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

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

- N96H in ECD1
- P927S in ECD1
- G1065D in NBD1
- E2096K in NBD2
Deletes portion of ECD1
Deletes portion of ECD1
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

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

• Hypomorphomic alleles

• Environmental factors
Limiting factors

• Small, retrospective study
• Unable to perform segregation analysis or copy number variant analysis
Thank you!