Longitudinal genotype-phenotype analysis of 86 aniridia patients with molecularly confirmed PAX6 mutations

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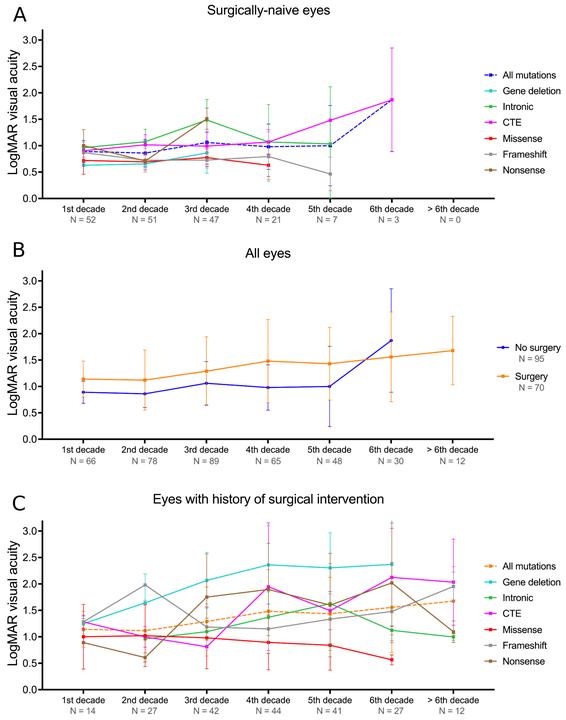
Introduction

Aniridia is most commonly caused by haploinsufficiency of the PAX6 gene, characterised by variable iris and foveal hypoplasia, nystagmus, cataracts, glaucoma and aniridia related keratopathy (ARK). It affects 1 in 40,000-100,000 individuals. Genotype-phenotype correlations have previously been described, however detailed longitudinal studies of aniridia to guide management are less commonly reported.

Method

We identified 86 patients from 62 unrelated families with molecularly confirmed heterozygous *PAX6* variants from a single-centre ocular genetics service. They were categorised into mutation groups (gene deletions, nonsense, frameshift, intronic, C-terminal extension and missense mutations) and retrospective review of baseline to their most recent clinical ocular characteristics were recorded.

Visual acuity



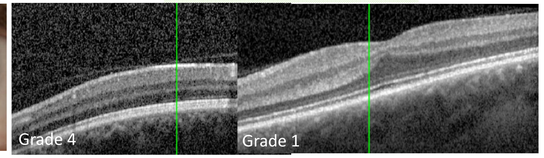
Amongst eyes which had undergone surgical intervention, only the missense group maintained a better visual acuity than the overall mean.

Iris hypoplasia



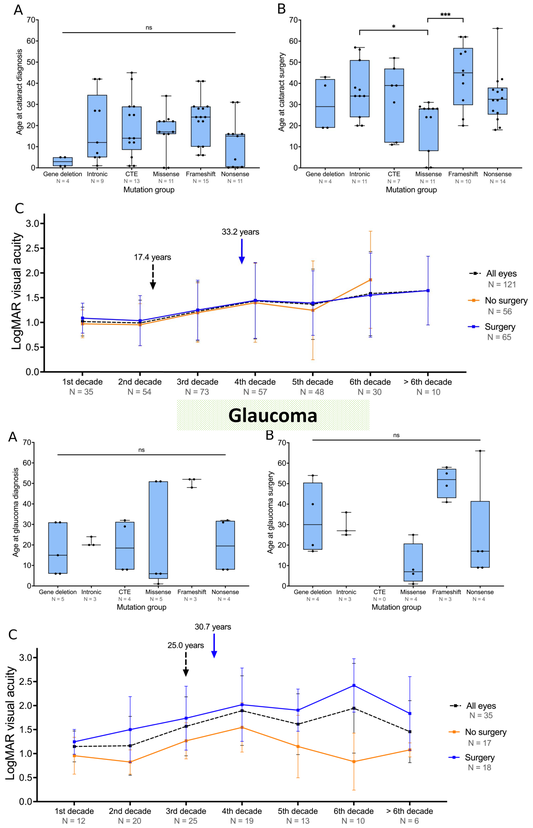
Iris hypoplasia were reported in 89.5% (154/172) eyes. Missense mutations had statistically milder grades of iris hypoplasia.

