# Molecular characterization of retinomas and their role in retinoblastoma pathogenesis

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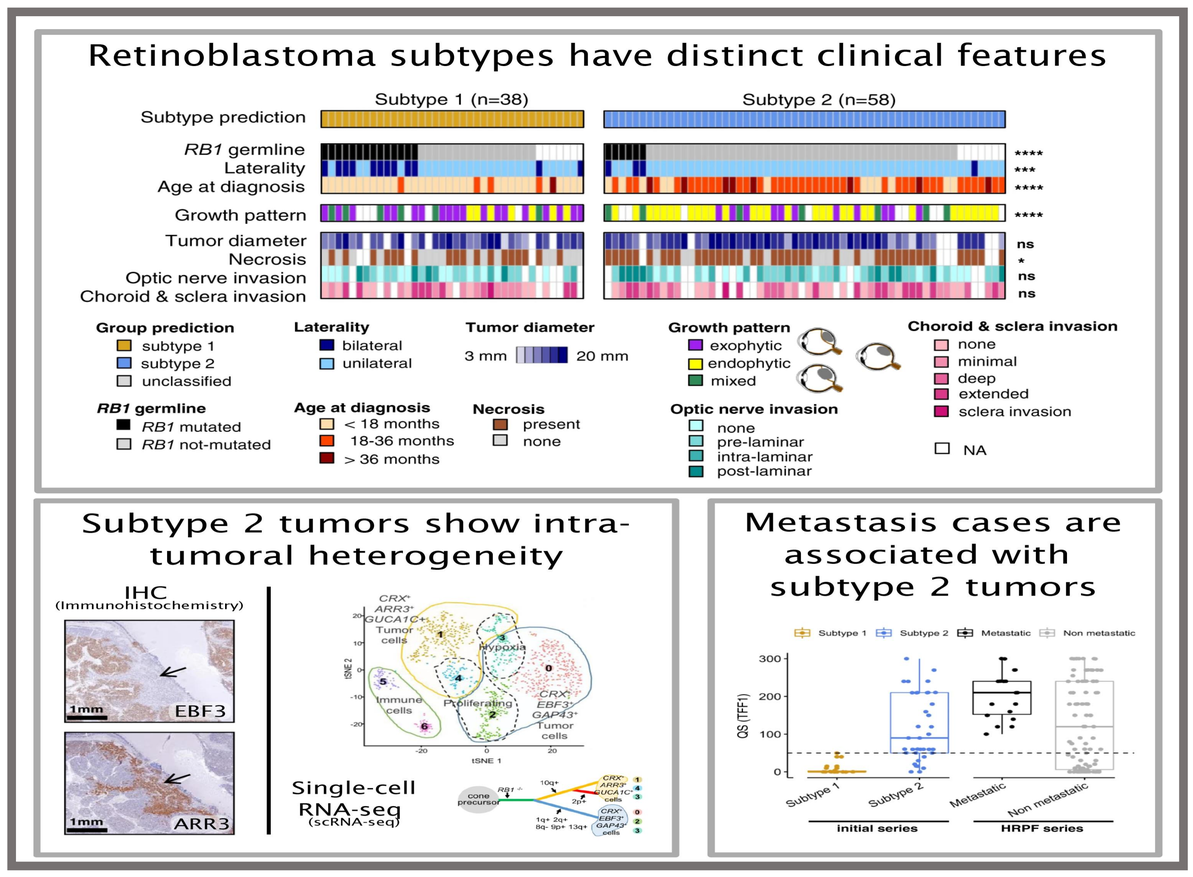
## Abstract

**Retinoblastoma is a tumor arising in the developing retina** and is the most common intraocular malignancy afflicting children. Despite a good prognosis, current treatments induce side effects and still 30% of the patients have their eye removed surgically. Using multi-omics data, we demonstrated the existence of two distinct retinoblastoma subtypes. Subtype 1, of earlier onset, includes most of the heritable forms. It has few genetic alterations other than the initiating RB1 inactivation and corresponds to differentiated tumors expressing more mature cone markers. By contrast, subtype 2 tumors have frequent recurrent genetic alterations, including MYCN-amplification. They express markers of less differentiated cone together with neuronal/ganglion cell markers intra-tumor heterogeneity. **Retinoma,** also known as retinocytoma, is a benign, non-proliferative lesion of the retina. It can accompany retinoblastomas or occur alone in patients with germline *RB1* mutations. These tumors are poorly studied for multiple reasons.

