

# Focus



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## Retinoblastoma for Life

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### Case Study

Tracey (Fig 1) lost both her eyes as a small child but being a determined character never let this stand in her way. She attended mainstream education and went on to Exeter University to study sociology but didn't complete the course for support reasons. She worked for Barclays for 17 years in customer services. She later worked for the Cornwall Blind Society and the Childhood Eye Cancer Trust, helping others affected by retinoblastoma (Rb) and offering encouragement. Tracey knew she had had Rb as a child and knew about the risks of getting other cancers later in life. Her parents looked for any changes in her skin or unexplained lumps as she grew up. When Tracey was 38, she developed a bad cough, went to her GP and was given antibiotics which didn't help. She then was prescribed inhalers, which she used for four months without improvement. It was only when she saw a different doctor, who knew the implications of having had Rb as a child that Tracey was sent for a chest x-ray. This showed extensive lung cancer and further examination revealed tumours in her liver and pelvis. She underwent chemotherapy but sadly, she died 6 months later in January 2007.

### Life long implications of retinoblastoma

It is well known that retinoblastoma is the most common intraocular cancer to affect children. Unfortunately a subset of patients may be at risk of cancer throughout their lives; many years after their initial presentation with retinoblastoma. Individuals with genetic retinoblastoma are at risk of non-ocular tumours in addition to the heritable nature of their condition. Anecdotal reports demonstrate that some adults who were treated as a child (often by enucleation or radiation) are not aware of the nature of their condition and have been lost to follow-up. They may however present to their local ophthalmologists with ocular and /or orbital problems and it is therefore essential that ophthalmologists

are aware of the long term systemic problems associated with Rb as they may be the only secondary care physician that sees the patient.



Figure 1 - Tracey (courtesy of her husband)

### Genetic Retinoblastoma

The RB1 gene is a cancer predisposition gene. Patients with a germline mutation including deletion of part or the whole of the RB1 gene are classified as having the heritable or genetic form of Rb. In addition to their risk of developing Rb, they also have an increased risk of developing certain other non-ocular cancers.

Whereas bilateral disease is always associated with a

germline mutation and the associated non-ocular cancer and genetic risks, it is important to be aware that approximately 15% of adults who had unilateral disease as children could potentially be at risk.

### Development of other tumours in adulthood

Everybody in the western world has a lifetime risk of approximately 1 in 3 of developing cancer. Patients with an abnormal RB1 gene reach this risk by the age of about 50 years of age.

The non-ocular cancers which have been shown to have an increased incidence in young adult patients with an abnormal RB1 gene include bone and soft tissues sarcomas during adolescence and early adulthood, malignant melanoma and epithelial cancers particularly lung (as illustrated in the case study), bladder, oesophagus and probably breast. There is a well recognised association between external beam radiation therapy in infancy and tumours within the radiation field.

The identification of patients with an abnormal RB1 gene is important, not only for counselling with regard to the risk of Rb in their offspring, but also with regard to their own increased risk of developing a non-ocular cancer in early adulthood. Emphasising the need to avoid known carcinogenic factors such as smoking, radiation, obesity and excess UV light is particularly important. As radiation is associated with an increased risk of cancers, routine X-rays and CT scans are not advised.

All patients with a past history of Rb should be offered molecular genetic analysis of their DNA so that the patients with the heritable form of Rb, and therefore at risk of second non-ocular cancers, can be identified and appropriately counselled. This is particularly important for the patients with unilateral disease who may carry a mutation of the RB1 gene and are unaware of this fact.

### Molecular Genetic Testing

Molecular and clinical genetic input should be seen as an integral part of the management of all patients with retinoblastoma.

#### Bilateral Cases

Familial and bilateral cases have an earlier age of diagnosis to unilateral cases (mean age 8 months compared to 25 months). Examination of epidemiological data led Knudson (1) 3 to postulate the two hit hypothesis of tumour development. This was subsequently confirmed when the retinoblastoma gene was cloned by Friend et al 1986 (2). Germline RB1 mutations are detectable in >85% of these cases and many of these can be proven to be de-novo. In the remaining 15% of patients without an identifiable mutation, linkage studies exclude the risk in siblings and/or offspring will be informative in up to 25 to 50% of cases. Therefore, the majority (>80%) of first degree relatives can be excluded from conventional surveillance.

#### Unilateral Cases

Sequential molecular analysis of tumour and blood DNA in unilateral cases confirmed that approximately 15% of these cases are heritable mutations and that many of the remainder (>80% of cases) have two identifiable mutations confined to the tumour and absent in the blood. Hence these are likely to be somatic mutations not present in the affected individuals with a low risk of transmission to offspring. Furthermore, the risk to siblings should be that of

the population. In these cases surveillance of siblings will not be necessary.

In addition to the obvious psychological and medical benefit to families from molecular investigations, a significant financial saving to may result (3).

### Risk of Rb to other family members

Retinoblastoma is inherited as an autosomal dominant trait and children of patients with genetic Rb have a 50% chance of inheriting the affected gene. If genetic testing is not performed or refused, empirical data (Table 1) shows that first degree relatives have a significant risk of retinoblastoma in childhood (>1%) and should be having regular clinic follow up and /or examinations under anaesthetic. The risk to other relatives increases if there is family history of cancer.

### Conclusions

Although retinoblastoma is a rare condition, it is essential that all patients who suffer from this condition are aware of advances in molecular genetic tests and the risk to their lives of initially minor complaints. From 2008 to 2010, the Childhood Eye Cancer Trust is funding a project to identify those at risk of having the heritable form of Rb and bringing those who should be followed up back into the system. Further molecular investigations will be undertaken as necessary. Increased vigilance amongst ophthalmologists will be of great benefit to these patients.

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**Table 1: Empiric risk data for relatives of isolated case of retinoblastoma (modified from Musaella et al (4) and Hodgson (5))**

Nature of Retinoblastoma in proband	Relationship to Proband	Likelihood of being a gene carrier	Likelihood of developing a retinoblastoma
Bilateral	Offspring	50%	45%
Bilateral	Sibling	5%	2.7%
Bilateral	Offspring unaffected sibling	0.5%	0.27%
Bilateral	First cousin	0.05%	0.027%
Unilateral	Offspring	7.5%	5.7%
Unilateral	Sibling	0.8%	0.4%
Unilateral	Offspring unaffected	0.08%	0.04%
Unilateral	First cousin	0.008%	0.004%§

\*The risk of developing a retinoblastoma was calculated assuming a 90% penetrance in gene carriers which is probably an underestimate  
§ 0.005% is considered the general population risk so first cousins of probands with unilateral Rb are not considered at risk.

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