Identification of novel genes/variants for pediatric cancer predisposition

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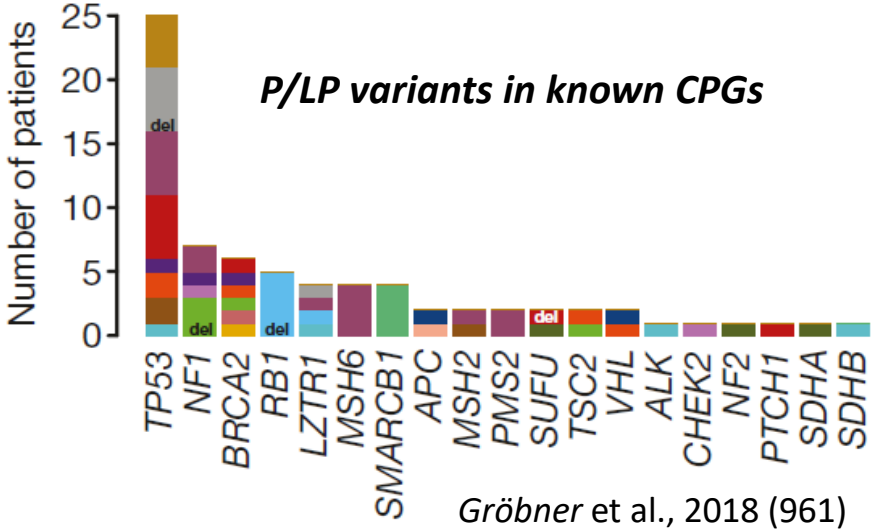
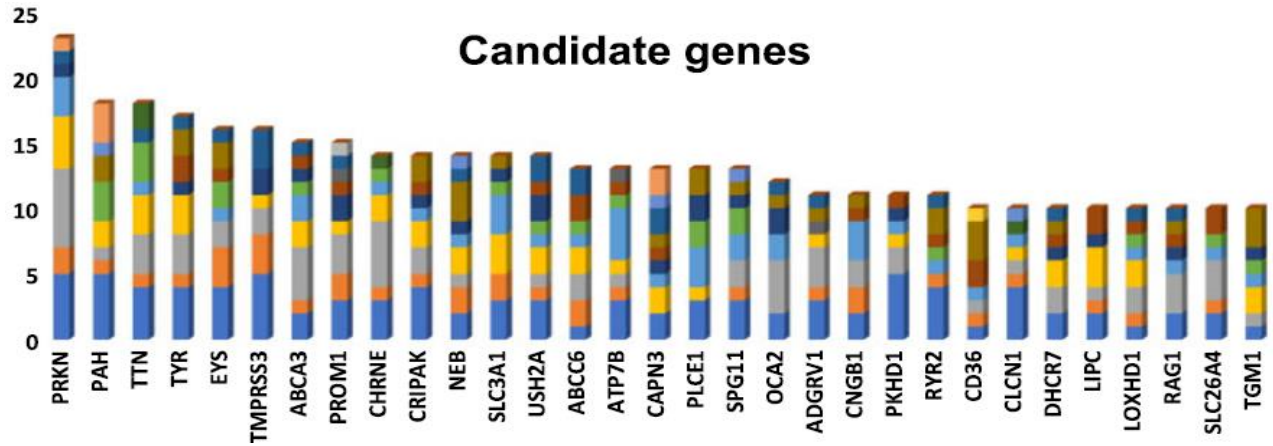
Pediatric cancer (PedCan) predisposition

- In Europe one out of 300 newborns will develop cancer before turning 20.
- In Greece we expect ~300 new cases every year.
- ~10% pediatric cancer patients carry a Pathogenic/ Likely pathogenic (P/LP) variant in Cancer Predisposing Gene (CPG)
- Novel candidate genes/variants related to pediatric cancer predisposition are expected to be found