Foveal hypoplasia (FH)



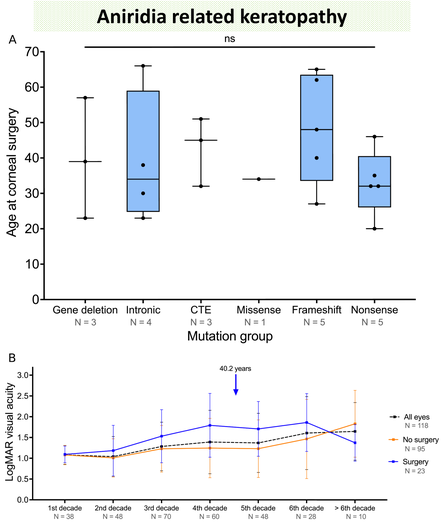
The severity of FH was significantly different between mutation groups ($p<0.001$) with the intronic and frameshift sub-groups associated with significantly more severe FH, while the missense sub-group presented milder grades.

Cataracts



Glaucoma

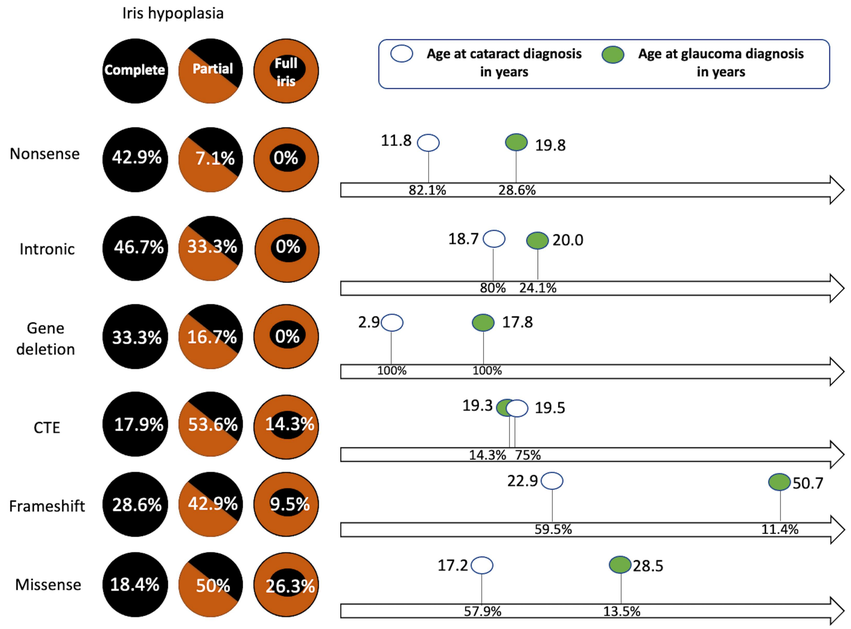
Aniridia related keratopathy



- Cataracts were diagnosed in 70.3%, glaucoma in 20.6% and ARK in 68.6% of eyes.
- Prevalence, age of diagnosis and surgical intervention varied amongst mutation groups.
- Overall, the missense mutation sub-group had the mildest phenotype, and surgically naïve eyes maintained better visual acuity.

Reference guide for age of cataract and glaucoma development relating to PAX6 variants

Unknown iris phenotype, age of glaucoma and cataract diagnosis are excluded from the reference guide



The degree of complete and partial iris hypoplasia, versus full iris structure amongst variant sub-groups are listed, but it shows no correlation with the average age at cataract and glaucoma onset based on mutation-types. Prevalence of the cataracts and glaucoma in percentages are shown within the arrow.

Conclusion

- To the best of our knowledge, this is the largest in-depth clinical description of *PAX6* genotype-phenotype correlation and natural history of aniridia in the United Kingdom to date, and the first to adopt a significant follow-up period with a mean of 16.3 years.
- The missense mutation group demonstrates better long term visual acuity, a lower prevalence of ARK, and milder iris and foveal hypoplasia grades.
- Identifying a patient's *PAX6* mutation may allow us to predict their long term visual prognosis and phenotype, and if corroborated by other studies, these provide valuable information that will facilitate both clinical management by clinicians and the definition of outcome measures for future clinical trials.