

Short Communication

HETEROCHROMIA IRIDIS - A CASE STUDY

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ABSTRACT: Eye color in human range from the darkest shades of brown to the lightest tints of blue. It is a polygenic phenotypic character, controlled by multiple genes and is determined by the pigmentation of iris of the eye and the frequency- dependence of the scattering of light by the turbid medium in the stroma of the iris. Eye color is an instance of structural color and the appearance of lighter-colored eyes also results from the Rayleigh scattering of light in the stroma. An instance of heterochromia iridis of one girl is reported in this paper, where one eye is light blue with brown spots/ stripes and the other eye is brown. The family history of the girl reveals that none of the members either from the paternal or maternal side are affected and the probable reasons behind such a condition has been explained.

Key words: Heterochromia iridis, Polygenic, Case study.

Eye colour variation ranging from darkest shades of brown to lightest tints of blue has long been a subject of interest but somehow eye colour genetics remained a neglected field. In recent times it has experienced a peak of interest in the scientific community. Heterochromia iridis is a condition in which the iris of one eye has a colour different from that of the other eye or the coloured part of the iris of an eye is composed of different coloured patches (Gladstone 1969). Inheritance of eye colour was previously simply explained by 'Mendelian Theory' but with the development of eye colour genetics it was discovered that eye colour in

human being is controlled by at least 16 genes (White and Smith 2011) and how they together control the development of eye colour is a complex process.

A girl is reported to have iris of one eye brown in color while the other one is blue with a few patches of brown. Interestingly, when her family history was traced it was observed that no other family member in the previous six generations either from her paternal side or from her maternal side was showing this kind of heterochromia.

In this context, the central issue of this paper is to re-investigate the different factors that may

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be responsible for heterochromia iridis and the probable cause of heterochromia iridis in the observed child.

Different eye colors in human

Anatomically the iris is composed of two layers of different embryological origin. The anterior layer is the iris stroma, which is derived from the mesoderm and consists of a loose collagenous network, which contains the sphincter pupillae muscle, blood vessels, nerves, and cellular elements, including fibroblasts, melanocytes, clump cells, and mast cells. The anterior border layer is a condensation of connective tissue of the anterior stroma and contains numerous pigment cells. The posterior pigment epithelium forms the posterior layer and is neuroectodermal in origin. The posterior pigment epithelium is derived from the anterior portion of the optic cup. It consists of two layers of cuboidal pigment cells, which are tightly joined to each other by numerous intercellular junctions (Bron *et al.*, 1997, Imesch *et al.*, 1997).

There are four main factors, which determine iris colour *viz.*, i) the pigment granules within the posterior pigment epithelium, ii) the concentration of pigment within the iris stromal melanocytes, iii) the nature of melanin pigment within the iris melanocytes, and iv) the light-scattering and absorption properties of the extracellular stromal matrix (Wilkerson *et al.*, 1996; Prota *et al.*, 1998).

Martin-Schultz (http://en.wikipedia.org/wiki/Martin-Schultz_scale) established a chart by the original Martin Scale according to which the eye color in human can be of various types. The eye color varies in different human populations according to their origin ranging from the darkest shades of brown which appears

to be almost black to the lightest shades of blue or green. Amber is an eye color that has a strong yellowish/golden and russet/coppery tint which may be due to the deposition of yellow pigment called lipochrome in the iris (which is also found in green eyes). Blue eyes have brownish black iris pigment epithelium due to the presence of melanin (Menon *et al.*, 1987) but it appears bluish because of the low concentration of melanin in the stroma of the iris, which lies in front of the dark epithelium. Longer wavelengths of light tend to be absorbed by the dark underlying epithelium, while shorter wavelengths are reflected and undergo Rayleigh scattering in the turbid medium of the stroma resulting in the blue eye coloration (Wang *et al.*, 2005). Brown eyes in humans result from a relatively high concentration of melanin in the stroma of the iris, which causes light of both shorter and longer wavelengths to be absorbed. Green eyes in humans results from a combination of an amber or light brown pigmentation of the stroma due to low or moderate concentration of melanin with the blue tone imparted by the Rayleigh scattering of the reflected light. Gray, hazel, red and violet are some other colors of the human eyes which are found in some individuals though not very frequent.

Heterochromia iridis

Heterochromia iridis (heterochromia – difference in color, iridium – within the iris of one eye) is a condition in which the iris, the colored part of the eye, is composed of different colored patches or segments, or when the iris of one eye is a different color than the iris of the other eye (Imesch *et al.*, 1997). The appearance of different coloration between the two eyes is usually the only symptom or sign

but sometimes it is found to be associated with other abnormalities of the eye or other parts of the body (Rehman 2008). Sometimes the difference in the colour of the two eyes is so slight that it is only noticed under certain lighting conditions or in close-up photographs.

The people with heterochromia iridis have an excellent prognosis and usually do not have any visual complaints. In patients, who do have associated visual problems, the treatment of underlying abnormality is often successful in removing the visual problem.

