Genomic analysis of low-grade serous ovarian cancer reveals unique therapeutic vulnerabilities

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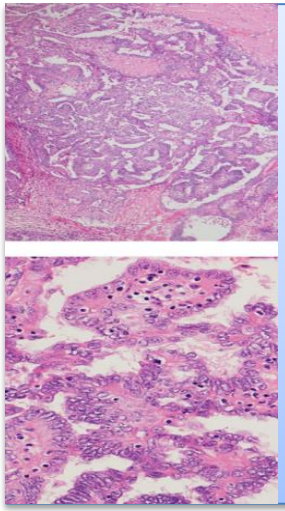
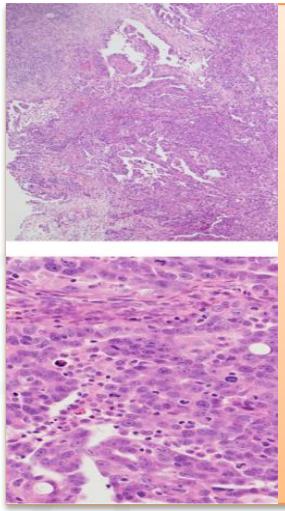
Serous ovarian cancer segregates into low- (LGSOC) and high grade (HGSOC)



Low-grade serous ovarian cancer

- ~5% of EOCs diagnosed
- *RAS/RAF* pathway frequently mutated
- Low-level DNA copy number change
- *TP53* wild-type
- Younger age of onset (45-57 years)
- Chemo resistant (increased recurrence)

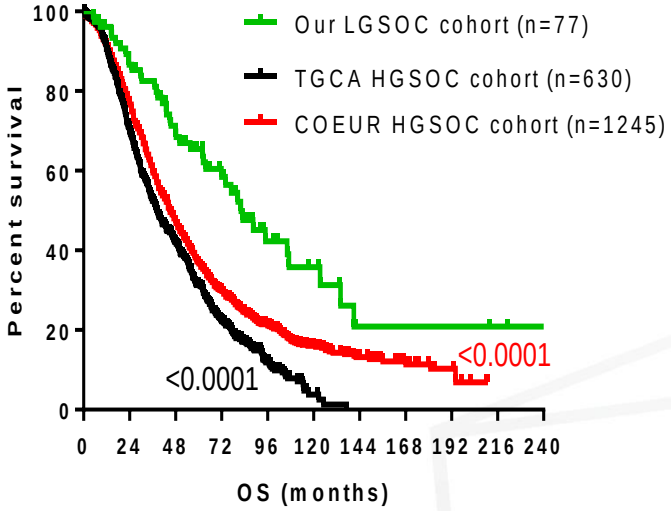


High-grade serous ovarian cancer

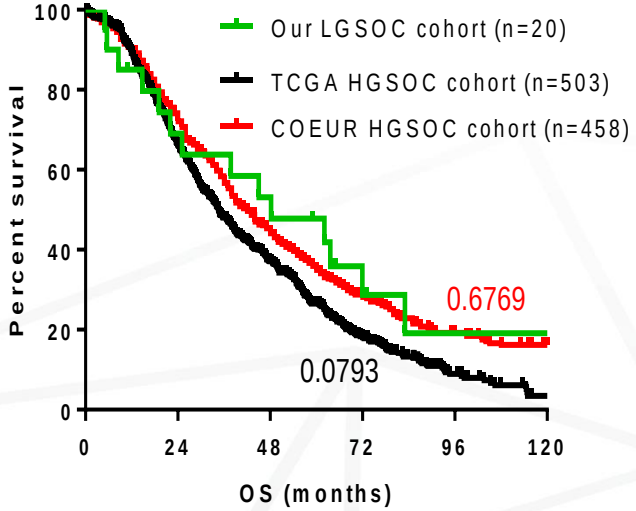
- ~75% of EOCs diagnosed
- *RAS/RAF* pathway wildtype
- Widespread DNA copy number change
- *TP53* mutated
- Older age of onset (55-55 years)
- Usually platinum sensitive

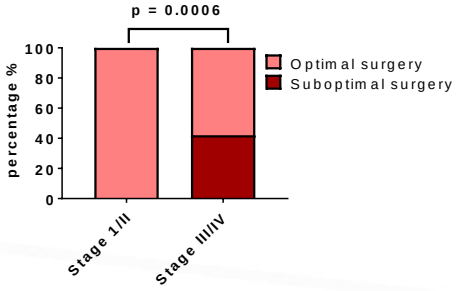
Survival analysis of LGSC compared to HGSC