A better understanding of retinoma will lead to a better understanding of the pathogenesis of these tumors and hopefully lead to more precise diagnostic tools, efficient therapies and thus avoiding invasive and toxic treatments.




## Background

### *About retinoblastoma*

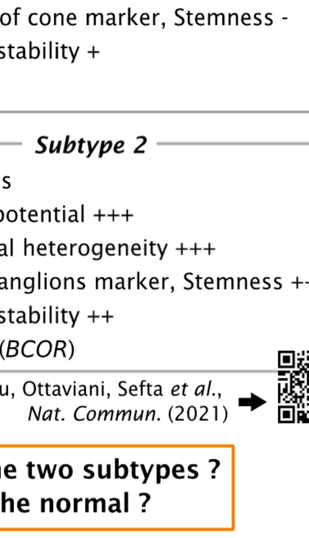
- Rare childhood cancer of the developing retina
  - 1 per 18000 childbirths
  - Institut Curie: French referral center
- A curable cancer if diagnosed early...
  - In high-income countries: ≈100% survival
  - In low-income countries: 30% survival
- ... but invasive treatments
  - Enucleation (≈ 30%)
  - Conservative chemotherapies: Side effects

### *About retinocytoma*

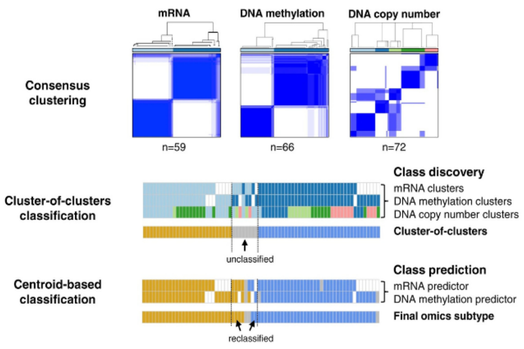
- Benign counterpart of retinoblastoma :
  - seen in 2 % of people with a mutant *RB1* allele
  - seen in 15-20% of surgeries done for retinoblastoma
- Understudied tumor for multiple reasons :
  - very rare tumor (1 per 1000000)
  - underdiagnosed
  - most tumors are not biopsied

### *Molecular alterations*

*RB1* loss initiates most of retinoblastoma but it is not sufficient to make it malignant; additional molecular alterations are necessary.




## Two subtypes retinoblastoma identified with multi-omic data




Retinoblastoma subtypes are identified by the integration of three omics data (transcriptome, methylome and copy-number). A total of 102 retinoblastomas were studied, including 72 tumors with at least two of the three omic approaches. Two classifers were built (from transcriptome or methylation of 9 CpGs) to classify the other samples. These subtypes have distinct clinical and molecular features.

**Distinct clinical and molecular features:**

### *Subtype 1*

- < 18 months
- Metastatic potential +
- Intra-tumoral heterogeneity -
- Expression of cone marker, Stemness -
- Genomic instability +
- Mutation -

### *Subtype 2*

- > 18 months
- Metastatic potential +++
- Intra-tumoral heterogeneity +++
- Neuronal/ganglions marker, Stemness +++
- Genomic instability ++
- Mutation + (*BCOR*)

Liu, Ottaviani, Sefta *et al.*, *Nat. Commun.* (2021)

**Understand the origins of the differences between the two subtypes ? Between tumor subpopulations ? Comparison the normal ?**

