Understanding the implications of defective colour vision is an integral part of the day-to-day role for many eye care practitioners. This first article in a series of three explores the foundation for normal colour vision and the underlying factors that determine congenital and acquired defects.

**Course code: C-34398 | Deadline: January 10, 2014**

### Learning objectives

**General Optical Council**

To be able to explain to patients about the implications of colour vision defects (Group 1.2.4)

To appreciate the genetic significance of colour vision defects (Group 3.1.4)

To recognise the significance of acquired colour vision defects with respect to systemic disease and ocular abnormalities (Group 6.1.13)

### Learning objectives

**General Optical Council**

To be able to explain to patients about the implications of colour vision defects (Group 1.2.4)

To understand the classification of colour vision defects (Group 3.1.4)

To understand the link between acquired colour vision defects and ocular abnormalities (Group 8.1.2)

**About the author**

Jennifer Birch was formerly a senior lecturer in Clinical Optometry at City University London. She is now a senior research fellow in the Henry Wellcome Research Laboratory in the Department of Optometry. She was a founder member of the International Research Group on Colour Vision Deficiencies and has written extensively on clinical aspects of defective colour deficiency and on occupational colour vision requirements. She was appointed to an Honorary Life Fellowship of the College of Optometrists in 2012.
Introduction
Congenital red-green colour vision deficiency is the most common X-linked inherited abnormality in the population and affects about 8% of men and 0.4% of women.1 Congenital tritan deficiency is rare and is inherited as an autosomal dominant trait. The characteristics of normal trichromatic vision and different types of congenital deficiency were established in the first half of the twentieth century. Developments in molecular genetic analysis have provided remarkable insight into the underlying mechanisms.5,6 The central mosaic can also be visualised using adaptive optics and the identity of individual cones determined with selective chromatic bleaching (retinal densitometry).7

Normal colour vision
Trichromacy, in accordance with the Young-Helmholtz theory, is present at the receptor level and opponent processing, as proposed by Hering, is established in the inner retina. Opponency is maintained in the visual pathway but spatial organisation changes at different levels.

Trichromatic vision, often described inappropriately as ‘red’, ‘green’ and ‘blue’, is derived from three cone classes which contain photopigment with relatively long (L), medium (M) and short (S) wavelength spectral sensitivity. The L and M cones have peak sensitivity in the yellow-green part of the spectrum, at about 560nm and 530nm, respectively, and have overlapping spectral sensitivities; S cones have peak sensitivity in the spectral violet at about 420nm (see Figure 1). Colour vision is dichromatic for wavelengths greater than 540nm. Short wavelength sensitivity reduces progressively after about 55 years of age due to physiological changes in lens density.

Normal cone photopigments
Genes that specify L and M photopigments are positioned in a tandem head-to-tail array at Xq28. The two genes evolved about 35 million years ago from duplication of an ancestral mid-wavelength photopigment gene that was similar to the L gene.4 The amino acid sequences have 96% identity. The opsin sequences have 364 amino acids divided into six exons separated by five ‘neutral’ segments or introns. Seven sites distributed between exons two, three, four and five, are in close proximity to the chromophore and collectively change the peak wavelength sensitivity of the M photopigment by about 30nm (exons two, three and four). A shift of about 17nm is produced at two sites on exon five. The shifts produced at other sites are relatively small. Polymorphism at site 180 on exon 3 of the L gene has a frequency of 40% and produces a marginal improvement in long wavelength sensitivity.

The array at Xq28 is headed by a locus control region (LCR) that regulates gene expression. The L gene is always first in the array and an M gene second. Proximity to the LCR is advantageous and there are usually more L cones than M cones that are randomly distributed in the cone mosaic. The mean L:M ratio is 2:1 but can vary between 1:1 and 1:9 without affecting hue discrimination ability (see Figure 2).7 About 25% of men have two genes at Xq28, 50% have an additional M gene and 25% have several more M-like chimeras, or gene fragments in the array. Only the first two genes are expressed.

Congenital colour deficiency
There are three classes of deficiency with differences in severity. Types of deficiency...
contrast (see Figure 3).

