Childhood Cancer Data Initiative Webinar Series

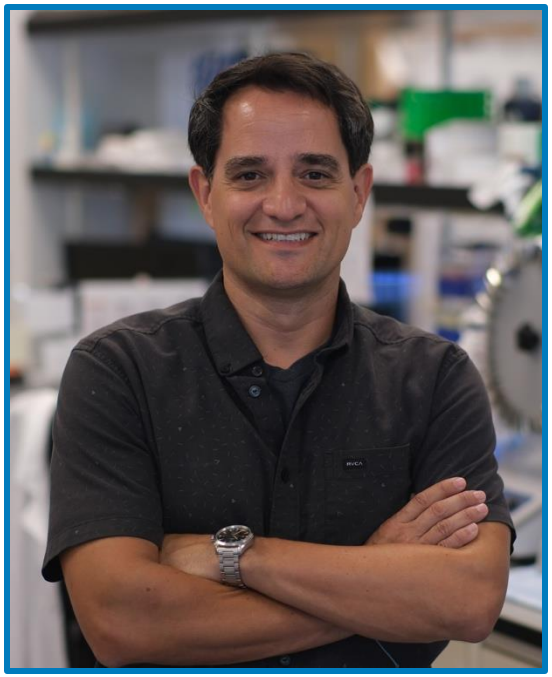
# Exploring Extrachromosomal DNA's (ecDNA's) Impact on Childhood Cancers

*Lukas Chavez*

NIH NATIONAL CANCER INSTITUTE

September 9, 2025

# Today's Speaker



## Lukas Chavez, Ph.D.

- Associate Professor, NCI-designated Cancer Center, Cancer Genome & Epigenetics Program, Sanford Burnham Prebys (SBP) Medical Discovery Institute
- Associate Adjunct Professor, Division of Genomics and Precision Medicine, Department of Medicine, University of California San Diego (UCSD)
- Scientific Director, Pediatric Neuro-Oncology Molecular Tumor Board, Rady Children's Institute for Genomic Medicine (RCIGM), Rady Children's Hospital, San Diego

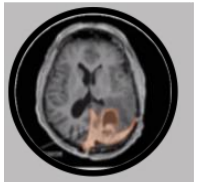
# Precision Diagnostics

## FOR CHILDREN WITH BRAIN TUMORS

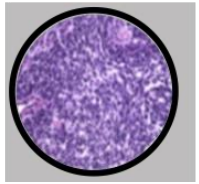
Rady Children's Health · Sanford Burnham Prebys · UC San Diego

Megan Paul, MD

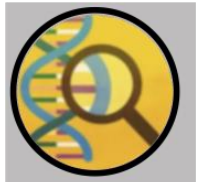
Lukas Chavez, PhD

MRI imaging



H&E Staining



DNA & RNA
Tumor & Germline

DNA
methylation

Drug Screen
CLIA-certified

Tumor Models

MHC Phenotyping
Antigen prediction

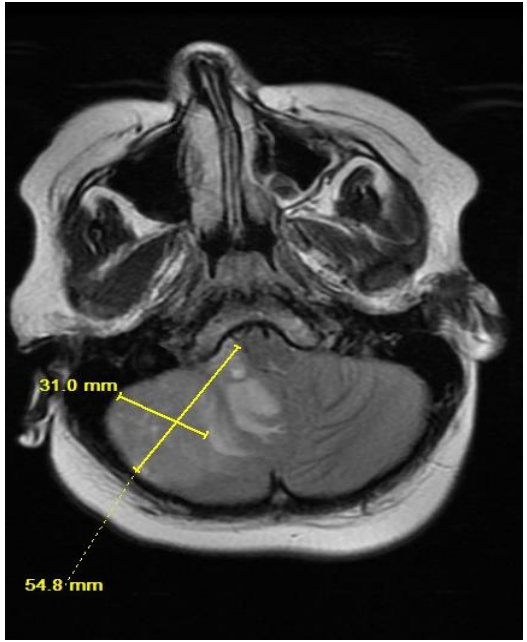
# Case 11 – Anaplastic Medulloblastoma (Part 1)

## Clinical Presentation

- Young male (<10y)
- presented with headache with nausea and vomiting for 3 weeks
- Unstable gait, episodes of fainting
- MRI revealed 5.5 cm ill-defined posterior fossa mass
- Neuro-Pathology: Anaplastic Medulloblastoma

## Molecular Profiling

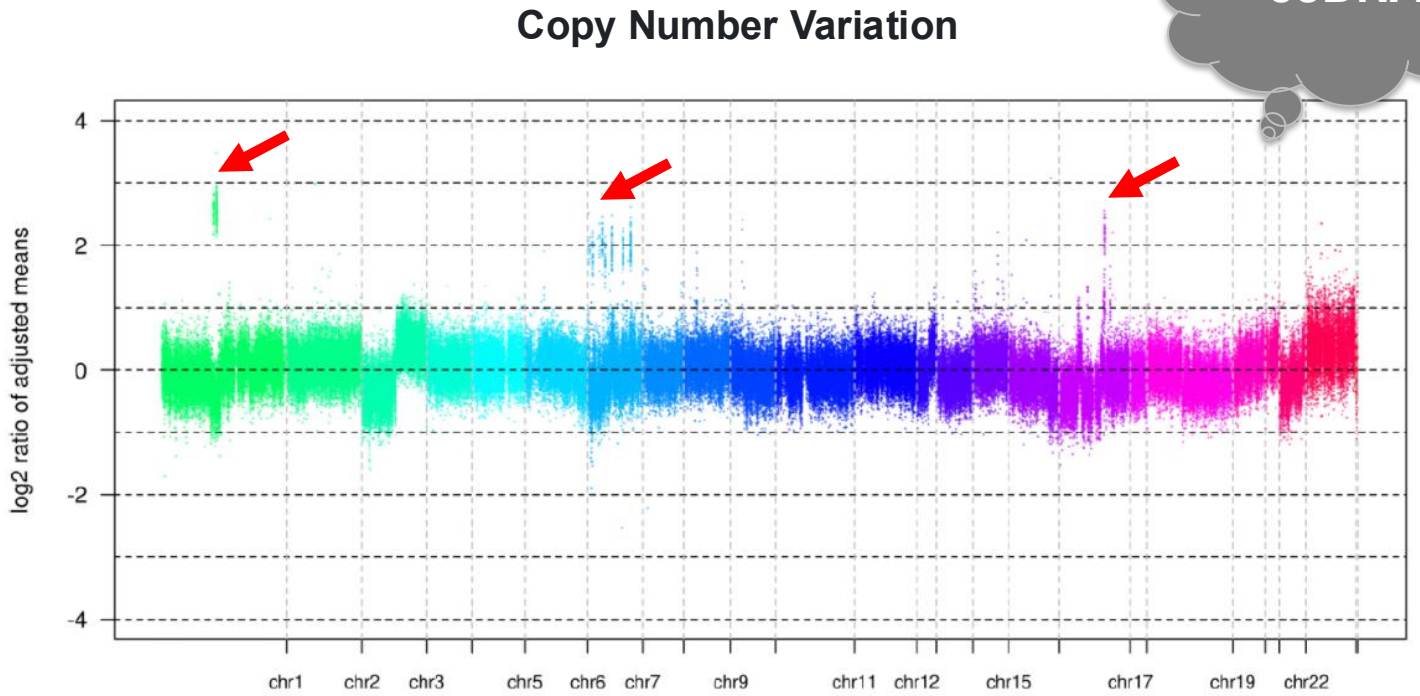
- DNA methylation Central Nervous System (CNS) classification: Sonic Hedgehog(SHH) Medulloblastoma subgroup
- Tumor DNA: somatic TP53 missense mutation
- No pathogenic germline variant
- No fusion gene




2017

# Case 11 – Anaplastic Medulloblastoma (Part 2)

ecDNA?

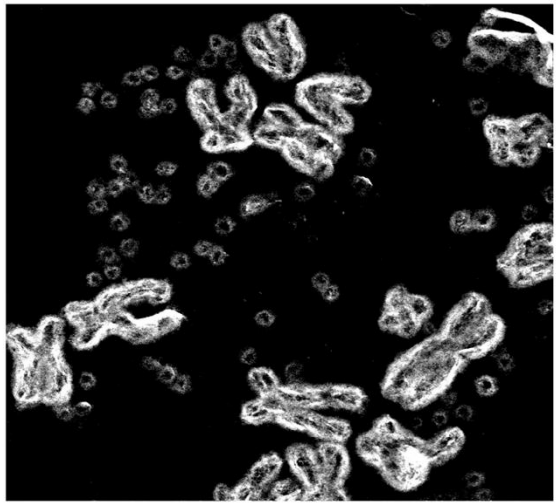



→ enrolled on COG trial ACNS0332, randomized to vincristine only arm during radiation.

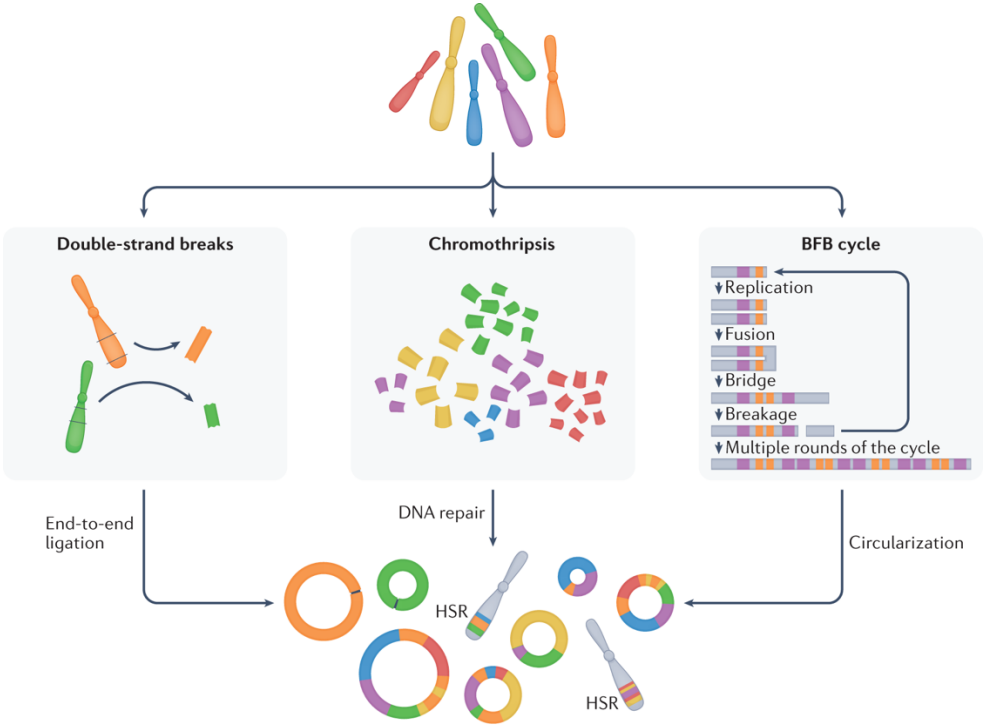
The New York Times

## *Scientists Are Just Beginning to Understand Mysterious DNA Circles Common in Cancer Cells*

For years, researchers weren't exactly sure what to make of these extra loops of genetic material . That's quickly changing.

