

## The Emerging Ophthalmic Phenotype of XXYY Syndrome

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### Abstract

48 XXYY is a sex chromosome tetrasomy condition which causes tall stature, hypergonadotrophic hypogonadism, facial dysmorphism, developmental delay and behavioural difficulties.

Over 100 cases have been published in the literature but there is little information on the ophthalmic findings in these patients. Previously reported ophthalmic findings have included Duane anomaly, high myopia and retinal dysfunction. We report a case of 48, XXYY syndrome in a child who presented with developmental delay. He was referred to Ophthalmology with a squint and on detailed examination was found to be hyperopic; with an unusual pigmented fundal appearance he had a normal electroretinogram and normal visual evoked potentials.

**Keywords:** XXYY syndrome; Ophthalmic phenotype

### Introduction

48 XXYY is a sex chromosome tetrasomy condition which causes tall stature, hypergonadotrophic hypogonadism, facial dysmorphism, developmental delay and behavioural difficulties.

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### Patients and Methods

The proband was a 6 years and 3 month old boy, who was referred to Clinical Genetics following an abnormal CGH-array result. Full antenatal and neonatal history were taken from the parents. Clinical examination was performed, and then he was referred to the Ophthalmology and Paediatric Endocrinology services for ocular examination and discussion about future hormone replacement therapy.

Ophthalmic examination including visual acuity testing (logMAR), refraction, orthoptic assessment, electrodiagnostic investigations and Heidelberg optical coherence tomography (OCT) was performed.

### Results

His antenatal and neonatal course was unremarkable. He was born at 40 weeks gestation with a birth weight of 2.8 kg. He suffered with intermittent gastroesophageal reflux which improved without intervention.

Gross motor milestones were within normal range. He sat unsupported at 6 months, crawled at 9 months and walked unaided at 15 months of age. There was limited babble in infancy and at 6 years of age; he was unable to speak in sentences. He had normal hearing. His behaviour was temperamental with emotional lability, outbursts of aggression and poor attention. He attended a mainstream school and received 15 hours per week of statemented education. He had multiple carious teeth requiring dental extraction.



**Figure 1:** A pictures of the patient's face showing mild hypertelorism and up-slanting palpebral fissures.

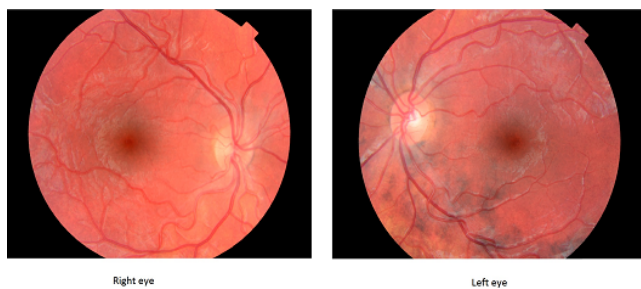
On clinical examination: the patient weighed 21.6 kg (25-50<sup>th</sup> centile), his height was 111 cm (2-9<sup>th</sup> centile) and his occipitofrontal circumference (OFC) was 53 cm (25-50<sup>th</sup> centile).

During the consultation, he made limited eye contact. He had mild hypertelorism, mildly upslanting palpebral fissures and inferior epicanthic folds (Figure 1). He had 5<sup>th</sup> finger clinodactyly bilaterally but no other limb abnormalities (Figure 2).

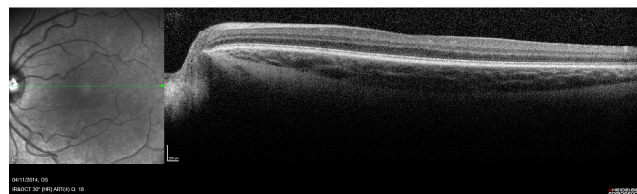


**Figure 2:** A picture of the patient's hands of demonstrating bilateral 5<sup>th</sup> finger clinodactyly.

The proband was seen by Ophthalmology services for the first time at 6 years and 6 months of age. He had had reduced visual acuity of 0.9 logmar right eye and 0.75 logmar left eye. Refraction revealed hyperopia for which he was prescribed glasses. Orthoptic assessment revealed a small angle esotropia. Visual acuity with glasses correction improved to 0.150 logmar right eye and 0.275 logmar left eye. The esotropia is being monitored, however the patient may require eye patching in the future. The electrodiagnostic investigations demonstrated normal cone and rod flash electroretinograms (ERG) and normal occipital pattern visual-evoked potentials (VEP). Interestingly, the left fundus had deep pigmented patches which were flat resembling subretinal hyperpigmentation. (Figure 3) Heidelberg OCT showed normal looking retinal and pigment epithelial (RPE) layers, indicating that the hyperpigmentation lies at the level of the choroid (Figure 4).



**Figure 3:** Patient's fundal photographs showing deep pigmented patches.



**Figure 4:** Heidelberg EDI OCT Image of Left Macula showing no RPE thickening with normal looking retinal layers.

## Discussion

48, XYY syndrome is a rare sex chromosome tetrasomy characterised by the presence of an extra X and an extra Y chromosome in a male. The incidence is estimated to be around 1:18,000-50,000 male births [1]. There are now around 100 cases reported in the literature. The majority of cases of 48, XYY are thought to occur as a random event when an aneuploid sperm (produced through two consecutive non-disjunction events in meiosis I and II) fertilises a normal female oocyte [1,2].

The syndrome was initially thought to represent part of the Klinefelter spectrum as there are many physical similarities between the two: tall stature, sparse body hair, gynaecomastia and hypergonadotrophic hypogonadism. However, 48 XYY patients tend to have greater intellectual disability, facial dysmorphism, congenital malformations and behavioural problems including autistic spectrum disorders, ADHD, mood and tic disorders [1,2].

The majority of case reports do not mention any ophthalmic features, however two case reports have been published recently describing patients with associated eye findings. Weis et al. described a patient with Duane anomaly. Although most cases of Duane anomaly are thought to be sporadic, an increased incidence is associated with chromosome duplication [3]. Karampelas et al. described an adult with a high myopia and night blindness. Pattern ERG and VEPs were undetectable in this patient bilaterally indicative of generalised retinal and macular dysfunction [4].

The case presented here had hyperopia, amblyopia and pigmented fundi with normal electrodiagnostic investigations thus demonstrating a unique ophthalmic phenotype in 48, XYY. We propose that all patients with this diagnosis are referred to ophthalmic services for a detailed review and electrodiagnostic investigations as the ophthalmic findings appear to be highly variable in this group of patients.

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