VHL IN THE GENOMIC LANDSCAPE OF PHEOCHROMOCYTOMA & PARAGANGLIOMA

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The Origins of the ‘Pheo Paris’ research team

Mitochondria and Hypoxia regulation

SDHB mutations in pheochromocytoma and paragangliomas
Adapted from Favier. Nat Rev Endocrinol 2015

> 40% of PPGL are genetically determined
> 40% of metastatic PPGL carry a mutation in a KC gene

SDHA SDHB SDHC SDHD SDHAF2 ATRX TMEM127 NF1 RET VHL HIF2A SLC25A11

A positive SDHB status is a high risk of malignancy and of poor prognosis.


PPGL genetic testing: a component of patient management

"...we recommend consideration of genetic testing in all patients, with testing by accredited laboratories. Patients with paragangliomas should be tested for SDHx mutations, and those with metastatic disease for SDHB mutations..."

European guidelines for the follow-up of PPGL patients

International guidelines for the management of PPGL patients

Team objectives

Clinical Genetics Genomics Molecular and Cell Biology Preclinical studies

Understand the impact of genetics in PPGL

Decipher the mechanisms of SDHB-related carcinogenesis

Promote precision medicine in PPGL

Understand the impact of genetics in PPGL
Transcriptome of 202 PGL from the COMETE collection

C1: VHL/SDHx 15% "SPORADIC"

C1A Krebs cycle genes

C1B VHL

C2: RET/NF1 85% "SPORADIC"

C2A RET/NF1 MAX, TMEM127, HRAS

C2B SPORADIC


Deciphering the transcriptome of genetically determined PPGL

451 genes p value < 10^-13

Invasiveness (MAPK, SIX1) Adhesion (DSP, CNTN4) EMT reactivation
Glycolysis (ENO1, SLC2A1)
Neuronal differentiation (SHANK2, GDF10, RET)

Burnichon, Hum Mol Genet, 2011

VHL in the genomic landscape of PPGL

Mutation
SDHx Other SDHx genes

Transcriptome
Cluster 1A Cluster 1B Cluster 2

Pathways
Adhesion Neuroendocrine differentiation (p-HIF1)

Burnichon, Hum Mol Genet, 2011

Loriot, J Clin Endocrinol Metab. 2012
Integrative multi-omics analysis

**Stratification of at high-risk patients**

>80% of PPGL carry a germline and/or a somatic mutation

Re-analysis of the COMETE cohort by NGS assay (17 genes)
Most of VHL variants in PPGL are missense

Distribution of germline variants identified by NGS assay in a prospective cohort of 541 patients with PPGL

Immunohistochemistry portfolio for VUS validation

SDHB

SDHB IHC

Van Nederven - Lancet Oncol 2009

VHL

CA IX IHC

Visit: Poster Burnichon et al.

The knowledge of genetic status opens the way to new therapeutic targets

PPGL molecular profiling: classification, prognosis, therapy

PPGL genetic testing: diagnosis, management, family counseling

The road is opened for precision medicine that will improve the prognosis of the disease
ACKNOWLEDGEMENTS

U970-Team 13
Judith Favier
Laurène Ben Aim
Alexandre Buffet
Nelly Burnichon
Lucas Castro-Vega
Judith Goncalves
Charlotte Luxey
Mélanie Ménara
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Mathilde Sibony
Frédérique Tisser

Necker hospital
Chris Ottolenghi

CIT program
Bioinformatics unit
Eric Letouzé
Aurélien de Reyms
Habib Elansh
Laure Vescovo
Jacqueline Méritat
Jacqueline Godet

Warburg effect in VHL-related PPGL

Hexokinase II expression

Lactate dehydrogenase activity

NF1/RET SDH VHL