Genotypic and phenotypic spectrum of foveal hypoplasia

M G Thomas, H J Kuht, J Han, V Sheth, G D E Maconachie, M Hisaund, R J McLean, F A Proudlock, H T Lim, I Gottlob

UNIVERSITY OF LEICESTER

SUPPORTED BY NIHR | National Institute for Health Research

FIGHT FOR SIGHT The Eye Research Charity

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 (LGS) for FH is a diagnostic and prognostic tool which divides typical FH into four grades.[1,3] LGS has been applied to various disorders including albinism, isolated FH (with or without *FRMD7* mutations), *PAX6* mutations, *SLC38A8* mutations,[4] and *AHR* mutations.

It is unclear whether mutations of certain genes are associated with worse foveal morphology and prognosis. Thus, we aimed to characterise the genotypic and phenotypic spectrum of FH.

Methods

(1) In this multi-centre study, patients with known genetic associations with FH (n=288) were identified.

(2) Genetic diagnosis was achieved using targeted panel-based sequencing or exome sequencing.[5]

(3) Optical coherence tomography of the fovea was obtained in all subjects and graded using the LGS.

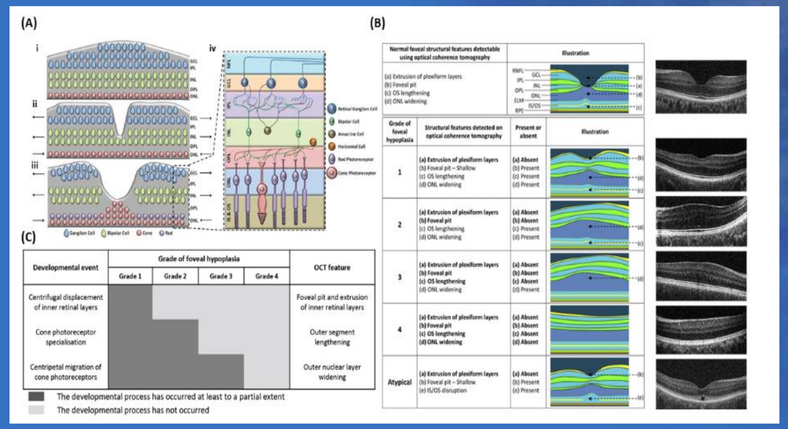


Figure 1: *(A) Schematic demonstrating the three foveal developmental stages. (B) The foveal hypoplasia grading scheme using OCT, with real foveal tomogram examples. (C) A schematic demonstrating the stage of arrested foveal development associated with the different grades of FH*

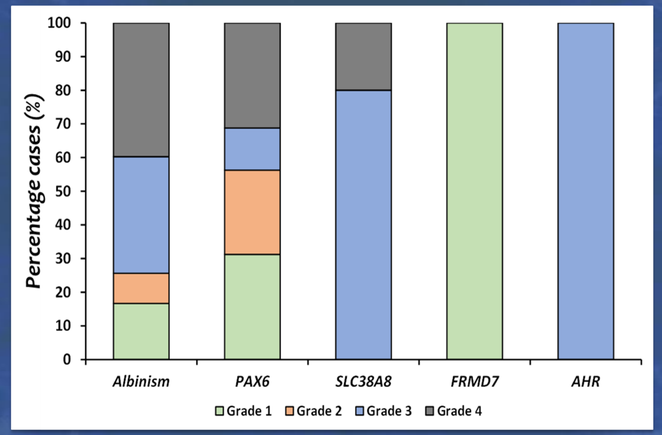


Figure 2: *A stacked bar chart representing the spectrum of foveal hypoplasia grades associated with each diagnostic group (as an accumulative percentage)*

Results

- The most common genetic aetiology for typical FH was albinism (74%), followed by *PAX6* mutations (15%) and *SLC38A8* mutations (9%).
- *AHR* and *FRMD7* mutations were rare causes of FH.
- All grades of FH were seen in albinism and *PAX6* mutations.
- In *SLC38A8* mutations, we only observe grade 3 (80%) and grade 4 (20%) FH.
- In *AHR* mutations only grade 3 FH has been reported.
- In cases of FH and *FRMD7* mutations only grade 1 FH was observed.

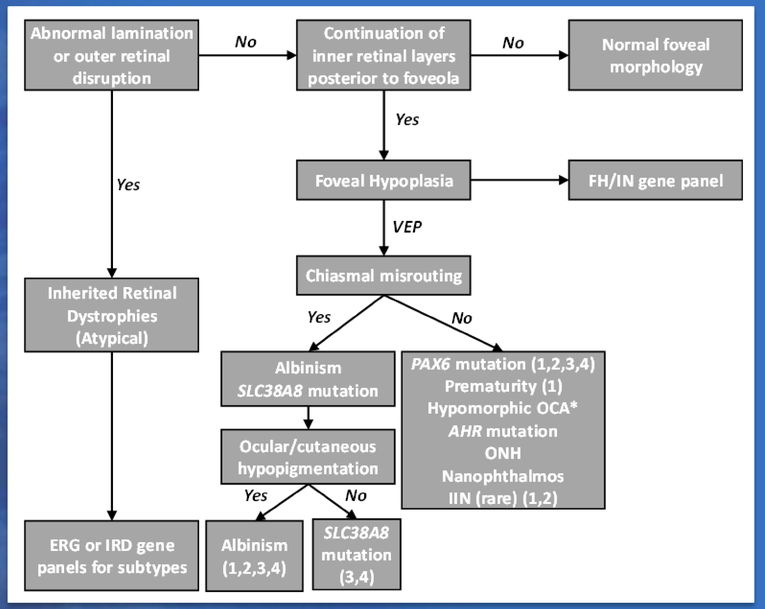


Figure 3: *Clinical diagnostic algorithm for abnormal retinal development.[2,4]*

Discussion

Albinism and *PAX6* mutations are associated with much wider spectrum of arrested retinal development, however *SLC38A8* mutations, *AHR* mutations and *FRMD7* mutations have much narrower spectrum.

Our data suggests that arrested retinal development occurs earlier in development in *SLC38A8* and *AHR* mutations and much later in *FRMD7* mutations. However, with albinism and PAX6 mutations the defined time period of foveal developmental arrest is more variable.

References

1. Thomas MG et al. Ophthalmology. 2011 Aug;118(8):1653-60.
2. Thomas MG et al. British Journal of Ophthalmology. 2020 (ahead of print)
3. Rufai SR et al. Ophthalmology. 2020 April: 127(4): 492-500
4. Kuht HJ et al. Hum Mol Genet. 2020 Nov: 29(18): 2989-3002
5. Thomas MG et al.. Eur J. Hum Genet. 2017 June: 25(6): 725-734