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Evaluating diagnostic challenges with *ABCA4*-related retinal disease - Experience with a 7500 IRD patient cohort sent for genetic diagnostics

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Introduction

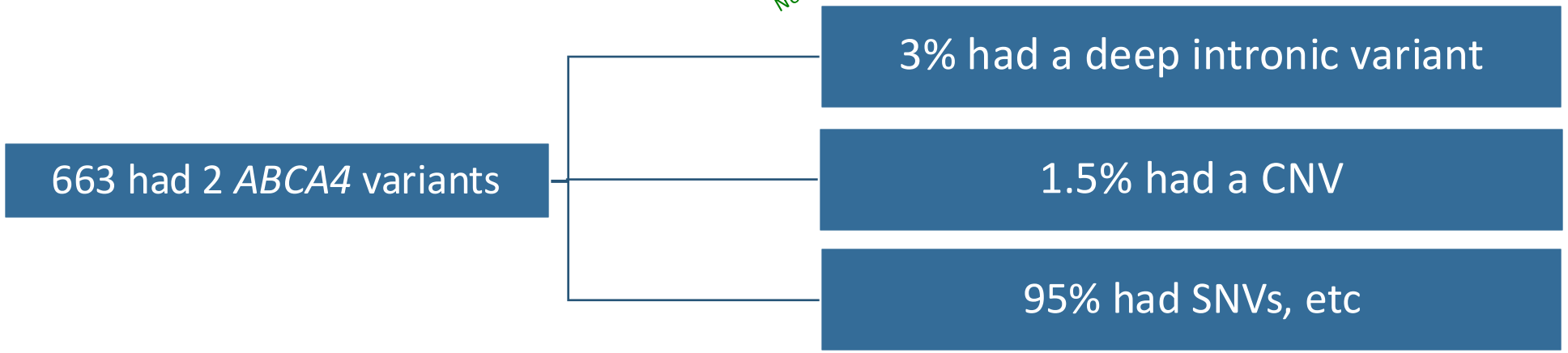
- Autosomal recessive Stargardt disease (Stargardt disease 1; STGD1) represents the most prevalent hereditary macular disease.
  - Caused by variants in *ABCA4*, which encodes a transmembrane protein expressed exclusively in retinal photoreceptors
- A proportion of clinically diagnosed STGD1 cases test positive for only one established *ABCA4* variant[1].
- Major challenges in STGD1 molecular diagnostics include:
  1. non-coding variants typically not targeted by available genetic tests
  2. copy number variants (CNV) missed by standard testing
  3. challenging interpretation of common hypomorphic variants, including *ABCA4* c.5603A>T, p.(Asn1868Ile)[2,3,4]
- We evaluated the clinical significance of challenging *ABCA4* variants and their contribution to STGD1 diagnostic yield in a cohort of inherited retinal disease (IRD) patients.

Materials and Methods

- 7500 IRD patients tested at our CLIA laboratory were included in the analysis
- Sequencing analysis was done by using an in-house developed and validated NGS platform, including:
  - established non-coding *ABCA4* variants
  - high resolution CNV detection

