

**Title: Vitamin A deficiency - there's more to it than meets the eye.**

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## **Vitamin A deficiency - there's more to it than meets the eye.**

### **Abstract**

Vitamin A deficiency (VAD) is the leading cause of preventable blindness in children worldwide and results in a well-recognised ocular phenotype. Herein we describe a patient presenting to the eye clinic with a retinal dystrophy and ocular colobomata. This combination of clinical signs, and consanguineous pedigree structure suggested a genetic basis for the disease, a hypothesis which was tested using whole genome sequencing. Bi-allelic mutations in *RBP4* were identified (c.248+1G>A), consistent with a diagnosis of inherited vitamin A deficiency. We describe a constellation of clinical signs that should in future allow this diagnosis to be made using a less expensive and more rapid investigation: serum retinol level.

### **Key Words**

Vitamin A deficiency

Serum Retinol Level

Microphthalmia

Whole Genome Sequencing

Iris Coloboma

## **Introduction**

Vitamin A deficiency (VAD) is the leading cause of preventable blindness in children worldwide and results in a well-recognised ocular phenotype. Its primary cause is inadequate dietary intake and is a public health problem in over half of the world. In developed countries it results from either malabsorption or poor vitamin A metabolism due to liver disease. Herein we report a patient presenting to the eye clinic without typical features of VAD, and describe the investigations that were necessary to make a diagnosis.

## **Case Report**

An Iranian lady from a consanguineous family presented with a history of left microphthalmia, bilateral iris and retinal colobomata and lifelong poor night vision.

She described progressive visual loss resulting in only perception of light vision by the age of 20 years. Her left microphthalmic eye had been enucleated in childhood and she now wears a prosthetic shell. When we examined her aged 25, the cornea and conjunctiva were normal and did not show the typical stigmata of VAD, including corneal clouding due to epithelial disease (xerophthalmia) or white, foamy conjunctival plaques (Bitot's spots). In addition to the colobomata, the optic nerve was pale, and the retinal arterioles attenuated, suggesting widespread retinopathy that was confirmed by functional testing (Figure 1). The macula was atrophic and photoreceptor structure could not be identified using high-resolution imaging (Figure 2). She also had multiple scleroses and malar skin pustules. In view of this

constellation of signs, and the prevalence of monogenic recessive disease in consanguineous families, a unifying molecular genetics diagnosis was sought. Whole genome sequencing was performed as part of a national collaborative project. [1] After bioinformatic processing, a previously unreported homozygous splice site mutation in *RBP4* (NM006744) (c.248+1G>A) was identified, predicted to abolish the canonical splice donor site of intron 3. *RBP4* encodes retinol binding protein 4, which is synthesised in the liver and responsible for transporting vitamin A to target organs. The patient's serum vitamin A levels were therefore assayed and found to be undetectable, despite a healthy diet.

### **Discussion**

Bi-allelic mutations in *RBP4* have only been reported twice before and are thus a poorly recognised cause of disease [2,3]. Our patient and the published cases appear to share a distinctive phenotype comprising of a severe rod-cone dystrophy with ocular colobomata. Skin disease and additional autoimmune conditions may also coexist. [2,3] Together these features may facilitate early diagnosis and therapy in other patients.

Vitamin A is an essential nutrient found mostly in animal products as retinyl esters, and in fruits and vegetables in the form of carotenoids (vitamin A precursors). Vitamin A and its derivatives regulate a range of essential biological processes both during embryogenesis, including closure of the optic fissure important for coloboma formation, and adulthood, producing the visual chromophore necessary for sight and maintaining epithelial cell health. Vitamin A also has an immunomodulatory role. It is likely therefore that the *RBP4* dysfunction identified in our patient has wider non-ocular implications. Her overlooked skin condition may be responsive to topical retinoid therapy and low serum retinol levels may impact her MS and benefit from correction. [4] One quarter of our Vitamin A is transported unbound to *RBP4*, and consequently has a short half-life due to renal excretion. Small regular meals rich in vitamin A would provide some compensation for this. There are also implications for family planning as foetal development

would be compromised, also now modifiable in light of the genetic diagnosis.

**Declaration of Interest**

None.

## **References**

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## **Figure Legends**

Figure 1. Colour fundus photograph of the right retina showing the posterior component of a large inferior chorioretinal coloboma, central retinal atrophy, pale and atrophic optic nerve and attenuated retinal arterioles.

Figure 2. (A) Near infrared en-face image of the patient's retina showing optical coherence tomography (OCT) line scan position through the macula, (B) Macular OCT scan with absence of lines in the outer retina localising damage to the photoreceptor layer (C) normal macular OCT scan and (D) histological section (from a donor eye) for comparison.