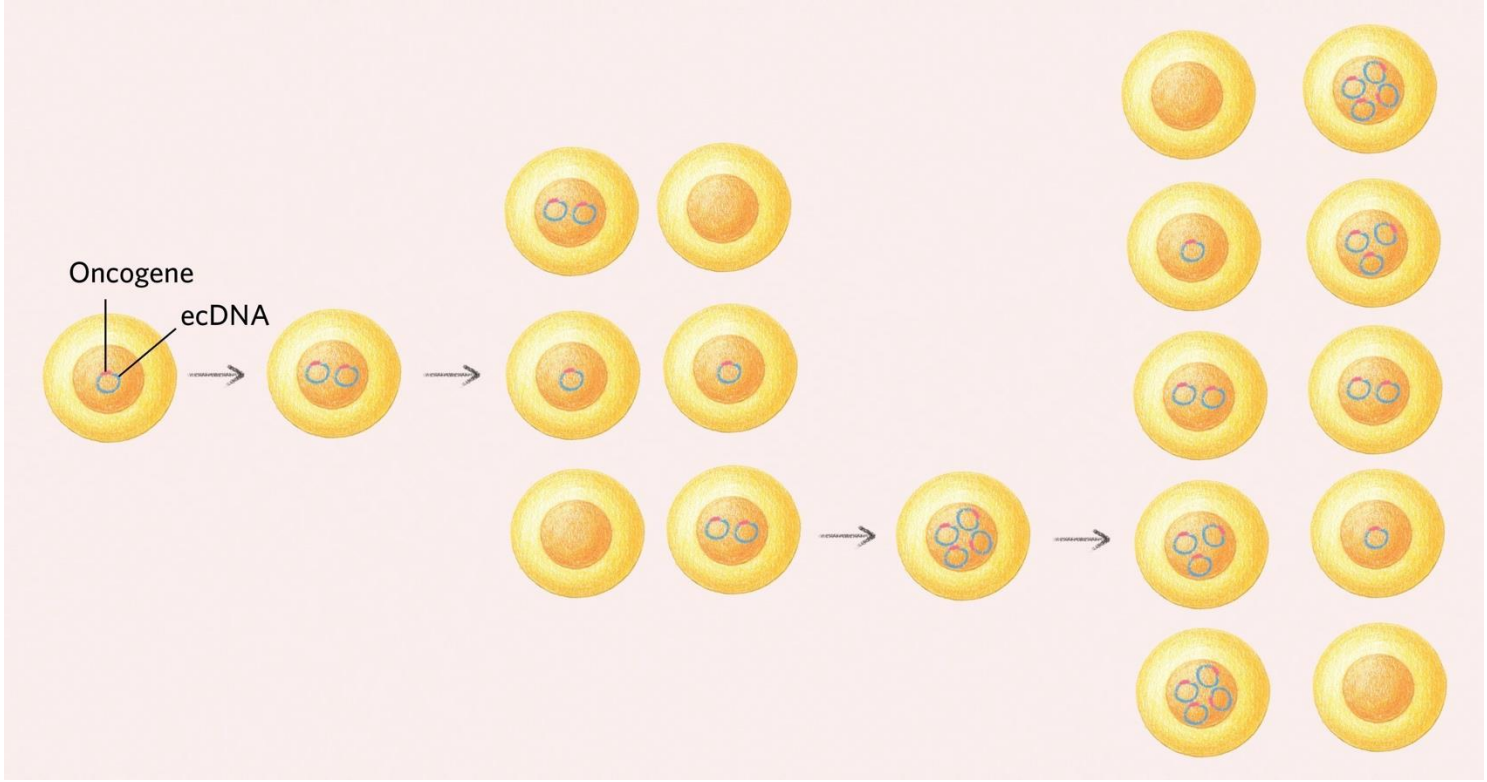


November 26, 2019



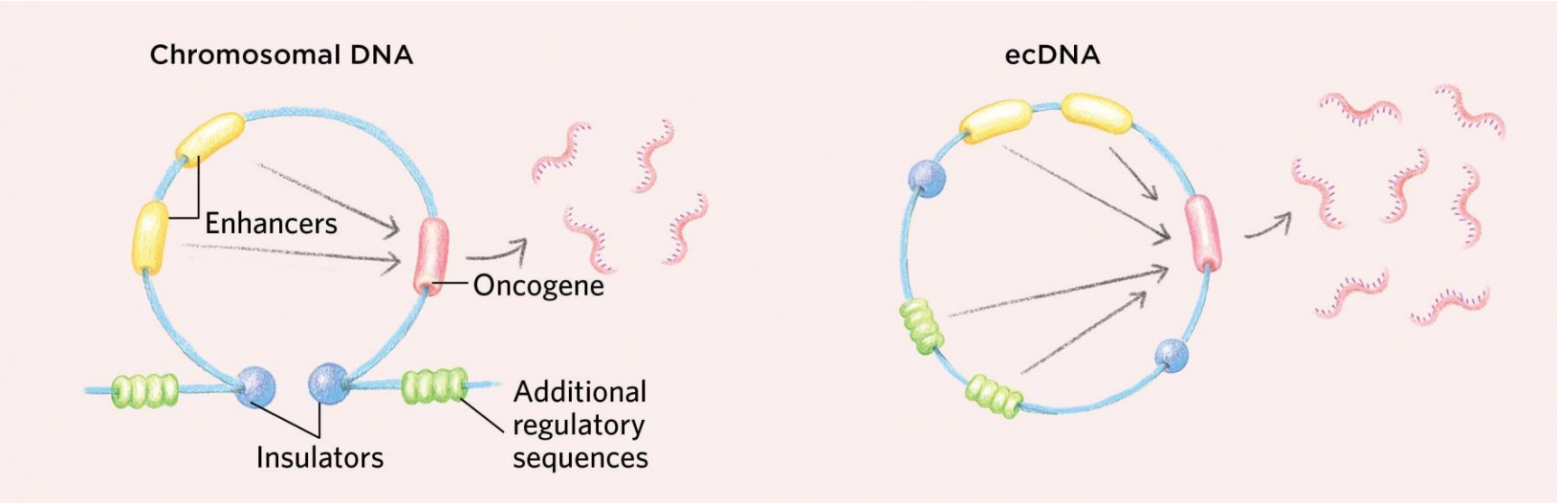

Eunhee Yi et al., Extrachromosomal DNA amplifications in cancer, Nature Reviews Genetics, 2022

# Intra-Tumoral Heterogeneity of ecDNA Copy Number



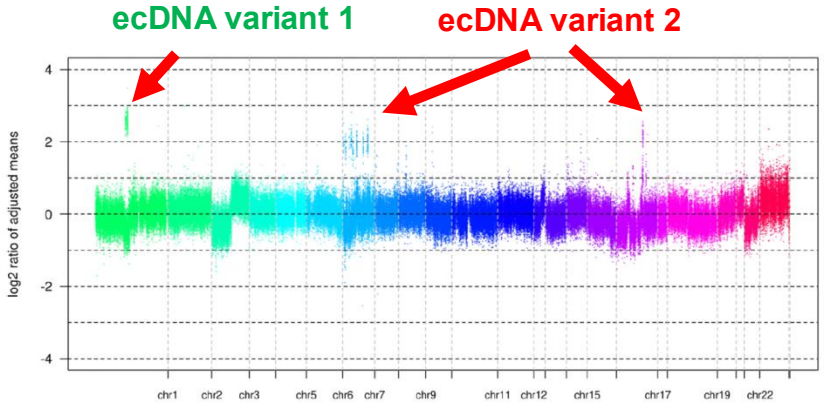

Paul Mischel, *Cancer May be Driven by DNA Outside of Chromosomes*, The Scientist, April 1, 2021

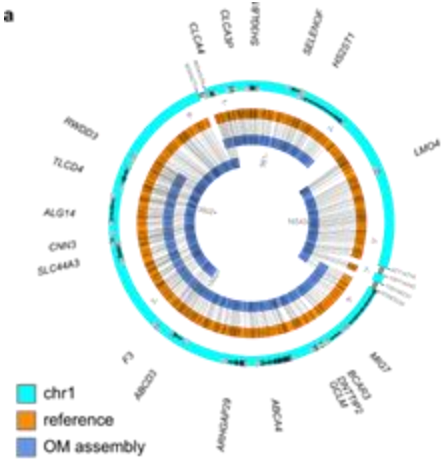
# Enhancer Rewiring Might Support Cancerous Growth



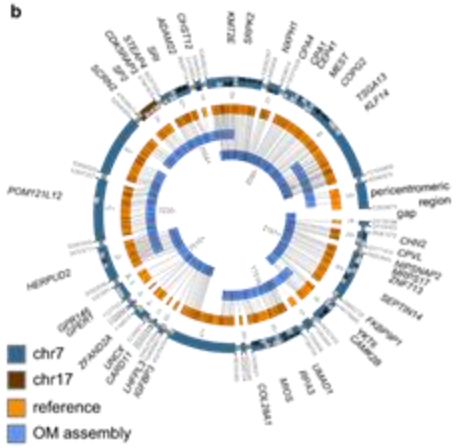

Paul Mischel, *Cancer May be Driven by DNA Outside of Chromosomes*, The Scientist, April 1, 2021
Andrew Morton et al., *Functional Enhancers Shape Extrachromosomal Oncogene Amplifications*, Cell 2019
Chapman et al., *Circular extrachromosomal DNA promotes tumor heterogeneity in high-risk medulloblastoma*, Nature Genetics 2023

