PRIMEVIEW

RETINOBLASTOMA

nature REVIEWS DISEASE PRIMERS

Retinoblastoma is a rare tumour of the eye that develops in infants or young children. The disease is characterized by inactivation of the *RB1* gene in almost all patients.

EPIDEMIOLOGY

Retinoblastoma is diagnosed in ~8,000 children each year worldwide. Retinoblastoma is a curable disease and high-income countries have a patient survival rate of >95%. However, global survival is only ~30% owing to health-care access barriers and socio-economic issues that lead to poor compliance, including family refusal to remove the affected eye. International collaborations have been initiated between patients, parents, support groups and medical care givers to improve outcomes by increasing awareness, developing guidelines and sharing expertise. An important online initiative is the 'One Retinoblastoma World', which directs families to the nearest treatment centre.

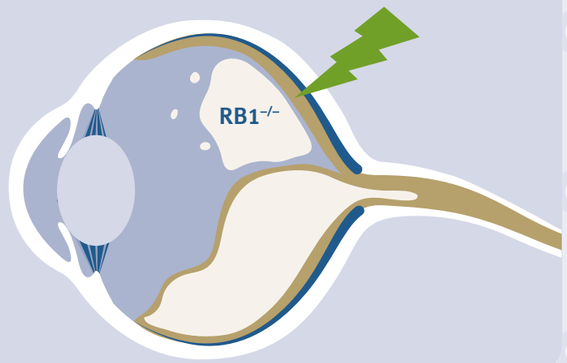
DIAGNOSIS

Genetic testing of *RB1* mutations can inform prenatal and follow-up strategies for children at risk — such as those with a family history of the disease or one affected eye

Detailed examinations under general anaesthesia are required to confirm the diagnosis and to classify severity. Histological examination of the affected eye after enucleation is the only way to evaluate high-risk features, such as tumour invasion beyond the confines of the eye.

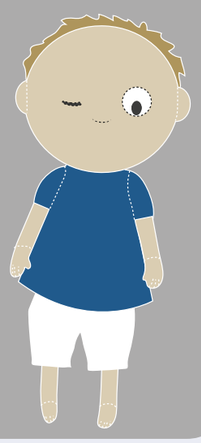
MECHANISMS

Retinoblastoma development involves biallelic inactivation of the *RB1* gene in one cell in the retina, either owing to a germline mutation and one additional somatic hit in heritable disease, or two somatic mutations in sporadic disease. Loss of the tumour suppressor function of the retinoblastoma protein, pRB, leads to uncontrolled cell division and genomic instability. However, additional mutations are required to develop malignant retinoblastoma tumours. A small subset of tumours (<2%) are not caused by *RB1* inactivation, but are the consequence of amplification of *MYNC*. Although pRB is ubiquitously expressed, the retina is especially sensitive to pRB loss; the mechanism remains to be elucidated.



MANAGEMENT

Treatment of retinoblastoma depends on disease severity and often involves removal of the affected eye (enucleation) followed by implantation of a prosthesis. Other options for less-severe tumours or to salvage the only remaining eye include focal therapy (cryotherapy or laser therapy) alone or in combination with intravenous or intra-arterial chemotherapy. External beam radiotherapy is not recommended owing to radiation hazards.



OUTLOOK

Retinoblastoma can be successfully treated when diagnosed early. A global survival rate of 100% could be achieved in the next 10 years, but international collaboration is essential. Uniform classification criteria that allow comparison between different studies and treatment centres are needed, and every death associated with retinoblastoma should be documented using these criteria. The evidence base for clinical management is weak and rigorous randomized clinical trials are needed to confirm the efficacy and safety of promising treatments. Finally, unravelling the molecular mechanism underlying retinoblastoma development will hopefully lead to better, targeted therapies.

QUALITY OF LIFE

Retinoblastoma often requires enucleation of at least one eye. Fortunately, the remaining eye at least partially compensates if binocular vision is lost early in life. The recurrent investigations under anaesthesia that are essential to track progression are associated with impaired neurocognitive development. Finally, the lifelong increased risk of developing other cancers, either due to the historical use of radiotherapy or *RB1*$^{+/-}$ genetic status, is a major concern and substantially impacts patients' lives.

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