Cat Eye Syndrome

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Introduction

We have chosen a rare but interesting syndrome to discuss. It highlights the ability of recent molecular techniques, such as fluorescent *in-situ* hybridisation (FISH), to diagnose many genetic anomalies *in utero*, and thereby provide valuable information in advance for both the parents and the medical team.

History

An infant female with a birth weight of 6lbs 5oz (in the 10th centile for her gestational age) and a head circumference of 35cm (in the 50th centile for her gestational age) was born to non-consanguineous parents. A lower section caesarian delivery was performed at term following rupture of membranes and failed induction. Apgar scores were 9 at 1min, 10 at 5 min. Clinical examination of the neonate revealed bilateral preauricular skin tags and pits, down sloping right palpebral fissure, anal atresia and bilateral fixed talipes equinovarus (Figure 1). Of note, she displayed no other dysmorphic features and her ophthalmic examination was normal. Echocardiography revealed a small atrial septal defect (ostium secundum), and ultrasound of kidneys and bladder was normal.

At ten days post partum, six anal dilation procedures had been performed to treat her anal atresia. She had gained 1.5lbs and was being fed 50ml of expressed breast milk every three hours by nasogastric tube. She was receiving daily physiotherapy for her talipes equinovarus.

On review of her family history, the mother stated that she also had anal atresia and bilateral preauricular skin tags at birth. These were subsequently surgically corrected. The father and two older siblings are normal. The mother neither smoked nor drank during pregnancy. She was immune to Rubella and there was no Rhesus incompatibility.

Diagnosis

Routine antenatal ultrasound screening during the second trimester revealed intrauterine growth retardation for gestational age and bilateral fixed talipes equinovarus. Amniocentesis was performed at 28 weeks and samples were sent for chromosomal analysis.

Analysis of the chromosomes by FISH revealed Cat Eye Syndrome (CES)[1]. This early diagnosis enabled prenatal counselling of the parents and alerted both the medical team and the parents to possible complications associated with this syndrome.

Although CES was initially defined as the combination of an additional chromosome with coloboma (Figure 2 & Table 1) and anal atresia as primary features, it became evident from several patients that neither anal atresia nor coloboma were obligatory findings[2]. The characteristic clinical features (Table 2) are helpful, but the diagnosis nowadays is based on the presence of an extra chromosome marker. FISH examination revealed that the extra chromosome marker is derived from chromosome 22 and contains two copies of the critical CES region in the proximal 22q11.

Fluorescent In-Situ Hybridisation

The hybridisation step consists of simply mixing single strand probes with the target DNA in aqueous solution. Denaturing of the target DNA is achieved by heating, thus allowing access of the single strand probes to their complementary combed single strand DNA. The probe has modified nucleotide sites, which possess a biotin molecule, to which fluorescent streptavidin molecules spontaneously bind. Anti-avidin antibodies also with a fluorescent marker and a biotin arm, then recognize and bind these molecules. Layers of alternating streptavidin and biotin/anti-avidin antibodies, all with associated fluorescent sites are created, thus amplifying the fluorescent signal (Figure 3)[3].

Genetics

Cat Eye Syndrome is an extremely rare chromosomal disorder[5]. There are no estimates on the incidence of the marker, a 2-Mb region of chromosome 22q11.2[6]. In observing CES patients in northeastern Switzerland during the last twenty years, an incidence of between 1:50,000 and 1:150,000 seems a reasonable estimate[6]. In CES

Table 1: Common causes of coloboma of the iris[1]

◆Cat Eye syndrome	◆Trisomy 13
◆Trisomy 18	◆Marfan's syndrome
◆Sturge-Weber disease	◆Basal cell nevus syndrome
◆Rubenstein-Taybi syndrome	

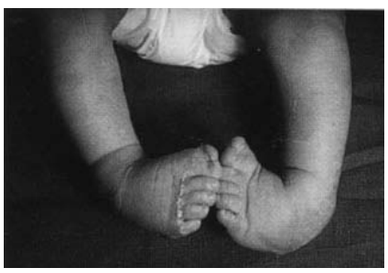


Figure 1 (far left): Talipes equinovarus

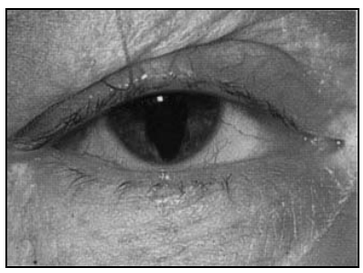


Figure 2 (left): Coloboma (cat eye)

Table 2: Cat eye syndrome major features[4]