# Case 11 – Anaplastic Medulloblastoma Contains Two Distinct ecDNA Variants



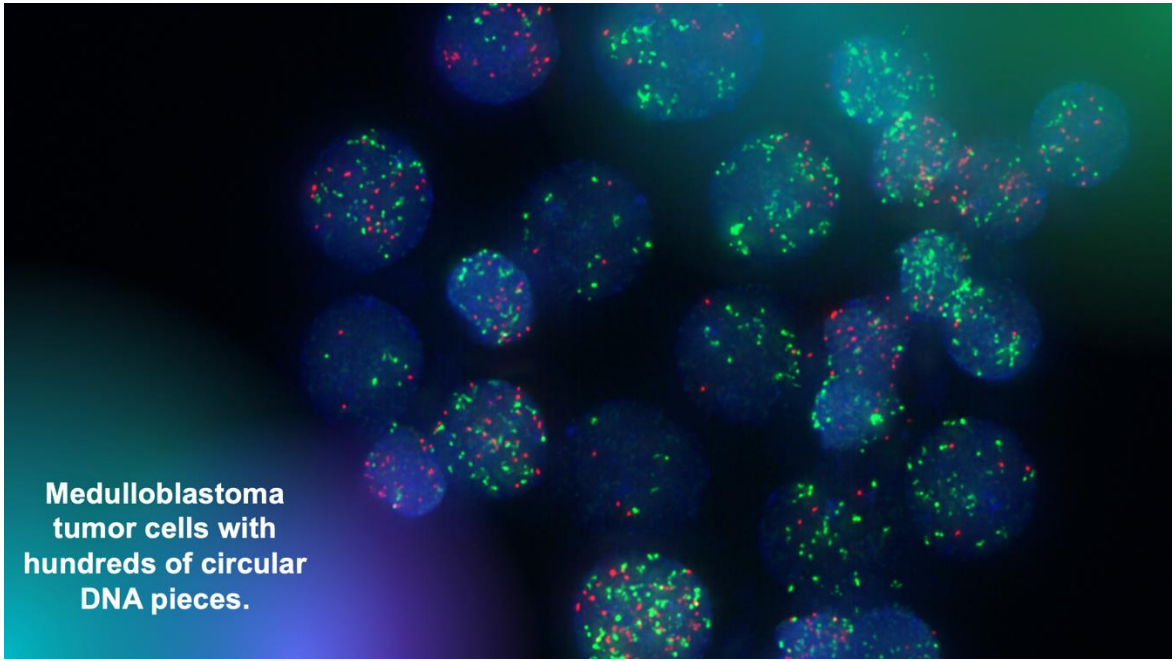

ecDNA variant 1




ecDNA variant 2

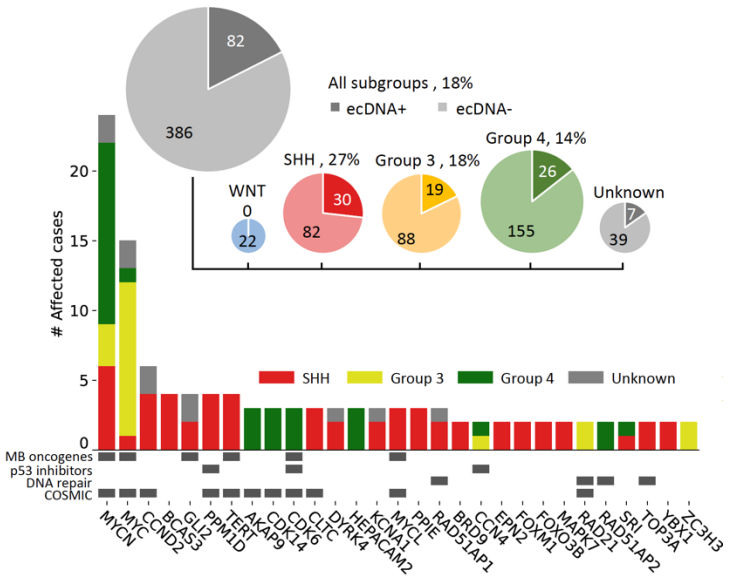
**AmpliconArchitect** (Desphande et al., Nature Communications 2019)

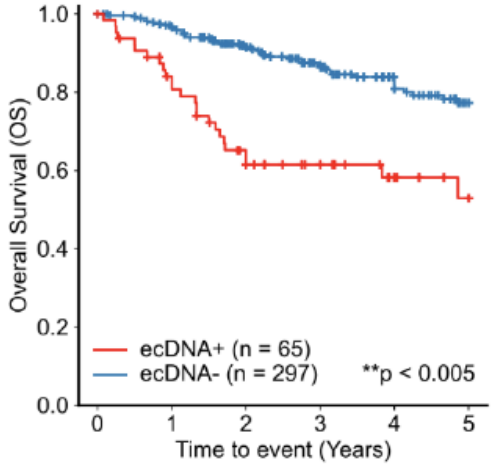
# Case 11 – Anaplastic Medulloblastoma Contains Two Distinct ecDNA Variants

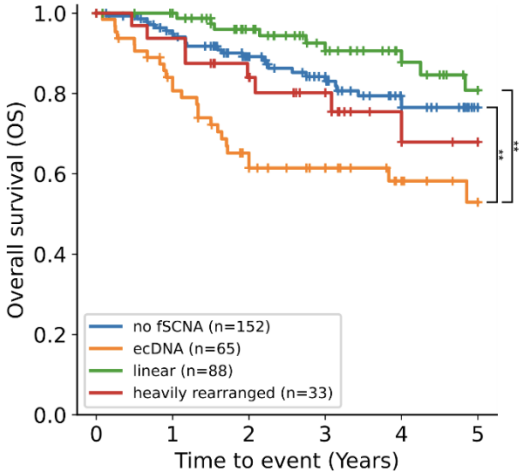



**Green: ecDNA variant 1** **Red: ecDNA variant 2**

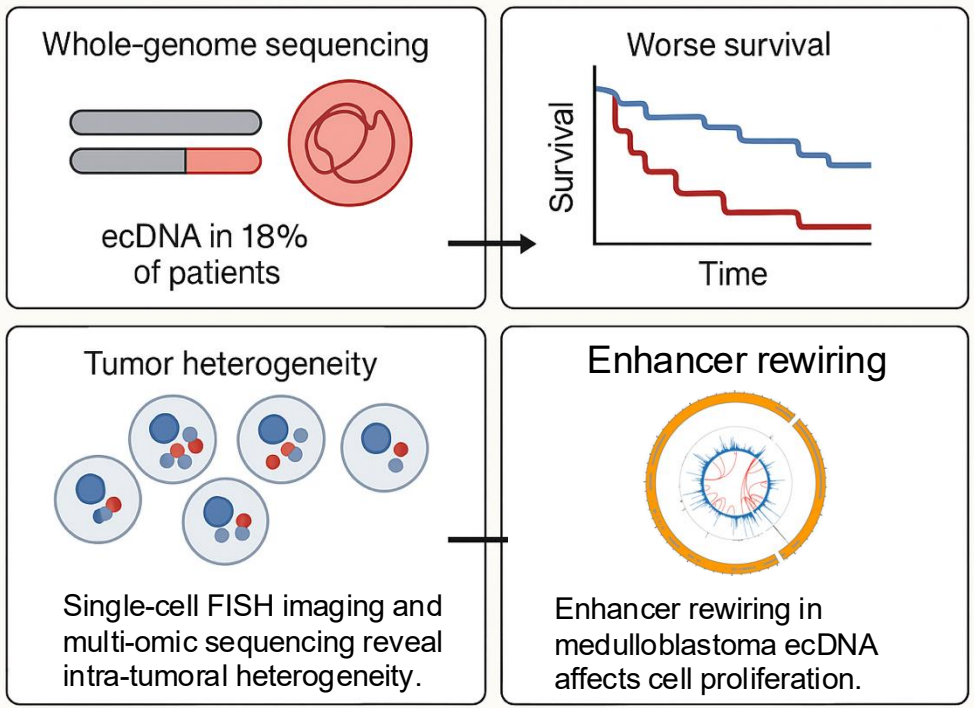
# ecDNA Associates with Poor Outcome in Medulloblastoma



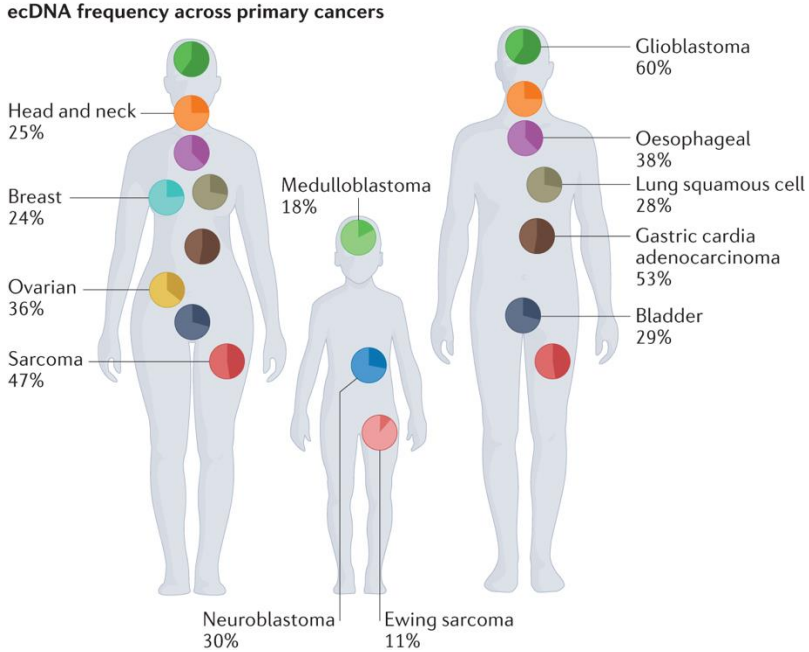
# Circular ecDNA Promotes Tumor Heterogeneity in Medulloblastoma



