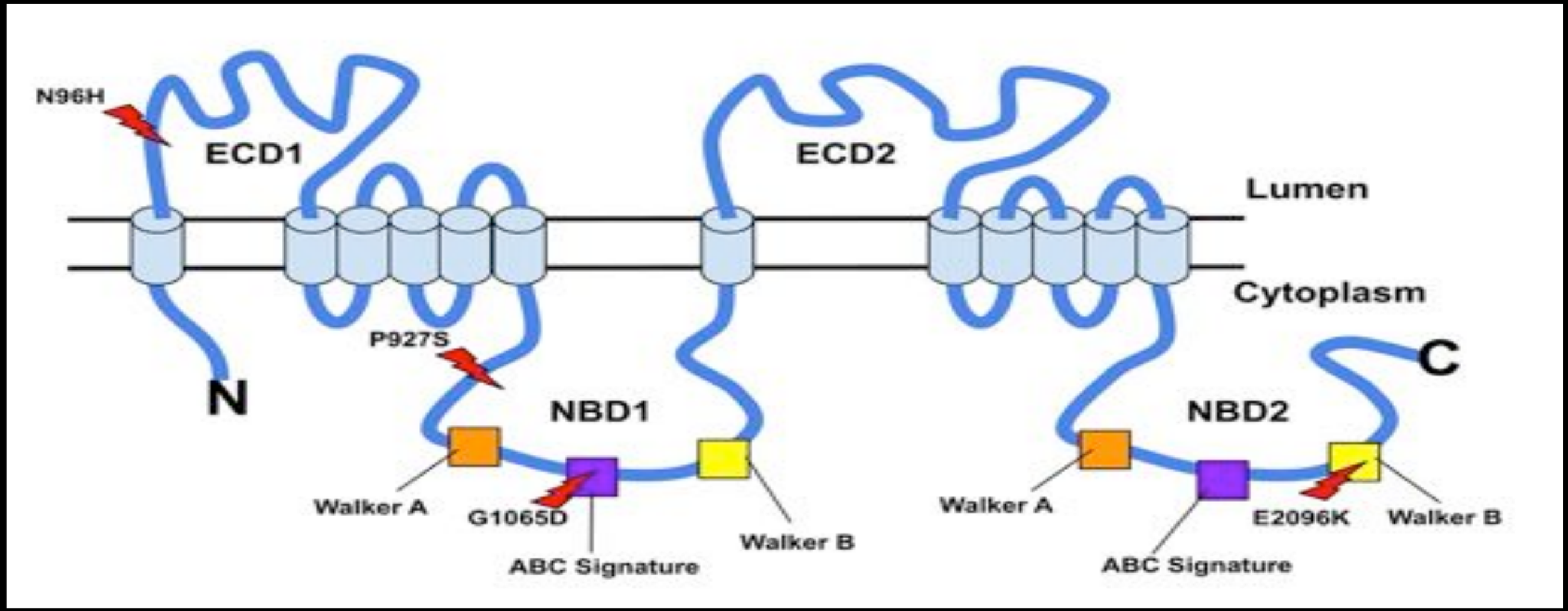
Occurs within ABC signature motif



c.6286G>A, p.E2096K

- Heterozygous presentation not previously described
- Walker B motif of NBD2 domain, abolishes ATP binding

Summary of Missense Mutations



ABCA4 heterozygotes

- late-onset Stargardt's disease: high rates of heterozygosity
- Age at onset may depend on zygosity
  - N96H variant produces early onset disease in homozygous or compound heterozygous state
  - Our patient had late onset disease

Westeneng-van Haaften *et al*. Clinical and genetic characteristics of late-onset Stargardt's disease. *Ophthalmology*. 2012;119(6):1199-1210.

ABCA4 heterozygotes

- Late-onset Stargardt's cohorts noted slower progression
- All of our patients had significant progression
- 'Single mutation' does not necessarily portend a good prognosis

Possible mechanisms

- Undetected mutations
  - Deep intronic variants
  - Regulatory mutations
  - Copy number variants (rare)
- Modifier gene mutations
- Hypomorphic alleles
- Environmental factors

Limiting factors

- Small, retrospective study
- Unable to perform segregation analysis or copy number variant analysis

Thank you!