Heterochromia is a condition which can be classified on the basis of the onset, as either congenital or genetic and acquired. Congenital heterochromia is usually inherited as an autosomal dominant trait. Acquired heterochromia is usually due to injury, inflammation, the use of certain eye drops that damages the iris (Liu 1999) or tumors.

Case study

A girl, aged about 16 years (residing at Paschim Medinipur district of West Bengal), is having brown-colored right iris and blue-colored left iris with brown patches/stripes from centre to margin (Fig.1). This is a case of heterochromia iridis. The girl was born with heterochromia as was observed by her parents soon after her birth. There is no depigmentation in any part of her skin or hair. She is neither suffering from hearing impairment nor is there any neural disorder which is sometimes observed in persons having heterochromia iridis. There are no other problems like inflammation or tumours associated with her eyes. She is having good eyesight and has not suffered from any serious disease since her birth and is maintaining good health condition till date.

Interestingly no other member in her family is having blue eyes or having heterochromia iridis. Both of her parents are having brown eyes and pedigree analysis of six generations showed that she is the lone member in her family having such kind of heterochromia.

Segregation of blue-brown eye color was previously described using Mendelian dominant-recessive gene concept, where brown eye color behaved as a simple dominant trait to the recessive blue but that was too simplistic and is also not applicable in cases like the one explained here as no other person in the family in the last six generations, either from paternal or maternal side has shown neither the blue eye color or heterochromia. Genetics of eye color has long been a somewhat neglected field by both genetics and pigmentation communities but in recent time it has experienced a peak of interest in the scientific community. A new molecular genetic perspective is needed to fully understand the biological complexities of this process as a polygenic trait.

Heterochromia iridis can either be congenital or may be acquired later during the life time due to certain diseases or injuries. It may be familial and is inherited as an autosomal dominant trait. Environmental or acquired factors can alter these inherited traits. Congenital heterochromia may also occur due to intrauterine disease or injury which may occur when the child develop within the mother's womb.

Different congenital syndromes like Waardenburg syndrome, Horner's syndrome, Sturge-Weber syndrome, Recklinghausen disease, Bourneville disease, Hirschsprung disease, Block-Sulzberger syndrome may be characterized by heterochromia iridis. Some of the common symptoms associated with most



Fig.1: Heterochromia iridis : A – Studied girl (inset face).

of these diseased conditions include changes in colour of the skin, hair, eyes, hearing loss and problems in the nervous system (Rehman *et al.*, 2008).

Acquired heterochromia iridis is a condition which may develop due to an eye disease, injury, inflammation, the use of certain eyedrops that damages the iris (Liu 1999) or tumours.

The two main genes associated with eye colour variation are OCA2 and HERC2 and both are localized in chromosome 15 in human. Different single nucleotide polymorphism or SNPs within OCA2 are strongly associated with variation in eye colour. Polymorphism in OCA2 regulatory sequence that influence the expression of the gene product may sometime affect pigmentation (Duffy *et al.*, 2007). HERC2 gene regulates OCA2 expression. A

specific mutation within the HERC2 gene is partially responsible for blue eyes (Kayser *et al.*, 2008).

Single nucleotide polymorphisms (SNPs) within the pigmentation related genes, mainly OCA2 were identified that significantly was associated with eye colour (Frudakis *et al.*, 2003). The transcript encoded by the OCA2 locus is divided into 24 coding exons covering approximately 345kb (Lee *et al.*, 1995). The gene encodes a 838 amino acid open reading frame producing a 110kD protein that contains 12 transmembrane spanning regions. Screening of the eye colour SNPs in the intergenic region upstream of OCA2 and HERC2 gene revealed that a single SNP in intron 86 of the HERC2 gene, rs1291383 T/C predicted eye colour significantly (Sturm *et al.*, 2009). Genetic

association tests revealed that the rs12913832 T/C base change within intron 86 of the HERC2 gene, 21.1kb upstream of the first exon of the OCA2 gene may account for blue-brown eye colour (Eiberg *et al.*, 2008). When active, the rs12913832*T allele allows HTLF recognition and chromatin unwinding thus exposing additional regulatory sequences such as MITF and LEF1 that lead to OC2 expression. The OC2 protein then acts in the maturation pathway of the melanosome to produce a fully pigmented brown iris. rs12913832*C allele leads to abrogation of HTLF binding, thus the chromatin remains closed and unavailable for transcription of the OCA2 locus and selective loss of OCA2 production in the melanocytes of the iris results in the blue colouration of the iris (Gardner *et al.*, 2005).

In the present case, Mendelian dominant-recessive gene inheritance cannot explain heterochromia. The different SNPs as explained above may be responsible for her eye color difference. In her case, an early viral infection or injury while in the womb which was not detected could also have turned the eye color gene on or off in just one eye. A molecular genetic perspective can thus explain the cause behind such a sudden appearance of heterochromia in a child having no other family member affected but this can only be confirmed by the application of biotechnology and advanced molecular genetic studies.

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