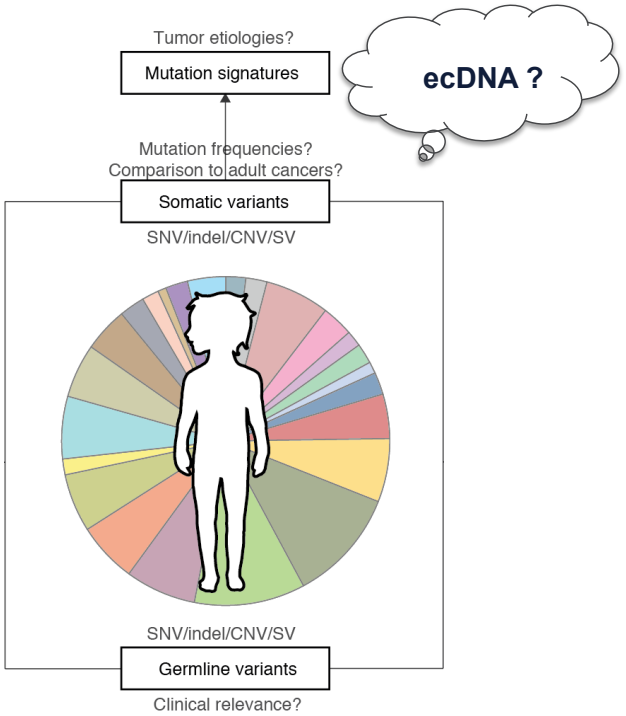

Owen Chapman

Chapman et al., Circular extrachromosomal DNA promotes tumor heterogeneity in high-risk medulloblastoma, Nature Genetics 2023

# ecDNA Amplifications in Cancer

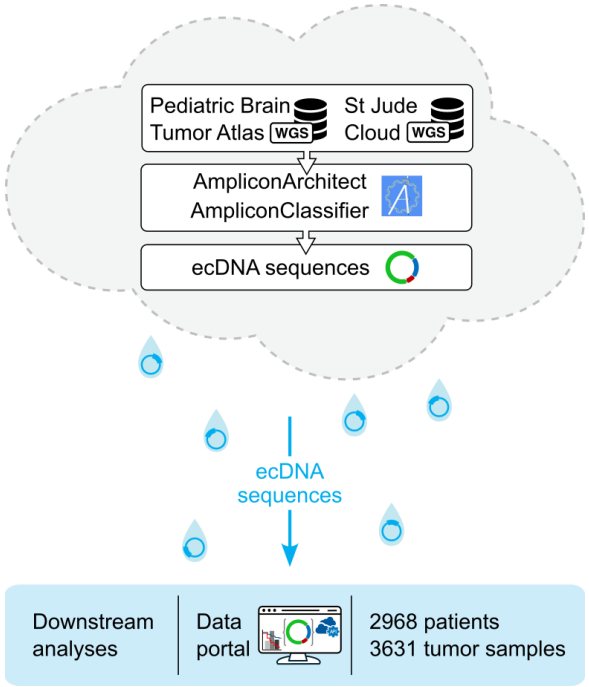



Kim et al., Nature Genetics 2020: 3,212 patients with 31 tumor types (TCGA/ PCAWG) Bailey et al., Nature 2024: 14,778 patients with 39 tumor types (100,000 Genomes Project) Yi et al., Extrachromosomal DNA amplifications in cancer, Nature Reviews Genetics 2022




Gröbner et al., The landscape of genomic alterations across childhood cancers, Nature, 2018

# ecDNA in Childhood Cancers (Part 1)




Owen Chapman

Sunita Sridhar

## Key Questions:

- Which pediatric tumor types have ecDNA?
- Which parts of the genome are amplified?
- ecDNA as an independent prognostic biomarker?
- Molecular evolution of ecDNA during disease progression?

Chapman, Sridhar et al., *Extrachromosomal DNA associates with poor survival across a broad spectrum of childhood solid tumors*, medRxiv 2025

Children's Brain Tumor Network
Until every child is cured

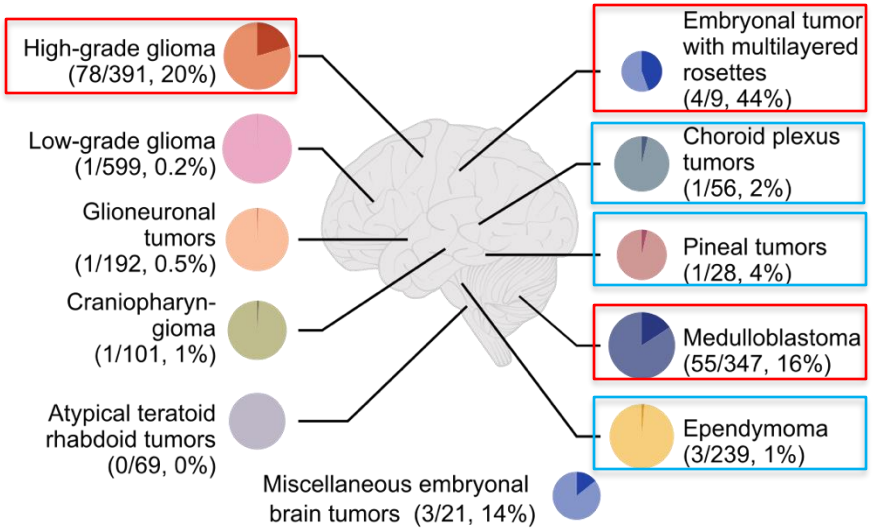
Dragon Master Initiative

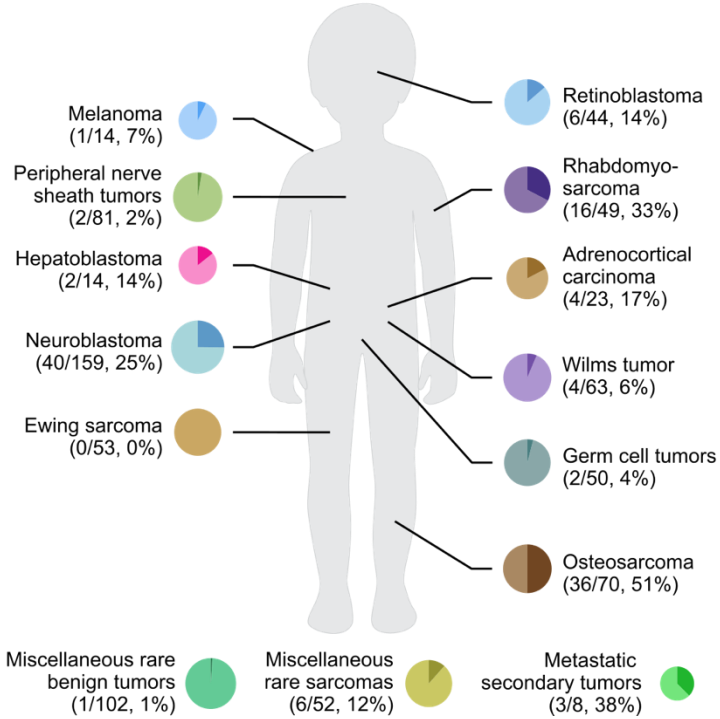
St Jude Cloud

CCDI
Childhood Cancer Data Initiative

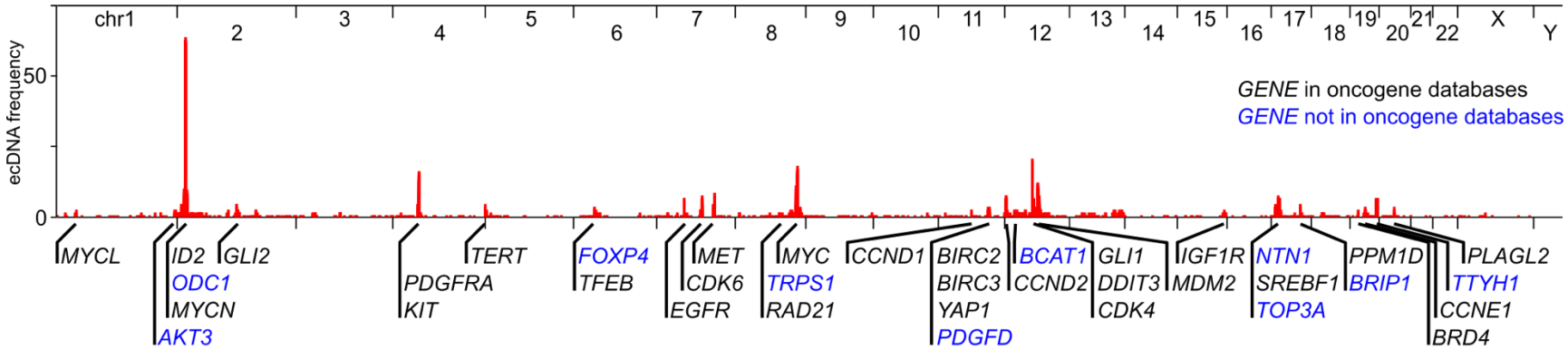
# ecDNA in Childhood Cancers (Part 2)

**Overall fraction of ecDNA+ tumors: 9% vs. 14-17% in adult cancers**



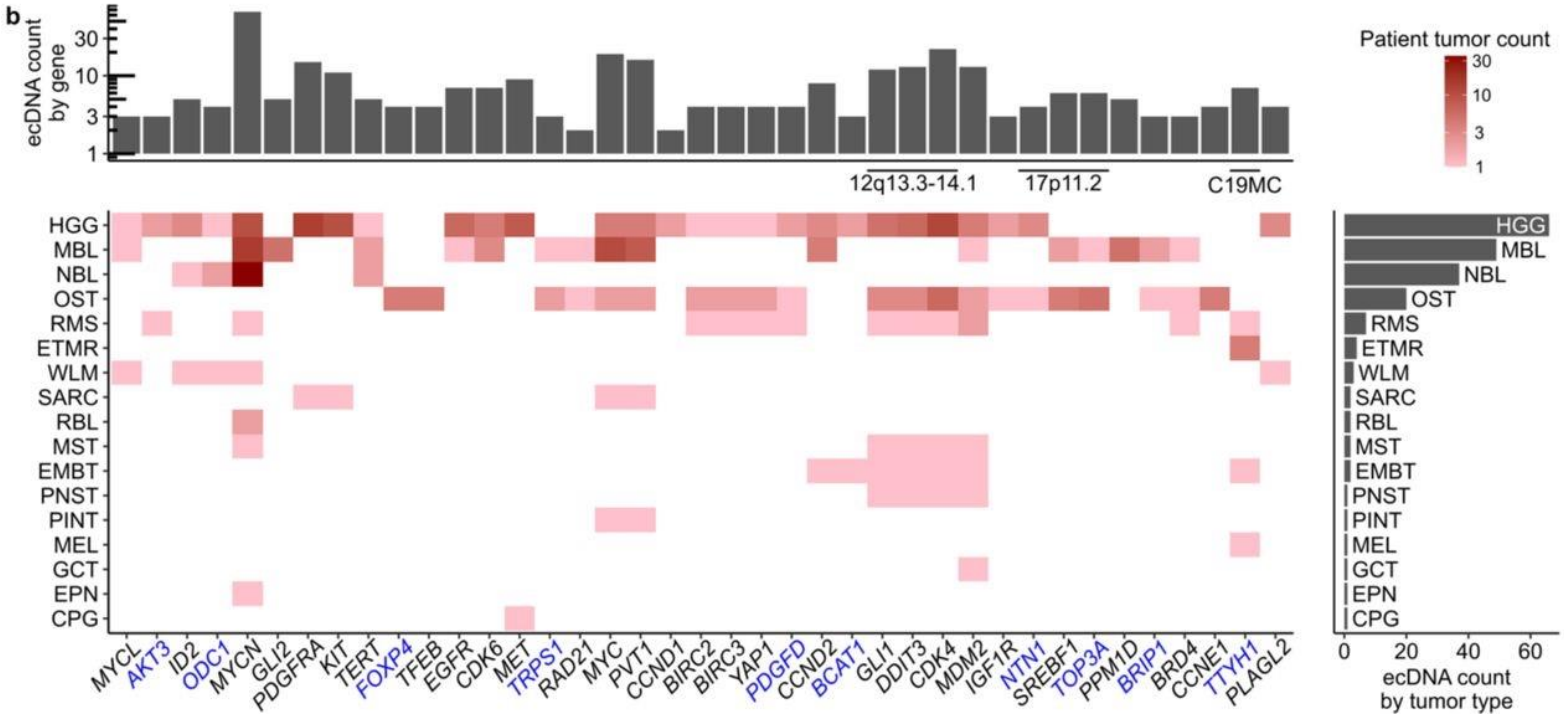
# ecDNA Amplifies Known and Putative Oncogenes (Part 1)