Protan deficiency is characterised by a shift in relative luminous efficiency from 555nm to about 535nm and by reduced sensitivity to long wavelengths (shortening of the red end of the spectrum). S cones comprise about 7% of cells in the central mosaic and ‘small field tritanopia’ occurs for objects subtending less than half a degree.⁸

**Red-Green deficiency**

All types of red-green deficiency are caused by loss of a photopigment gene needed for normal trichromacy.⁷ L and M genes are highly homologous and cross-over events readily occur during meiosis when paternal and maternal X chromosomes exchange part of their material. If the genes are misaligned, one chromosome may lose a gene and the other gain one (intergenic crossover). If the break occurs in an intron, complete exon sequences are exchanged and recombine to form a chimera consisting of conjoined sections of the normal L and M genes (intragenic crossover).⁷ An L/M chimera consists of exons derived from the L gene joined to exons from the lower

**Table 1** Prevalence of congenital colour deficiency types classified according to the number of colour matching variables needed to obtain all the spectral hues

<table>
<thead>
<tr>
<th>Type of colour deficiency</th>
<th>Classification from colour matching variables</th>
<th>Prevalence</th>
<th>Class</th>
<th>Denomination</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protan</td>
<td>Dichromat</td>
<td>1%</td>
<td>Men</td>
<td>Protanopia</td>
<td></td>
<td>0.01%</td>
</tr>
<tr>
<td></td>
<td>Protanomalous trichromat</td>
<td>1%</td>
<td>Women</td>
<td>Severe deficiency</td>
<td></td>
<td>0.03%</td>
</tr>
<tr>
<td></td>
<td>Anomalous trichromat</td>
<td>5%</td>
<td>Men</td>
<td>Deuteranopia</td>
<td></td>
<td>0.35%</td>
</tr>
<tr>
<td></td>
<td>Deuteranomalous trichromat</td>
<td>5%</td>
<td>Women</td>
<td>Severe deficiency</td>
<td></td>
<td>0.35%</td>
</tr>
<tr>
<td></td>
<td>Abnormal trichromat</td>
<td>5%</td>
<td>Women</td>
<td>Incomplete Tritanopia</td>
<td></td>
<td>0.35%</td>
</tr>
<tr>
<td></td>
<td>Abnormal trichromat</td>
<td>5%</td>
<td>Men</td>
<td>Tritanopia</td>
<td></td>
<td>0.35%</td>
</tr>
<tr>
<td></td>
<td>Abnormal trichromat</td>
<td>5%</td>
<td>Women</td>
<td>Incomplete Tritanopia</td>
<td></td>
<td>0.35%</td>
</tr>
</tbody>
</table>

All people with colour deficiencies see fewer separate hues in the environment and confuse colours that are easily distinguished by normal trichromats (see Table 2). Colour confusions are specified in isochromatic zones in the reference system approved by the Commission Internationale d’Eclairage (CIE) in 1931. Colours with X, Y chromaticity co-ordinates within an isochromatic zone are confused if there is no perceived luminance
portion of the M gene and codes an M-like photopigment because the major wavelength tuning sites are derived from exon 5 of the M gene (see page 49). Similarly M/L chimeras have exons from the M gene joined to lower exons from the L gene and code L-like photopigments. Other structural changes are produced from a series of cross over events and result in a wide range of photopigments with peak wavelength sensitivities between 560nm and 530nm.

Different genotypes produce the same phenotype. Most dichromats have a single gene in the array. Protanopes have a normal M gene, whereas deuteranopes have a normal L gene. The foveal mosaic is complete and all cones have the same photopigment. A minority of dichromats has two identical genes at the head of the array or two genes that code photopigments with the minimal peak wavelength separation of 3–4nm.11

Some dichromats appear to have two normal genes but a mutation at site 203 on exon four, is present in one gene. In this case large gaps are seen in the foveal mosaic and microscotomas can be detected. Visual acuity is not affected although 30% of the receptors may be lost.11 Deuteranopes with this genotype may have a normal M gene third in the array that is not expressed.

Most protanomalous trichromats have two L/M chimeras. It is less common to have a single L/M chimera followed by a normal M gene. Similarly, deuteranomalous trichromats have either two M/L chimeras or a normal L gene followed by an M/L chimera. Severity of deficiency varies according to the peak wavelengths of the photopigments and loss of hue discrimination ability is inversely proportional to the peak wavelength separation. Clusters of L/M photopigments have peak sensitivity within 8nm of the normal M photopigment, whereas M/L photopigments cluster within 12nm of the normal L photopigment. These pairings produce slight colour deficiency but protanomalous trichromats have a 40% reduction in hue discrimination ability compared with a 30% reduction in deuteranomalous trichromatism.