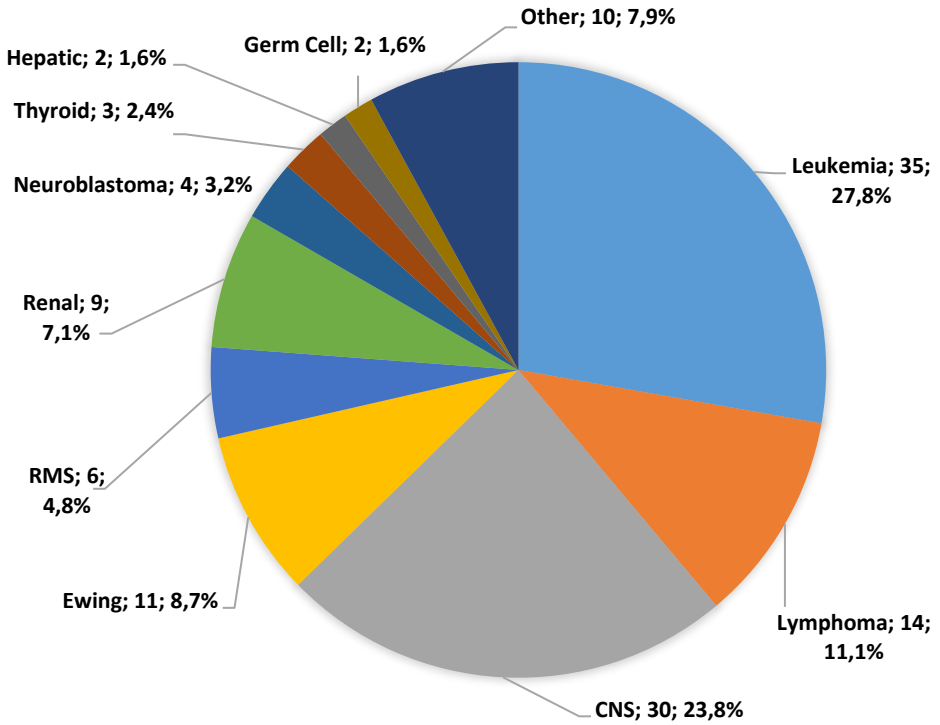
Gröbner et al., 2018 (961)

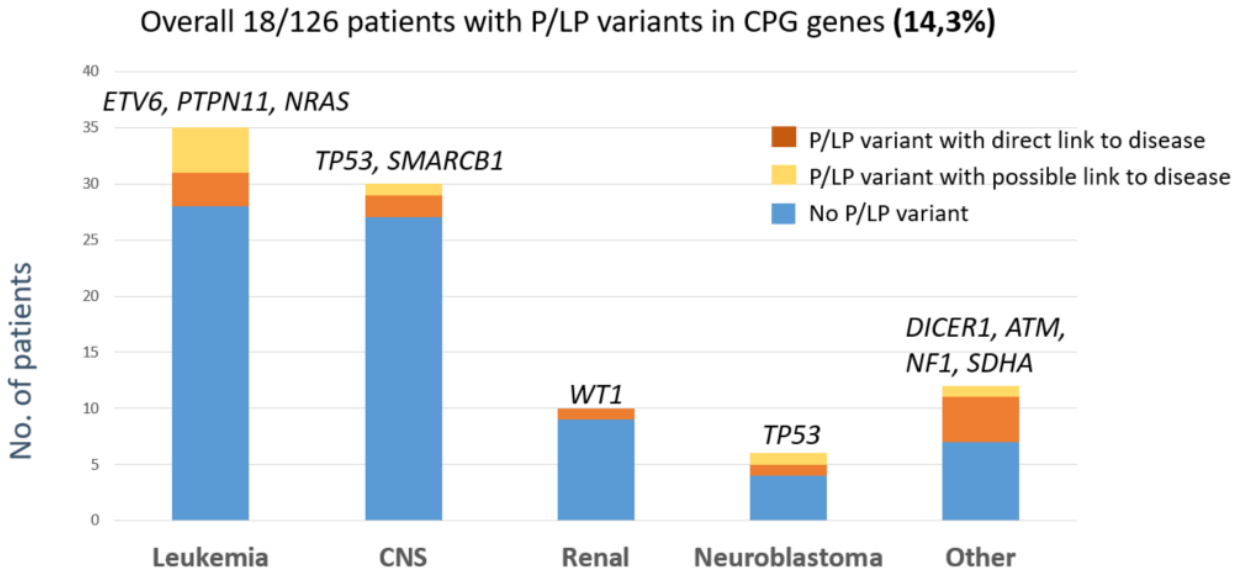


Akhavanfard et al., 2020 – Nature Commun

POHemU work on PedCan predisposition analysis

- POHemU laboratory has developed an NGS-based CPG Panel that targets ~200 genes and so far we have screened 126 PedCan patients with average age at diagnosis 9 years (0-16 years old)
- Patient inclusion criteria: cancer family history, rare tumor type or site, relapse or refractory disease