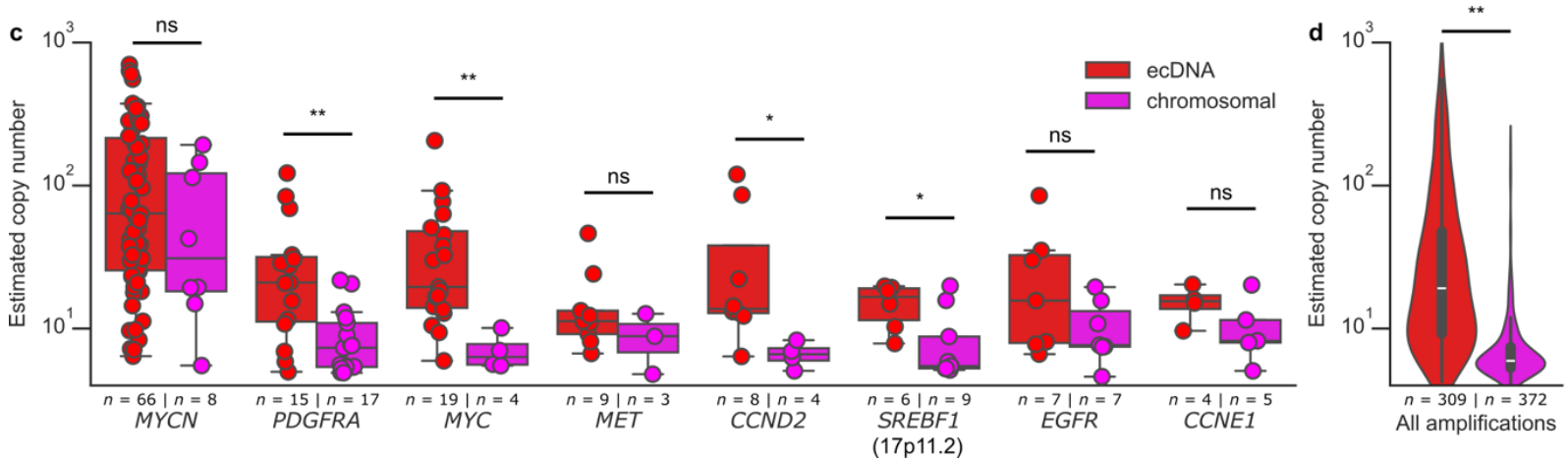

Frequency of ecDNA amplifications in pediatric tumors across the genome

Chapman, Sridhar et al., *Extrachromosomal DNA associates with poor survival across a broad spectrum of childhood solid tumors*, medRxiv 2025

# ecDNA Amplifies Known and Putative Oncogenes (Part 2)

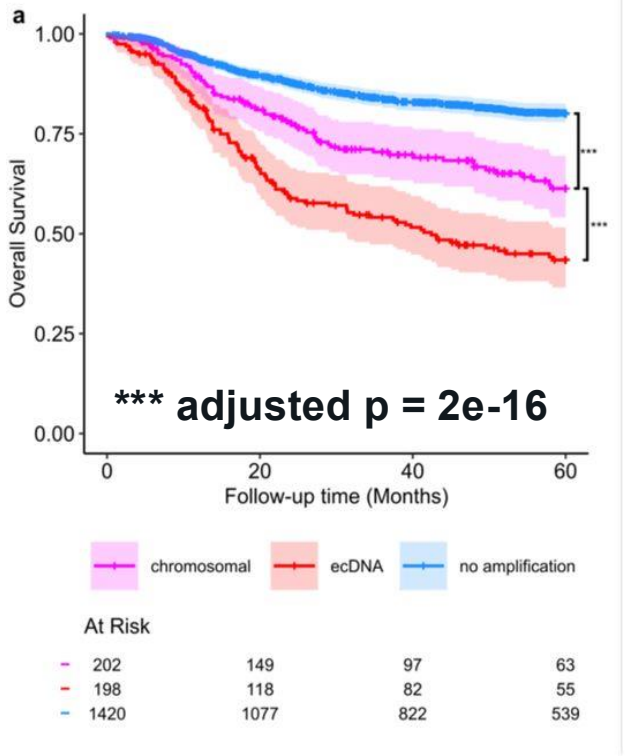


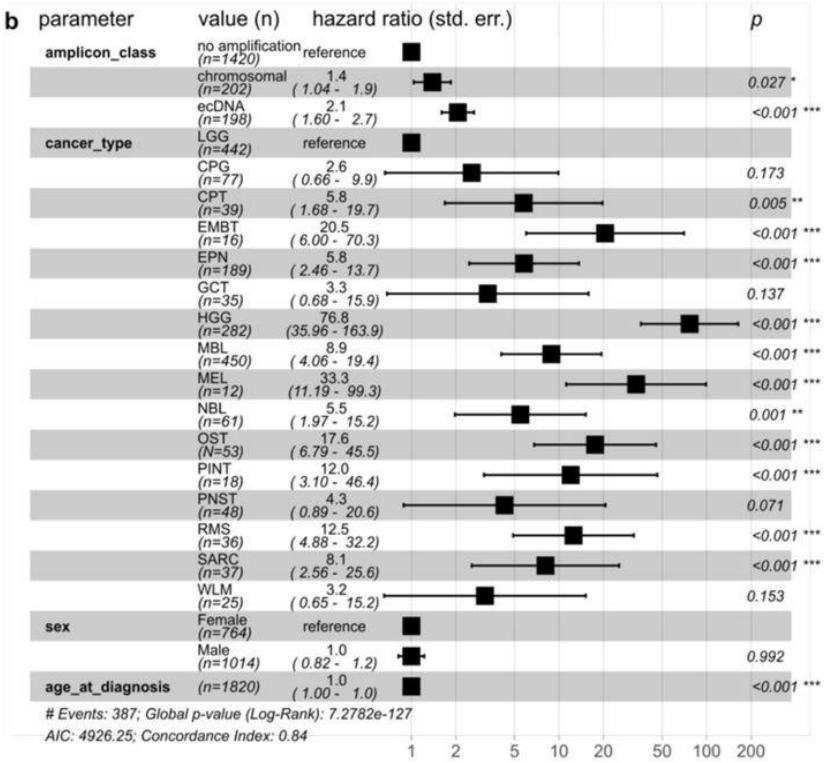
# ecDNA Oncogene Amplifications Have Increased Copy Number



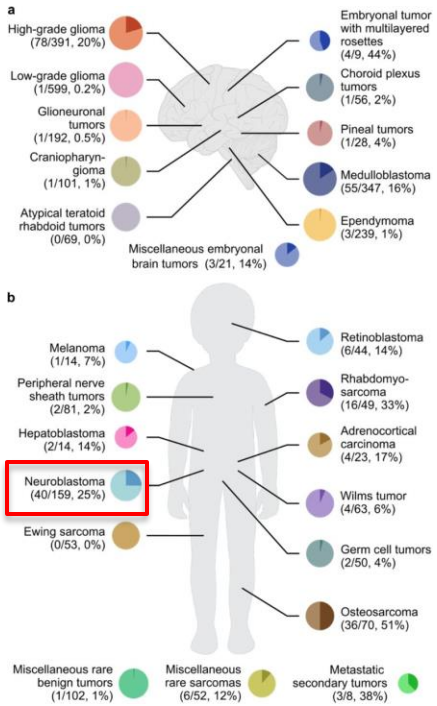

Chapman, Sridhar et al., *Extrachromosomal DNA associates with poor survival across a broad spectrum of childhood solid tumors*, medRxiv 2025

