**Final Report (As written by Dr C McConville):** Finding the best treatment for retinoblastoma presents some unique challenges. The first challenge is not just to cure the cancer but also to try to preserve sight - avoiding enucleation if possible. A second challenge is the development of a 'personalised medicine' approach to therapy.

Not all retinoblastomas are the same and selection of the optimal treatment for each patient should take into account not just the clinical and pathological features of the cancer but also, perhaps more importantly, the genetic characteristics.

Mutation of the RB1 gene is necessary, but not sufficient for the development of retinoblastoma in isolation. Relatively little is known about other genetic abnormalities which contribute to development of the cancer, and which also determine how it will behave (e.g. propensity for optic nerve invasion). The aim of our CHECT research project was to investigate high grade retinoblastomas (i.e. those which are often enucleated) from 20 different patients in order to determine the extent of genetic variability among these retinoblastomas, to identify the genetic pathways involved and to determine if these are correlated with clinical characteristics.

Our results showed very clearly that not all retinoblastomas clinically classified as high grade (Group D or E), are the same at the genetic level. Most retinoblastomas fell into one of two main groups (Figure 1). Group 2 retinoblastomas had some genetic similarities to cone photoreceptor cells (for a description of retinal cell types see <http://webvision.med.utah.edu/book/part-i-foundations/simple-anatomy-of-the-retina/> ). In contrast group 1 retinoblastomas did not clearly resemble any specific retinal cell type but may be derived from a progenitor-type cell (slightly more progressed than a stem cell) which has not yet developed a specific identity or function in the retina. Significantly, the frequency of optic nerve or choroid invasion was more frequent in patients with Group 1 retinoblastomas suggesting that these may represent a more aggressive cancer type. Group 2 retinoblastomas on the other hand may be less aggressive and patients with these retinoblastoma may benefit from more conservative treatment.

This research is a first step towards the development of customised treatment for retinoblastoma patients and we are currently working further towards this goal, through analysis of the genetics of a much larger number of patients, and by investigation of genes specific to Group 1 retinoblastomas, which could potentially be targeted using novel therapeutic agents.