<table>
<thead>
<tr>
<th>Typical confusions in Red-Green deficiency</th>
<th>Protan</th>
<th>Deutan</th>
<th>Typical confusions in Tritan deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Green-Yellow / Yellow / Yellow-Red</td>
<td>*</td>
<td>*</td>
<td>Green / Blue-Green</td>
</tr>
<tr>
<td>Green / Orange (Amber) / Red</td>
<td>*</td>
<td>*</td>
<td>Purple / Red</td>
</tr>
<tr>
<td>Brown / Green</td>
<td>*</td>
<td>*</td>
<td>Yellow / White</td>
</tr>
<tr>
<td>Red-Purple / GREY / Blue-Green*</td>
<td>*</td>
<td>*</td>
<td>Violet / GREY / Yellow-Green*</td>
</tr>
<tr>
<td>Blue-Purple / GREY / Green*</td>
<td></td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Red / Black</td>
<td>*</td>
<td></td>
<td>Navy-Blue / Black</td>
</tr>
<tr>
<td>Green / Black</td>
<td></td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Threshold Red / White discrimination</td>
<td>*</td>
<td>*</td>
<td>Threshold Blue / White Discrimination</td>
</tr>
<tr>
<td>Threshold Green / White discrimination</td>
<td>*</td>
<td>*</td>
<td></td>
</tr>
</tbody>
</table>

Table 2 Typical colour confusions in protan, deutan and tritan congenital colour deficiency.

*Neutral or complementary colours
Red-Green deficiency in women

Women inherit two sets of genetic characteristics on paired X chromosomes and random inactivation (suppression) occurs at an early stage of development so that either the maternal or paternal gene is expressed in an individual cell (Lyonisation). Approximately 50% of women inherit genes for subtypes of the normal L photopigment and post mortem analysis shows that both photopigments are expressed in the cone mosaic. A further 12% of women are heterozygous for a gene that produces anomalous trichromatism in men. Some women, therefore, have the potential for tetrachromatic vision if the visual pathway has the capacity to transmit and preserve information from four spectrally distinct cone types, although there is no evidence for this. On the contrary, psychophysical measurements show that most heterozygous women have poorer red-green discrimination than normal trichromatic men suggesting that information from a fourth photopigment creates 'noise' that degrades chromatic signals in opponent pathways.

Tritan deficiency

The gene which specifies the S photopigment is located at 7q 31-32. The S opsin has 348 amino acids and has about 45% identity with X chromosome opsins. Single mutations at three separate sites produce tritan deficiency in different families – prevalence is about 0.02%.

Phenotypical variations are characteristic of autosomal inheritance and some family members are tritanopes while others are incomplete tritanopes that express some S photopigment. There is no mechanism for changing peak wavelength sensitivity and the term ‘tritanomalous trichromatism’ is misleading. Mature expression of inherited prevalence is about one in 100,000. Some hue discrimination is possible in mesopic illumination when S cones and rods are active. Visual acuity is often about 6/18 with a relative central scotoma, moderate photophobia and low-grade nystagmus; the foveal mosaic is irregular and reduced in density. Inheritance is X-linked with about 60% of cases caused by the mis-sense mutation at site 302 of exon 4, in both genes. An abnormality at the LCR at Xq28 that prevents all gene expression is found in 40% of cases. Some patients develop slowly progressive macular degeneration and visual acuity declines with age.

Acquired deficiency

Abnormal colour vision can be associated with disease or injury to any part of the visual pathway, from the retina to the cortex. Poor visual acuity and/or visual field defects are present and monocular differences in severity are common. Colour vision is very poor if macular oedema is present. Loss of hue discrimination is usually progressive. Colour vision remains abnormal following episodes of central serous chorio-retainopathy or retrobulbar neuritis and after successful treatment for wet AMD, even if visual acuity has recovered (see Figure 4).

Monochromatism (inherited achromatopsia)

Monochromats cannot distinguish wavelength differences in photopic illumination and are able to match all the spectral hues using a single variable. Typical, ‘complete’ or ‘rod’ monochromats are found to have structurally abnormal cones within a disrupted foveal mosaic. Visual acuity is typically 6/36 – 6/60 in these individuals, with an absolute central scotoma, severe photophobia and nystagmus. Inheritance is autosomal recessive and consanguinity is a predisposing factor – prevalence is about one in 35,000. Single miss-sense mutations, on either chromosome 1, 2, 8 or 14, which prevent transcription of key enzymes in the cone transduction pathway, have been identified in different families.

Atypical, ‘incomplete’ or ‘blue cone’ monochromats (BCM) have S cones only -
Loss of short wavelength discrimination is found in the early stages of diabetic retinopathy, due to loss of S cones, but both R/G and B/Y thresholds are raised as the disease progresses.

Raised R/G thresholds are found in the early stages of glaucoma and both R/G and B/Y thresholds are raised symmetrically in later stages of the disease — similar results are obtained in AMD.

Lesions in the visual pathway result in abnormal colour vision in specific quadrants of the visual field or hemianopic loss of colour perception. Cortical injury causes additional sensory deficits, including colour agnosia (the inability to remember colour names), coloured hallucinations (phosphenes), photopsia, migrainous ‘fortification spectra’ or episodes of chromatopsia in which the environment appears suffused in a single colour. Cortical centres dedicated to the perception of red, yellow, green and blue have been identified using functional magnetic resonance imaging and localised damage may result in the loss of perception of a single colour.