# ecDNA and Prognostic Relevance (Childhood Cancers)

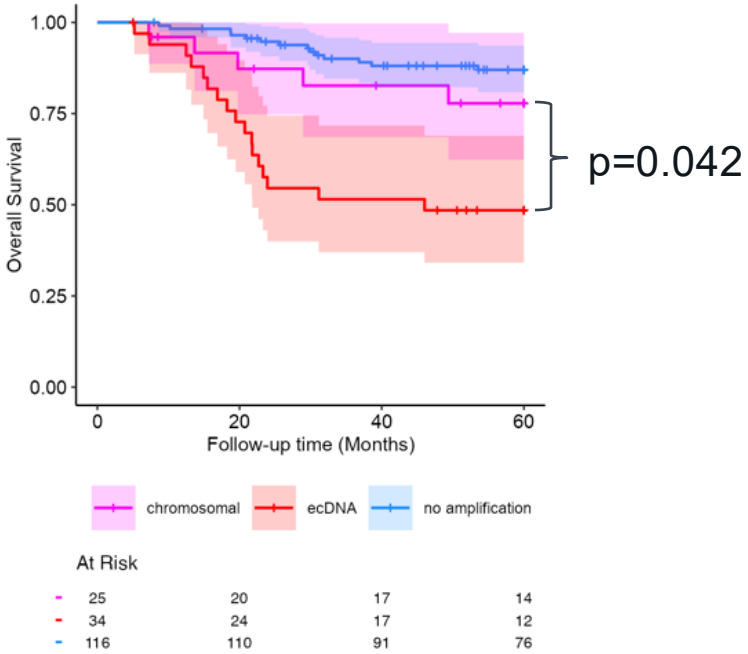


# ecDNA and Prognostic Relevance (Neuroblastoma)

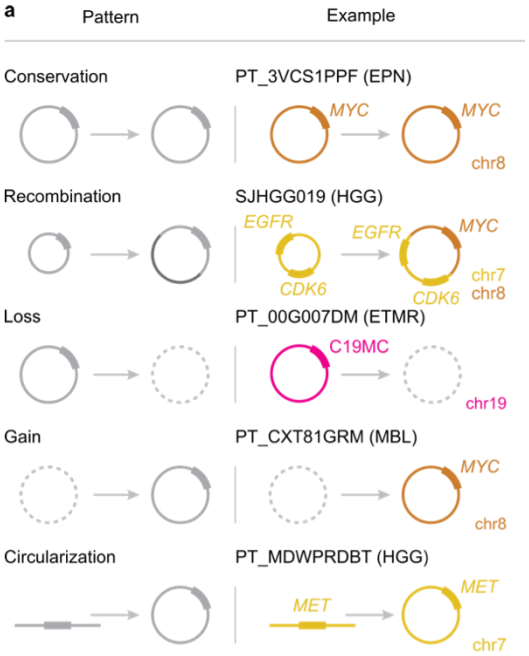



Neuroblastoma (n=175)




61 NBL tumors from this cohort supplemented with 114 from Rodriguez Fos *et al.*, 2023

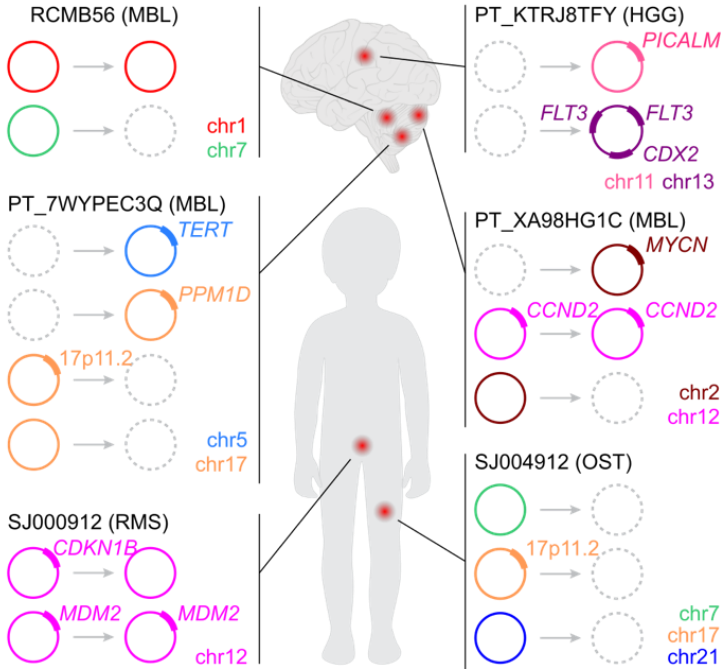
# Frequent Molecular Evolution of ecDNA During Disease Progression (Part 1)




Chapman, Sridhar et al., *Extrachromosomal DNA associates with poor survival across a broad spectrum of childhood solid tumors*, medRxiv 2025

# Frequent Molecular Evolution of ecDNA During Disease Progression (Part 2)



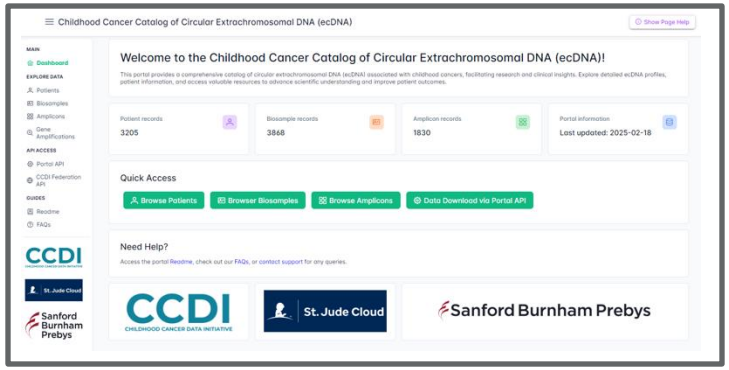




Chapman, Sridhar et al., *Extrachromosomal DNA associates with poor survival across a broad spectrum of childhood solid tumors*, medRxiv 2025

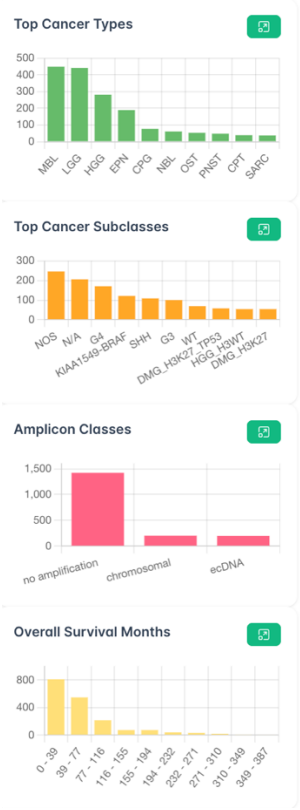
# Childhood Cancer Catalog of ecDNA

*https://ccdi-ecdna.org/*

# Childhood Cancer Catalog of ecDNA (https://ccdi-ecdna.org)

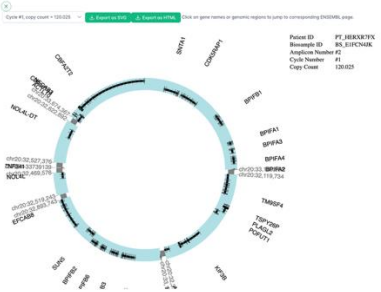







Eugene Chow

Kevin Yip



# Data Availability In the Portal

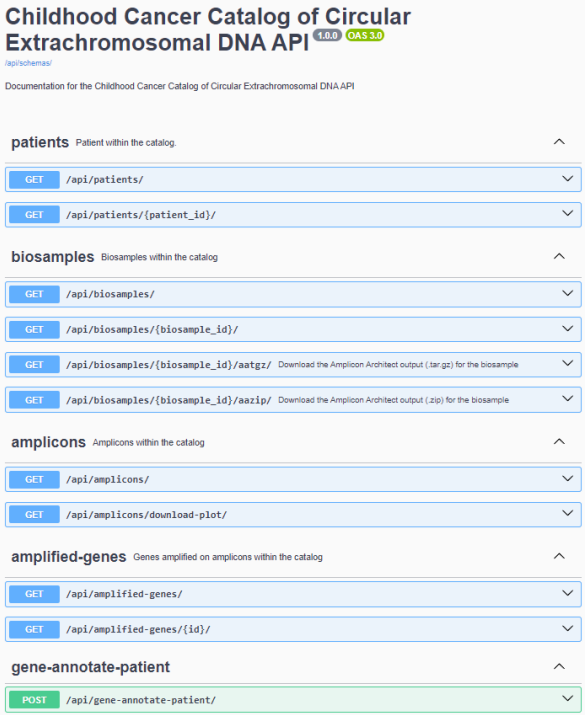
## Users Can Access ✅

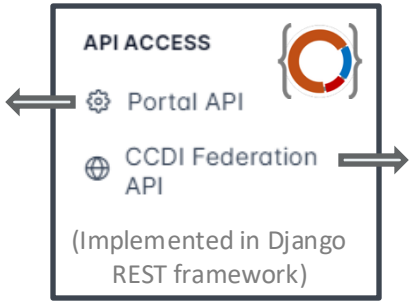
- Patient-level metadata (cancer type, diagnosis age, survival status)
- Biosample information (tumor history, extent of resection)
- Processed genomic data (ecDNA classification, gene amplification frequencies)
- Precomputed visualizations and summary statistics

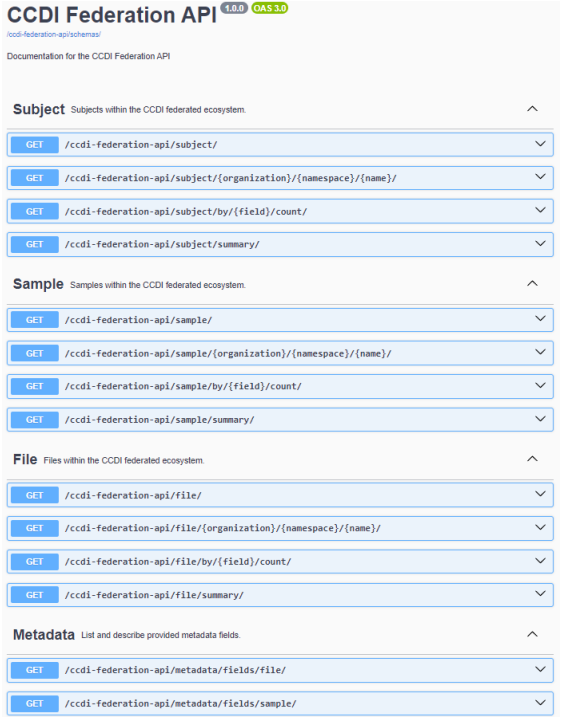
## Users Cannot Access ❌

- Raw sequencing data
- Personally identifiable information
- Live patient updates or clinical records
- Other restricted items as specified in the Data Use Agreements (DUA) with upstream databases

