Paired germline and somatic mutations in VHL in a patient with recurrent endometrial cancer: driver for therapeutic targeting?

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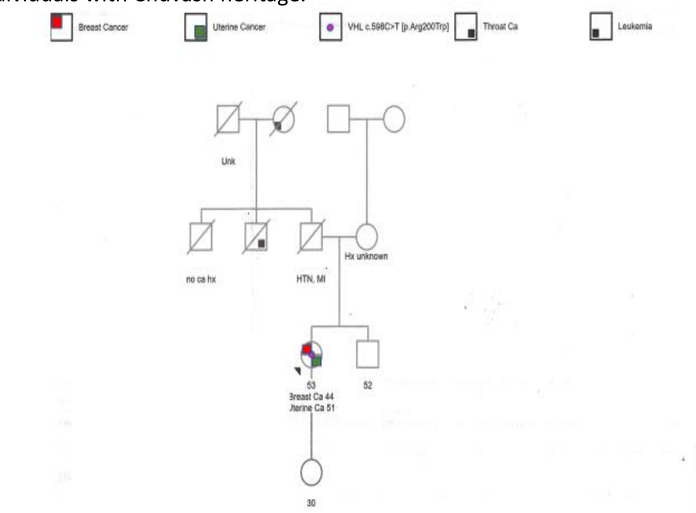
CASE REPORT & PEDIGREE

- 53 year old postmenopausal Caucasian female with history of early-stage breast cancer at age 44 (treated with surgery, and adjuvant chemotherapy), who then developed a high-grade papillary serous adenocarcinoma of the endometrium at age 53, and was treated with standard adjuvant chemotherapy (**carboplatin and taxanes**) followed by addition of **bevacizumab** for recurrent disease (metastatic).
    - CBC with chemotherapy-induced pancytopenia, elevated MCV (reactive to treatment)

- Germline testing ruled out mutations in *BRCA1, TP53, MMR,* or *PTEN;* found **heterozygous pathogenic variant in *VHL* (c.598C>T [p.Arg200Trp]),** associated with ARFE, with classic VHL syndrome in only 1 family in literature (including the VHL Alliance compilation below), and seen in 1/20 individuals with Chuvash heritage.



GENETIC COUNSELING CONSIDERATIONS:

- Offering cascade testing to offspring
- Tracking variant in sibling
- Offering breast, uterine, and kidney cancer screening

VHL c.598C>T [p.Arg200Trp]

From "An Overview of VHL Mutations" from VHL Alliance Genetic Mutations resource:

From https://www.vhl.org/wp-content/uploads/2017/07/VHL-Genetic-Mutations.pdf

- 7 entries as missense mutations across 9 studies
- 1 incidence VHL Type I
- 2 incidences RCC (sporadic after TCE exposure)
- 12 incidences polycythemia at young age

INTRODUCTION

- Pathogenic variants (PVs) in the *VHL* gene are associated with autosomal dominant von Hippel-Lindau syndrome, classically known to increase risks of renal cell cancers (RCCs), pancreatic neuroendocrine tumors, retinal and CNS hemangioblastomas, with **sensitivity to HIF inhibitors.** Variants in other locations in the VHL gene can cause autosomal recessive familial erythrocytosis (ARFE), without increased risks of these cancers.

HISTOLOGY

High-grade serous carcinoma (grade 3) of uterus with:

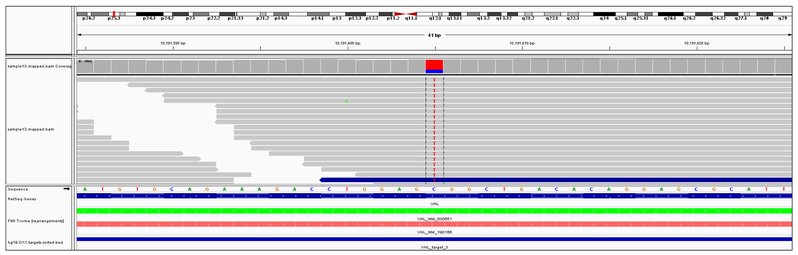
- invasion throughout myometrium
- extension to serosal surface
- extensive cervical stromal extension
- lymph-vascular space invasion
- ovaries involved by implants of serous carcinoma
- bowel nodule involved
- frozen-section showing psammoma bodies

MOLECULAR PATHOLOGY

Genomic sequencing of the original tumor was later sent at time of disease progression

- identified the same alteration in *VHL* (VAF 74%), as well as microsatellite stability, low tumor mutational burden (TMB) at 6 mutations/Mb, *ERBB2* amplification, and alterations in PIK3CA H1047R and TP53 R273C

Microsatellite status MS-Stable§	*PIK3CA* H1047R
Tumor Mutational Burden 6 Muts/Mb§	*TP53* R273C
ERBB2 amplification§	*VHL* R200W



International Genome Viewer map of the germline R200W *VHL* short variant mutation. This missense mutation was present in 73.6% of Reads.

VHL in Endometrial Cancer

Mutations in *VHL* are rare in endometrial cancer

- Xu *et al (*Int J Gynecol, 2011) reported VHL mRNA levels in endometrial carcinoma observed significantly lower than those in normal endometrium, simple hyperplasia, or complex hyperplasia ($P < 0.01$) but similar to those in atypical hyperplasia ($P > 0.05$) in study of n=47 total cases.
- Lu Y et al showed expression of VHL mRNA versus protein levels in normal human endometrium changed during menstrual cycle: mRNA levels decreased during the proliferative to secretory phase but protein levels were higher in proliferative phase than those in the secretory phase ($P<0.05$).
- **To date, VHL mutations have been identified in only 0.3% of all 12,895 endometrial carcinomas and 0.3% of 3,221 papillary serous carcinomas in the Foundation Medicine database.**

DISCUSSION QUESTION 1:

- Would this patient now have been eligible for further therapeutic intervention with belzutifan, and **would evaluating the VHL pathway in endometrial cancer have clinical benefit?**
- As the HIF pathway may be part of endometrial carcinogenesis, and could lead to poor clinical outcome, clinical trials have been proposed for therapeutic targeting.

INDICATIONS FOR BELZUTIFAN:

Mechanism of action: to inhibit hypoxia-inducible factor 2a

Indicated for (per Study 004 [NCT 03401788]):

- VHL-associated RCC (VHL-RCC) with at least one measurable solid tumor localized to the kidney
    - based on a VHL germline alteration
- Or other VHL-associated tumors including CNS hemangioblastomas and pancreatic neuroendocrine tumors (pNET)
- Tumors requiring therapy for associated renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastomas
- But not requiring immediate surgery.

DISCUSSION QUESTION 2:

- Could other cancer types be considered part of an extended spectrum of VHL-related cancers?

FUTURE DIRECTIONS:

- To query other cancers which have PVs in VHL and correlate with germline PVs
- To follow prospectively the clinical progress of patients with PVs in VHL and extended spectrum of VHL-related cancers
- To consider additional therapeutic targeting for those patients for whom conventional treatment is not optimal with **a reinterpretation of somatic genomic profiling at the time of need for therapeutic change, as this may lead to new treatment options**

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