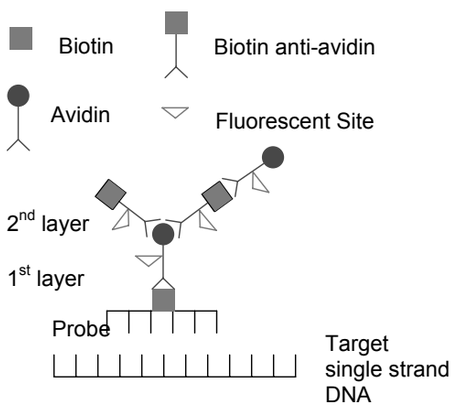
Head & Neck	Micrognathia and retrognathia
Ears	Preauricular skin tags or fistulae, prominent anthelices, hypoplastic ear lobes, and atresia of auditory canals.
Eyes	Coloboma, hypertelorism, downslanting palpebral fissures, and occasional micropthalmia.
Nose	Broad and depressed nasal bridge and minimal epicanthal folds.
Cardiovascular System	Anomalous pulmonary venous return, tetralogy of Fallot, ventricular septal defect, persistence of left superior vena cava, absence of the inferior vena cava, tricuspid atresia.
Gastrointestinal System	Anal atresia and mobile caecum.
Urogenital System	Kidney hypoplasia or aplasia, bladder fistula, and hydronephrosis.
Growth and Development	Mild to moderate mental retardation and growth retardation.
Behaviour and Performance	Mild conductive deafness.

patients, the short arm (p) and a small portion of the long arm (q) of chromosome 22 (critical region being 22pter – 22q11.2) are present three (trisomy) or four (tetrasomy) times rather than twice in cells of the body[4].

CES is usually the result of a *de novo* genetic mutation with an unknown aetiology. A particular feature of familial CES cases as opposed to acquired cases is the frequent occurrence of mosaicism; a condition in which two or more genetically different populations of cells exist in the same person. Mosaicism results from early loss of the chromosome marker during post-zygotic divisions, and is occasionally transmitted through several generations. Therefore Mendelian factors may be important in its causation. The mild presentation of the mother at birth, in the case presented above may indicate mosaicism.

There is no available information on the recurrence risk for siblings of a CES patient. However, because mosaicism may produce a normal phenotype, chromosomal examination of both parents is indicated after the birth of an affected child. Even if a chromosome study indicates a non-mosaic diploid karyotype, a hidden, including germline mosaicism cannot be fully excluded, and a small risk of recurrence will remain. Luleci *et al.* concluded that for offspring of an affected individual who does not appear to have reduced fertility, the risk of recurrence would approximate 50%[7].

Figure 3: Indirect biotin-avidin fluorescent *in-situ* hybridisation technique



Using exon trapping and genomic sequence analysis, Riazi *et al.* at The Hospital for Sick Children in Toronto Canada, have isolated and characterised a gene, CECR-1, that maps to 22q11.2, the critical chromosomal region in CES[8]. CECR-1 is alternatively spliced and expressed in numerous tissues, primarily expressed in human adult heart, lung, lymphoblasts and placenta as well as foetal lung, liver, and kidney. FISH examination of a human embryo shows specific expression of CECR-1 in the outflow tract and atrium of the developing heart, the ganglia of cranial nerves VII and VIII, and the notochord. The location of the CECR-1 gene in the CES critical region, and its embryonic expression suggest that the over-expression of the CECR-1 gene may be responsible for at least some of the features of CES, particularly the heart defects.

McTaggart *et al*. from the University of Alberta, Canada, have found that the duplication breakpoints are clustered in two intervals[9]. The more proximal to the centromere, and most common duplication breakpoint interval, is a 450-650 Kb region which corresponds to the proximal deletion breakpoint interval in the 22q11 deletion syndrome, DiGeorge Syndrome (DGS). The more distal duplication breakpoint interval overlaps with the common distal deletion interval of DGS. DGS and the velo-

cardiofacial syndrome are the most common syndromes associated with 22q11 rearrangements[10]. McTaggart *et al.* have therefore classified CES chromosomes into two types based on the location of the two breakpoints required to generate them[9]. The smaller type 1 CES chromosomes are symmetrical, with both breakpoints located within the proximal interval, and the large type 2 chromosomes are either asymmetrical, with one breakpoint located in each of the two intervals, or symmetrical, with both breakpoints located in the distal interval. The colocalisation of the breakpoints of these different syndromes, in addition to the presence of repeats adjacent to each interval, suggests the existence of several specific regions of chromosomal instability in 22q11.2, which are involved in the production of both deletions and duplications. Since the phenotype associated with the larger duplication does not appear to be more severe than that of the smaller duplication, determination of the type of CES chromosome does not presently have any prognostic value.

Summary

Genetic disorders are common, with 2% of live born infants having a significant congenital malformation and approximately 5% having a genetic disorder[11]. Current research in CES is focusing on the use of DNA sequence dosage analysis in determining whether or not a person can be a carrier for the disease without expressing the phenotypes. New techniques in molecular biology have resulted in a surge in the amount of knowledge gained about these diseases. Antenatal diagnosis is possible for an ever-widening range of disorders. Genetic information underlies the development of every individual, and application of genetic advances means that both parents and doctors have valuable information at a very early stage as to how the child will develop and what complications to expect.

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