# REST API Features



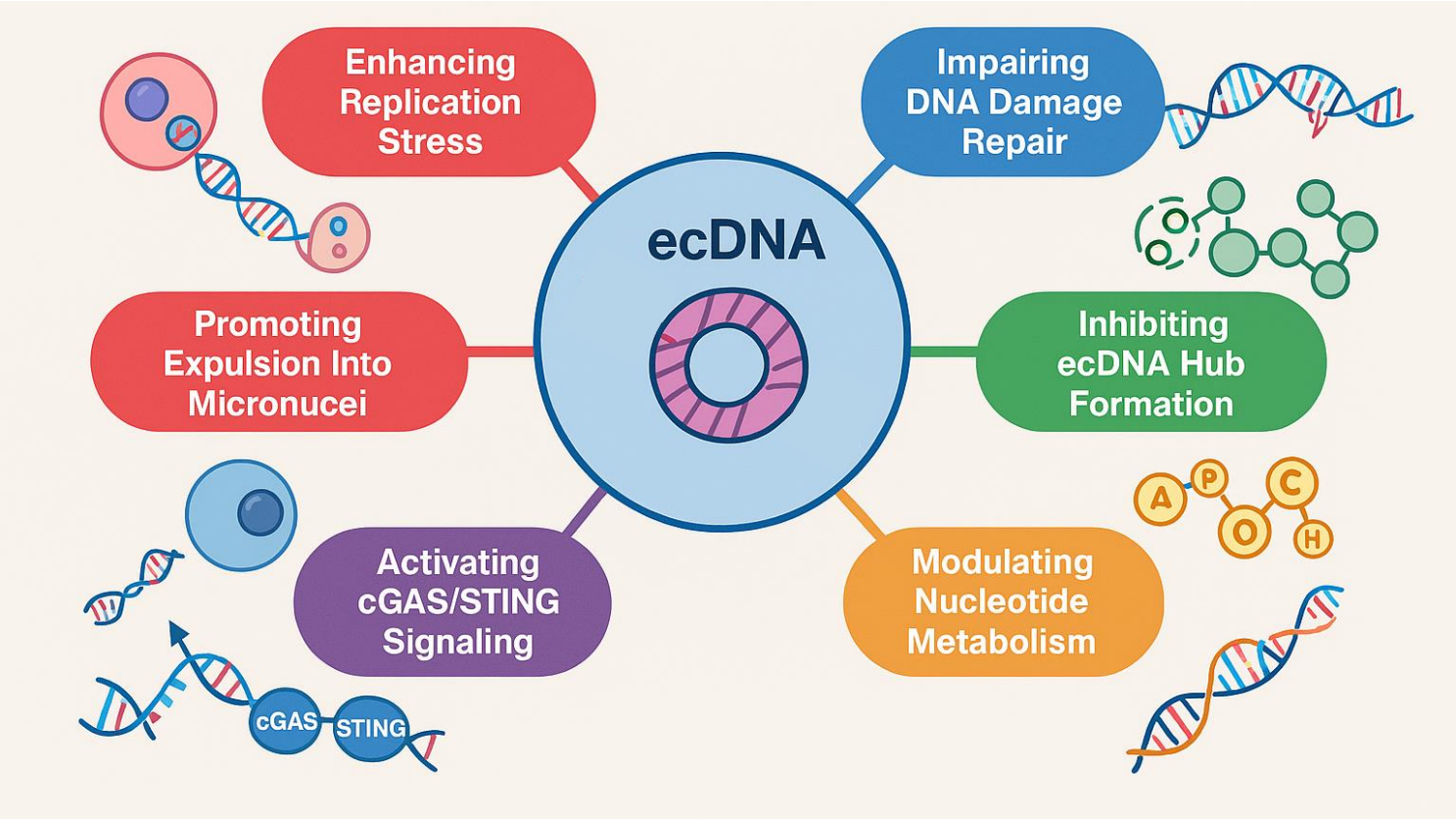




The Portal API provides a data schema that mirrors the structure presented in the GUI

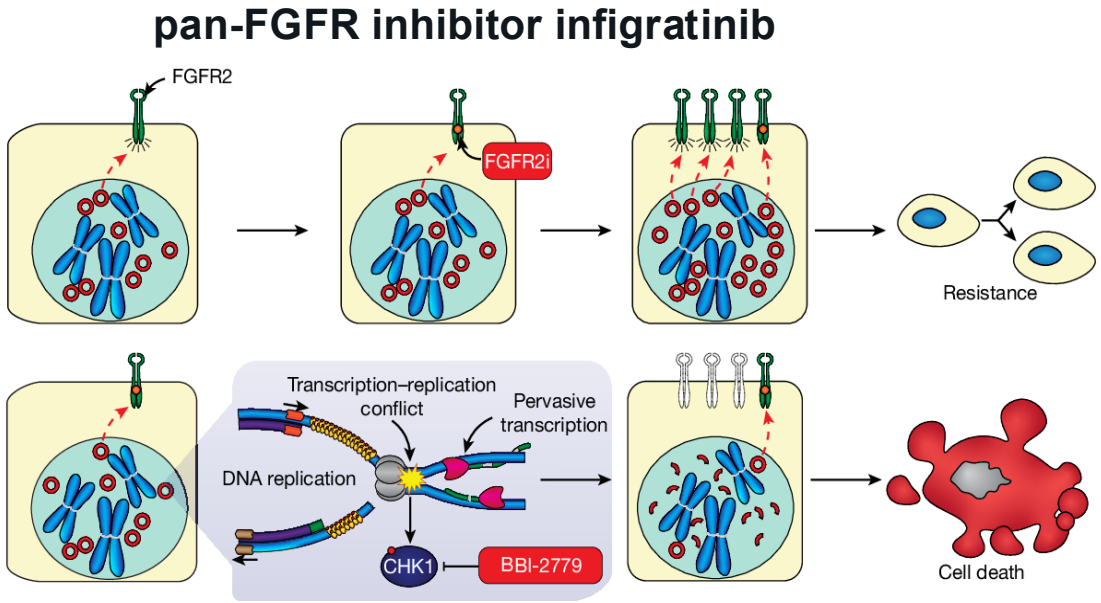
The CCDI Federation API provides harmonized data compliant with the standard schema

# Therapeutic Strategies Targeted Against ecDNA

# Therapeutic Strategies Targeted Against ecDNA



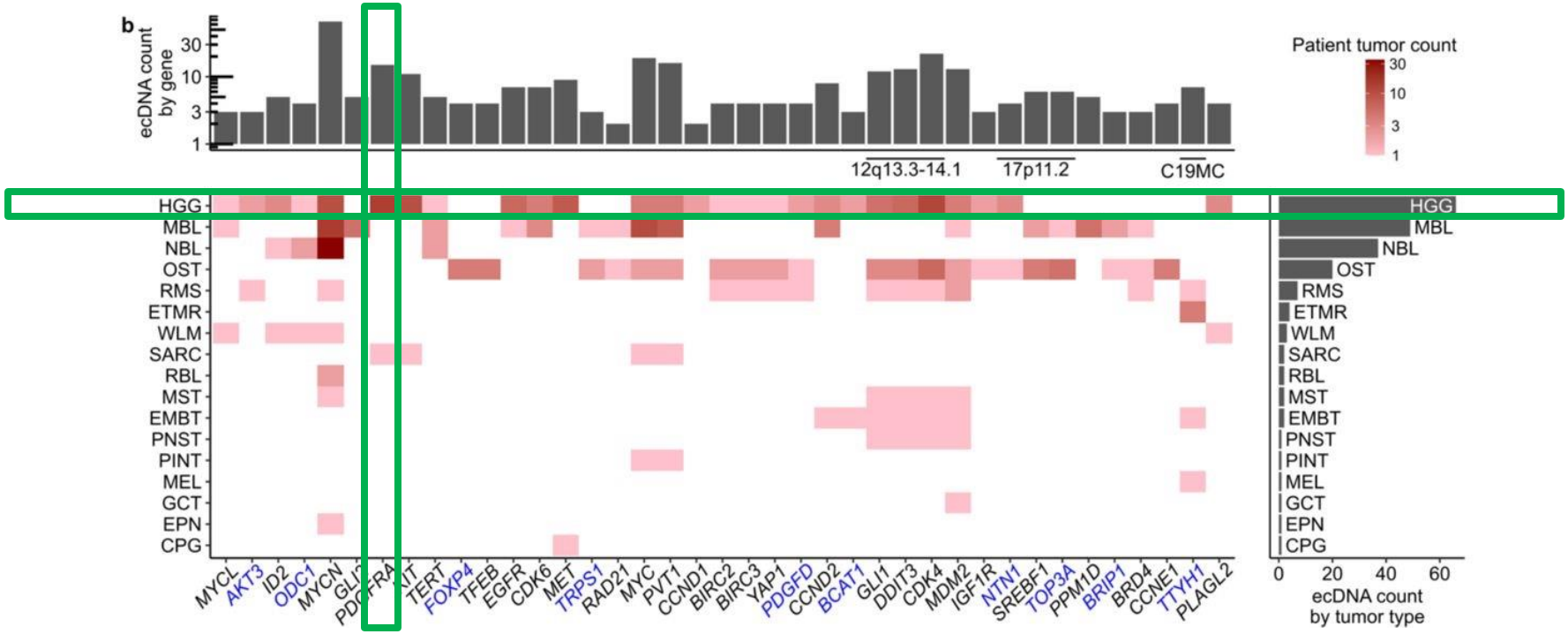
# Enhancing Replication Stress in ecDNA-Driven Tumors




Synthetic lethality to CHK1i in ecDNA$^{+}$-oncogene-amplified tumor cells is synergistic with targeted therapy resulting in enhanced cytotoxicity.

