Genotypic and Phenotypic Spectrum of Foveal Hypoplasia: A Multi-centre Study by the Foveal Development Investigators Group (FDIG)

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Introduction

Foveal hypoplasia (FH) is characterised by the continuation of inner retinal layers posterior to the foveola (figure 1).[1,2] The Leicester Grading System for FH is a diagnostic and prognostic tool which divides typical FH into four grades.[1] The Leicester Grading System has been applied to various disorders including albinism, isolated FH (with or without *FRMD7* variants), *PAX6* variants, *SLC38A8* variants,[3] *AHR* variants and achromatopsia.

To date, it is unclear whether variants of certain genes are associated with worse foveal morphology and prognosis. Thus, we aimed to perform a multi-centre study with the Foveal Development Investigators Group (FDIG) (figure 4) to characterise the genotypic and phenotypic spectrum of FH.

Methods

(1) Patients (n=907) with a confirmed molecular diagnosis of albinism, *PAX6*, *SLC38A8*, *FRMD7*, *AHR* variants, or achromatopsia from FDIG sites (n=523) (figure 4) or extracted from publicly available datasets from previously reported literature (n=384) were included.

(2) Genetic diagnosis was confirmed by sequence analysis, using site-specific protocols.[4]

(3) Optical coherence tomography (OCT) of the fovea was obtained in all subjects and graded using the Leicester Grading System (figure 1)[1]

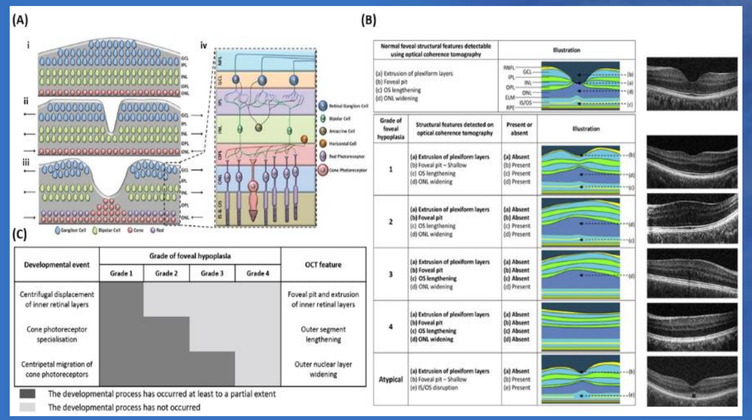


Figure 1: *(A) Schematic demonstrating the three foveal developmental stages. (B) The foveal hypoplasia grading scheme using OCT, with real foveal tomogram examples. (C) A schematic demonstrating the stage of arrested foveal development associated with the different grades of FH*

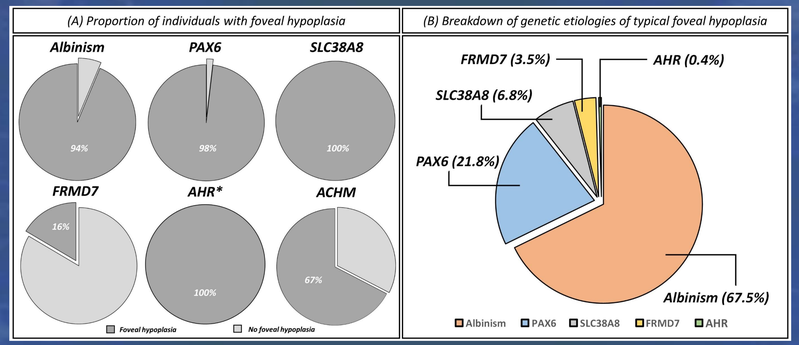


Figure 2: *(A) Proportion of individuals with foveal hypoplasia (FH) within each genetic diagnosis. (B) Breakdown of genetic etiologies causative of typical FH. ⁎Only 2 cases of AHR variants with FH were identified. ACHM = achromatopsia.*

Results

- The most common genetic etiology for typical FH in our cohort was albinism (67.5%), followed by *PAX6* (21.8%), *SLC38A8* (6.8%), and *FRMD7* (3.5%) variants (figure 2). *AHR* variants were rare (0.4%).
- There was a significant difference in the spectrum of FH grades based on the molecular diagnosis (chi-square = 60.4, P < 0.0001).
- All grades of FH were seen in albinism and *PAX6* variants (figure 3).
- In *SLC38A8* and *AHR* variants, only high grades of FH were present (grades 3 and 4) (figure 3)
- In cases of FH and *FRMD7* variants, only grade 1 FH was observed.
- Analysis of albinism subtypes revealed a significant difference in the grade of FH (chi-square = 31.4, P < 0.0001) between oculocutaneous albinism (OCA) compared with ocular albinism (OA) and Hermansky–Pudlak syndrome (HPS).

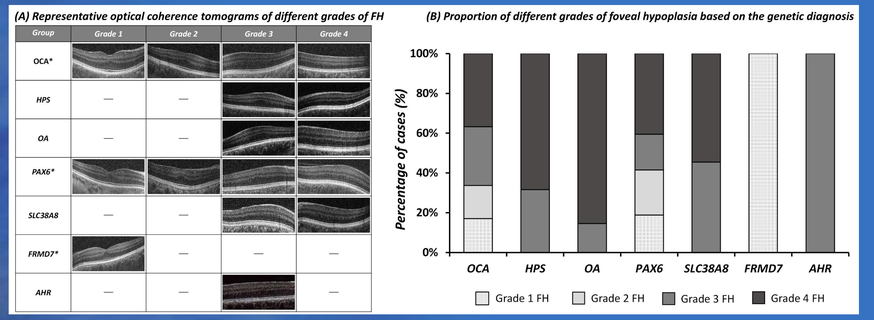


Figure 3: *(A) Representative tomograms of typical foveal hypoplasia (FH) in different genetic etiologies. (B) The relative proportions of each grade of FH within each genetic diagnosis is shown in this bar chart.*

Discussion

We characterised the phenotypic and genotypic spectrum of FH. Atypical FH is associated with a worse prognosis than all other forms of FH. In typical FH, our data suggest that arrested retinal development occurs earlier in *SLC38A8* variants, OA, HPS, and *AHR* variants and later in *FRMD7* variants. The defined time period of foveal developmental arrest for OCA and *PAX6* variants seems to demonstrate more variability. Our findings provide mechanistic insight into disorders associated with FH and have significant prognostic and diagnostic value.

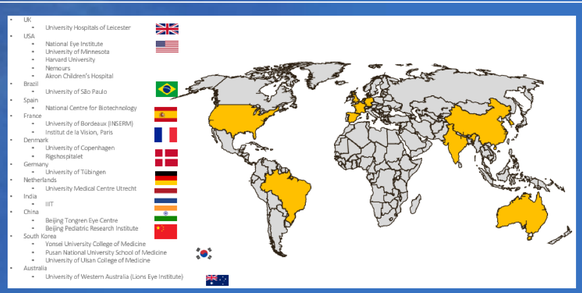


Figure 4: *The Foveal Development Investigators Group (FDIG)*

References

1. Thomas MG et al. Ophthalmology. 2011 Aug;118(8):1653-60.
2. Thomas MG et al. British Journal of Ophthalmology. 2020
3. Kuht HJ et al. Hum Mol Genet. 2020 Nov: 29(18): 2989-3002
4. Thomas MG et al.. Eur J. Hum Genet. 2017 June: 25(6): 725-734