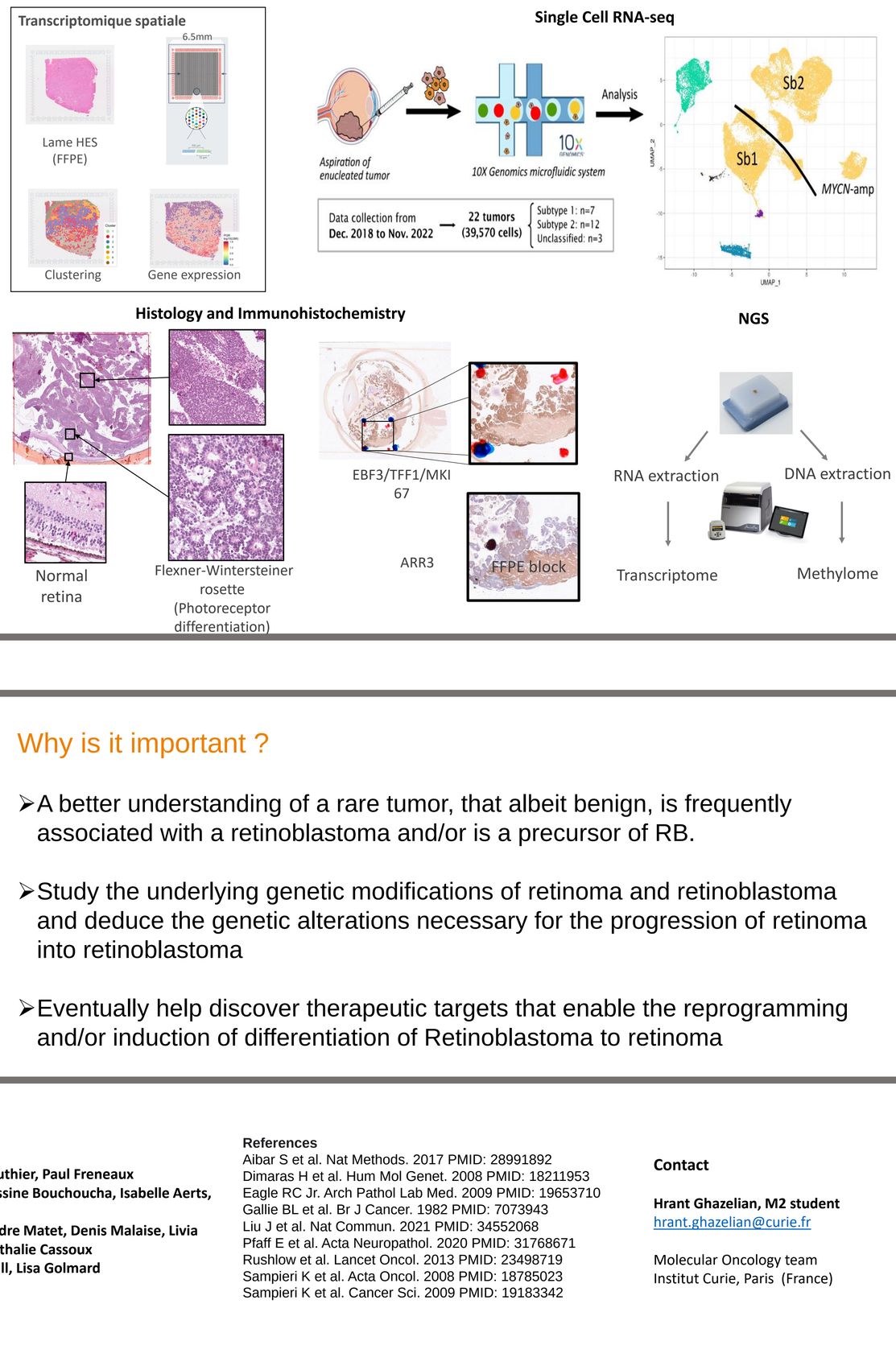
## Objectives

1) Determine whether retinoma is the precursor to retinoblastoma or whether it is an abortive progression pathway distinct from that of retinoblastomas,

2) Understand why retinomas have halted their proliferation,

3) Verify that retinoblastomas associated with retinomas belong exclusively to subtype 2, as suggested by our preliminary data.

## Methods




## Why is it important ?

- A better understanding of a rare tumor, that albeit benign, is frequently associated with a retinoblastoma and/or is a precursor of RB.
- Study the underlying genetic modifications of retinoma and retinoblastoma and deduce the genetic alterations necessary for the progression of retinoma into retinoblastoma
- Eventually help discover therapeutic targets that enable the reprogramming and/or induction of differentiation of Retinoblastoma to retinoma

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