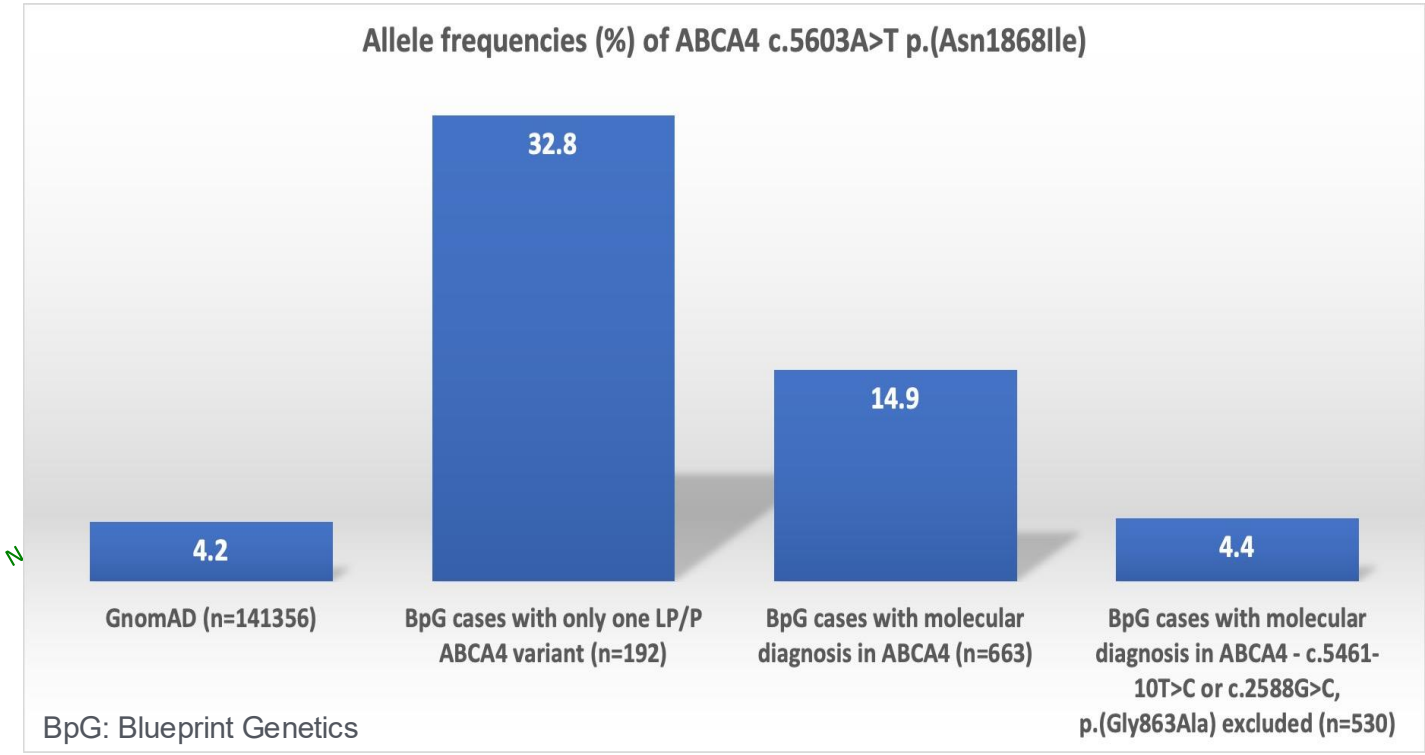
Results

- Two disease-causing *ABCA4* variants were identified in 663/7500 (8.8%) patients
- Out of the 663 patients:
  - 20/663 (3%) patients had an established disease-causing, deep-intronic variant
  - 11/663 (1.5%) patients had a CNV
    - All CNVs were deletions affecting one or more coding exons of *ABCA4*



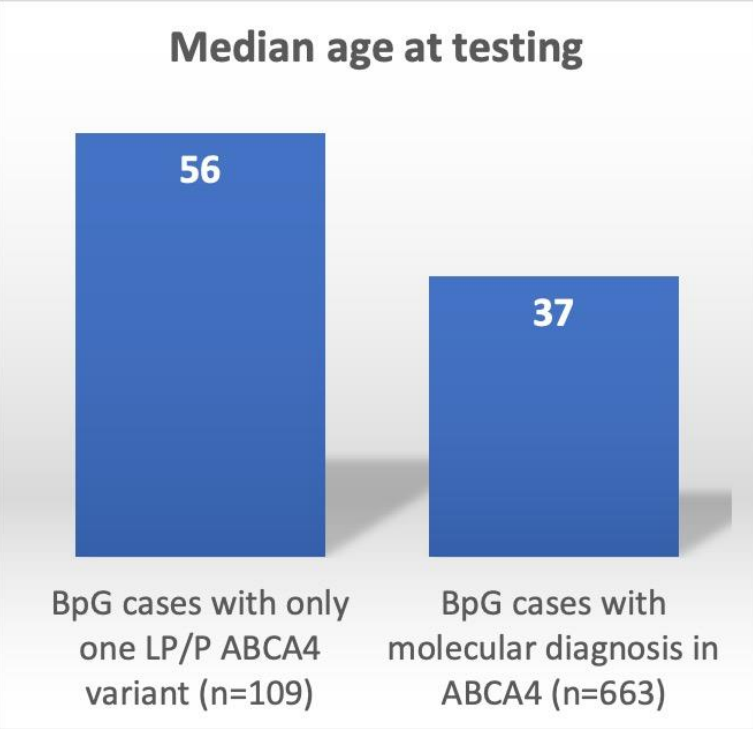
Results

- In 192 patients with clinically diagnosed *ABCA4*-related disease, only one disease-causing *ABCA4* variant was identified.
  - 109 patients (109/192: 57%) had the hypomorphic allele *ABCA4* c.5603A>T, p.(Asn1868Ile)
    - All with diagnosis of Stargardt disease, fundus flavimaculatus, macular dystrophy, or cone dystrophy
  - Significantly increased allele frequency in patients (126/384=0.328) vs. gnomAD (11928/282712=0.042) (OR: 11.087, 95% CI: 8.953–13.73, p<0.001)
- Two pathogenic variants, c.5461-10T>C and c.2588G>C, p.(Gly863Ala), occur frequently *in cis* with *ABCA4* c.5603A>T, p.(Asn1868Ile)[4]
- Complex allele may be required in order for c.2588G>C, p.(Gly863Ala) to be penetrant



Results

- The median age at genetic testing was significantly higher in 109 patients with p.(Asn1868Ile) compared to patients with two disease-causing *ABCA4* variants.



Conclusions

- Deep-intronic variants and CNVs together contribute significantly to diagnostic yield in *ABCA4*-related disease.
- Our large dataset supports the important role of the hypomorphic allele *ABCA4* c.5603A>T, p.(Asn1868Ile) in the diagnosis of late-onset STGD1.

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