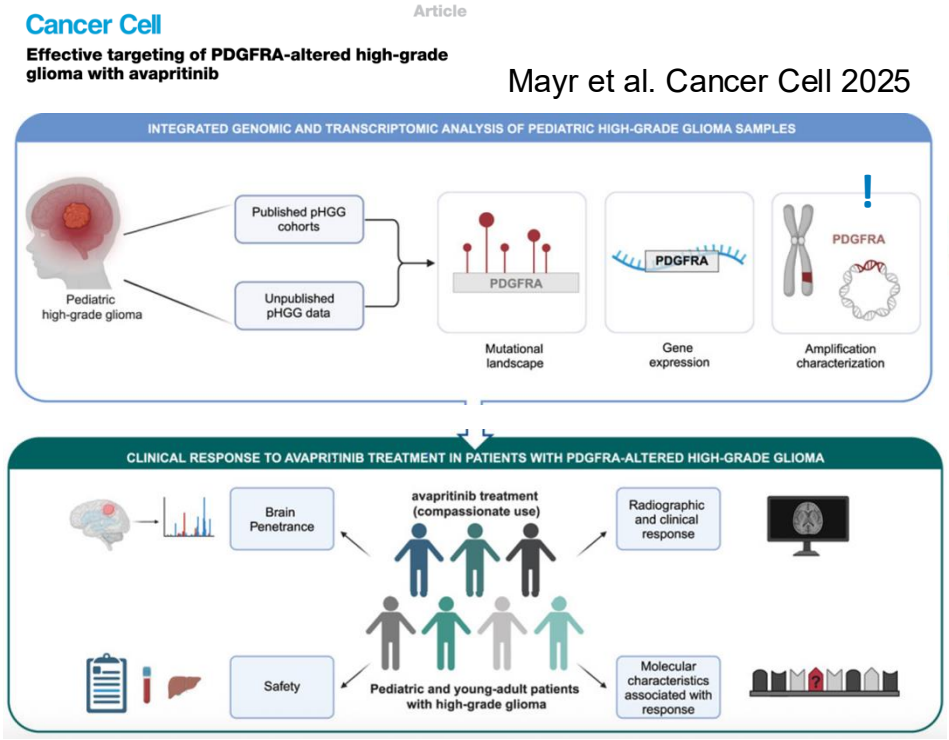
Tang et al., *Enhancing transcription-replication conflict targets ecDNA-positive cancers*, Nature 2024
Jaworski et al., *ecDNA replication is disorganized and vulnerable to replication stress*, Nucleid Acid Research 2025

# Pediatric High-Grade Glioma with PDGFRA Amplifications

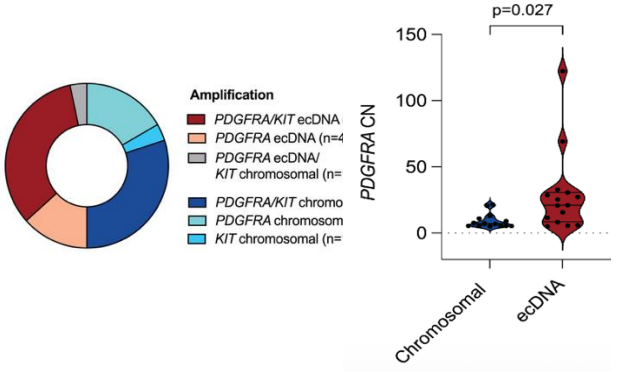


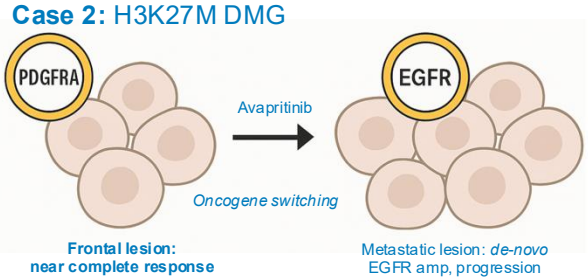

**pHGG ecDNA(PDGFRA)**

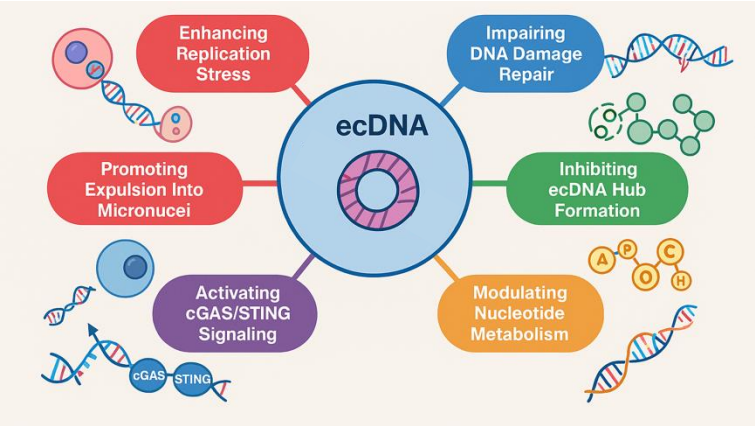
# Targeting of Pediatric High-Grade Glioma with PDGFRA Amplifications

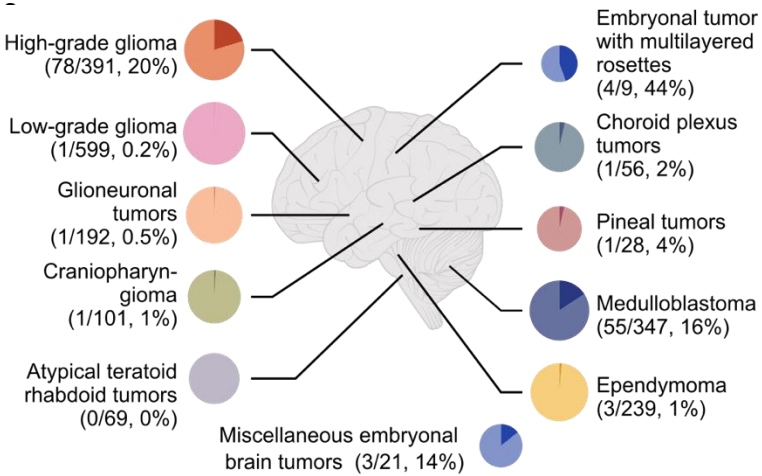


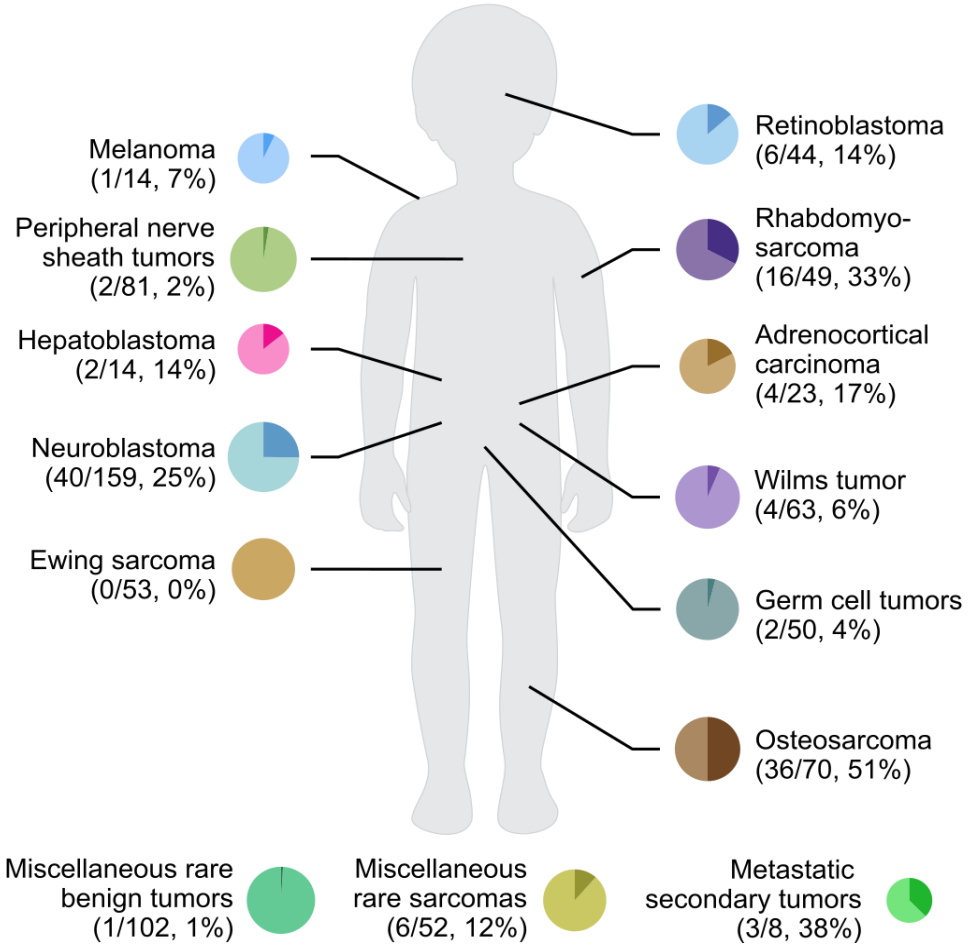

Mayr et al. Cancer Cell 2025




ecDNA
Enhancing Replication Stress
Impairing DNA Damage Repair
Promoting Expulsion Into Micronucei
Inhibiting ecDNA Hub Formation
Activating cGAS/STING Signaling
Modulating Nucleotide Metabolism
cGAS
STING


High-grade glioma (78/391, 20%)
Low-grade glioma (1/599, 0.2%)
Glioneuronal tumors (1/192, 0.5%)
Craniopharyn-gioma (1/101, 1%)
Atypical teratoid rhabdoid tumors (0/69, 0%)
Miscellaneous embryonal brain tumors (3/21, 14%)
Embryonal tumor with multilayered rosettes (4/9, 44%)
Choroid plexus tumors (1/56, 2%)
Pineal tumors (1/28, 4%)
Medulloblastoma (55/347, 16%)
Ependymoma (3/239, 1%)


Melanoma (1/14, 7%)
Peripheral nerve sheath tumors (2/81, 2%)
Hepatoblastoma (2/14, 14%)
Neuroblastoma (40/159, 25%)
Ewing sarcoma (0/53, 0%)
Retinoblastoma (6/44, 14%)
Rhabdomyo-sarcoma (16/49, 33%)
Adrenocortical carcinoma (4/23, 17%)
Wilms tumor (4/63, 6%)
Germ cell tumors (2/50, 4%)
Osteosarcoma (36/70, 51%)
Miscellaneous rare benign tumors (1/102, 1%)
Miscellaneous rare sarcomas (6/52, 12%)
Metastatic secondary tumors (3/8, 38%)

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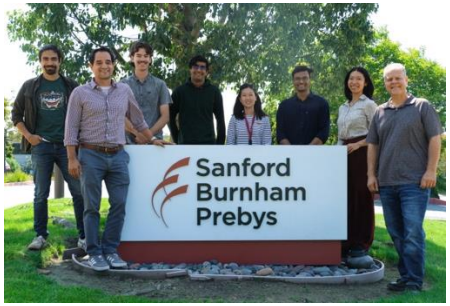


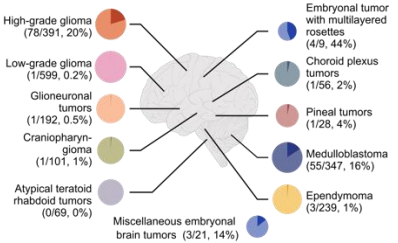


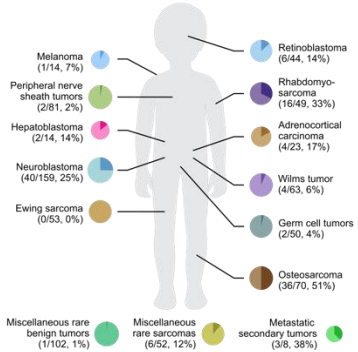

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