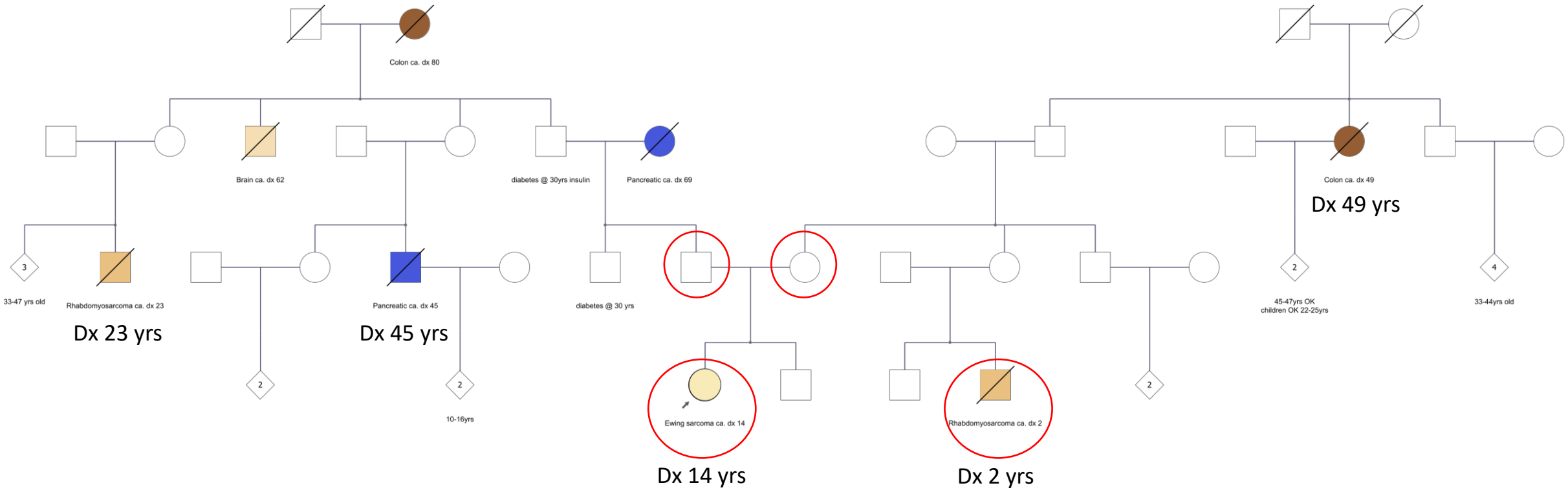




108 patients with negative results

Aim of the project

- Our aim was to perform extensive genetic analysis in families with ≥ 2 PedCan patients in order to identify new candidate causal genes/variants



Project's outline

PedCan patients who fulfill specific criteria

Negative for pathogenic (P) variants

Additional family samples collection and informed consent

Whole exome sequencing

QC, Bioinformatic analysis

Mapping, alignment, variant calling

Multiple analyses strategy

- ✓ Rare variants shared in family patients
- ✓ Digenic inheritance
- ✓ De novo variants
- ✓ Integration of data with larger studies

Whole Exome Sequencing (WES) prioritization analysis

Proband WES detected variants: 54,575

Screen for variants shared with patient

Shared variants with relative patient: 21,212

i) Screen against internal WES database

ii) Screen against large genetic databases (1000Genomes, Gnomad, MAF ≤ 0,01%)

Number of rare variants: 120

Screen for variants for Digenic inheritance

ORVAL: Oligogenic Resource for Variant AnaLysis

Screen for variants with functional impact

Number of Candidate variants: 27

8 Gene-pair combinations

ex. *GEN1* frameshift

Acknowledgments

Prof Kattamis Antonis

Avgerinou Georgia

Binenbaum Ilona

Fillipidou Maria

Glentis Stavros

Katsibardi Katerina

Perari Panagiota

Rigatou Efthimia

Roka Kleoniki

Solomou Elena

Vlachou Antonia

pMedGR

η Πίστη

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Children' s Hospital "Agia Sofia"