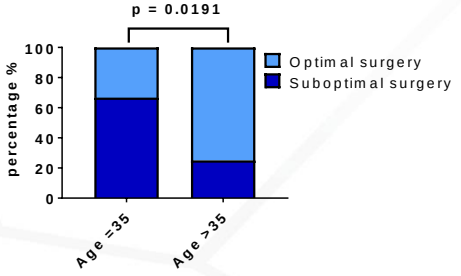
Entire cohort



Residual disease



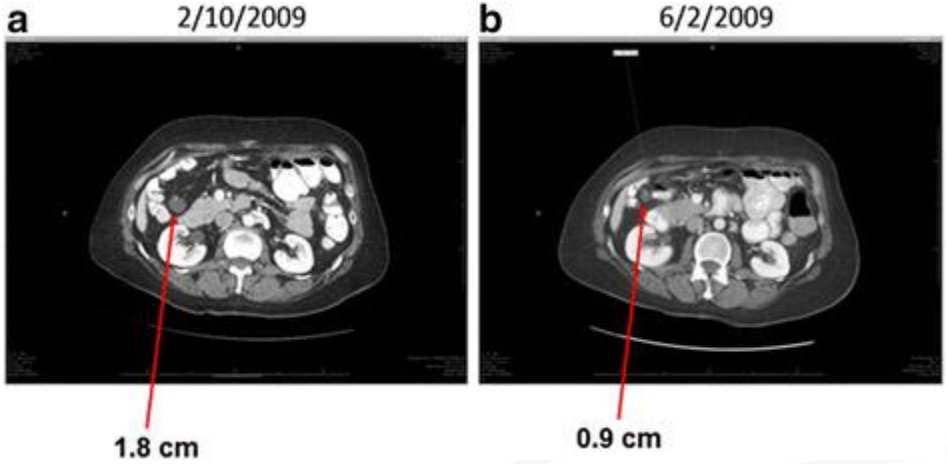




Cécile Lepage (Canadian Ovarian Experimental Unified Resource)

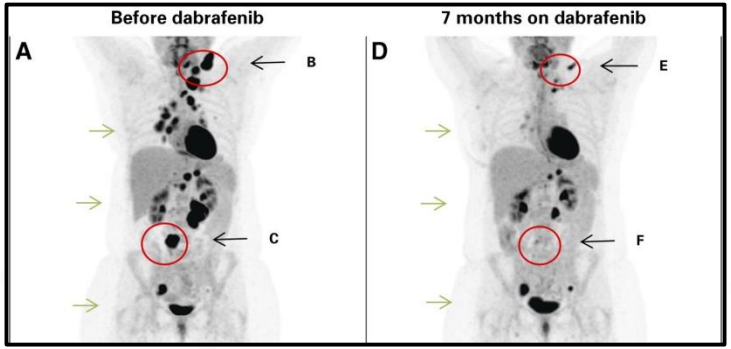
Current MEKi trials for LGSOC

KRAS G12V (Selumetinib)



Farley *et al.* (2013)

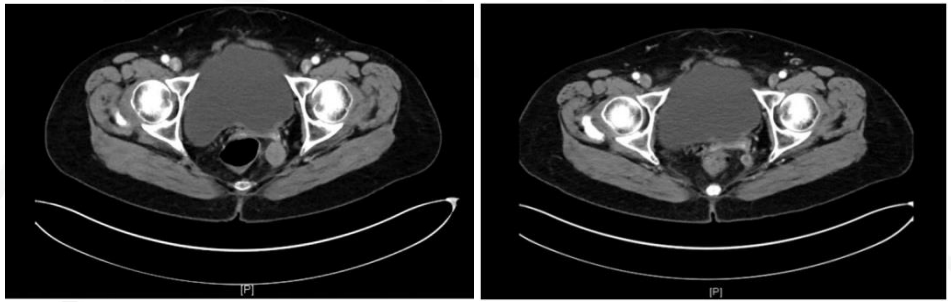
BRAF V600E (Dabrafenib)



Moujaber *et al.* (2018)

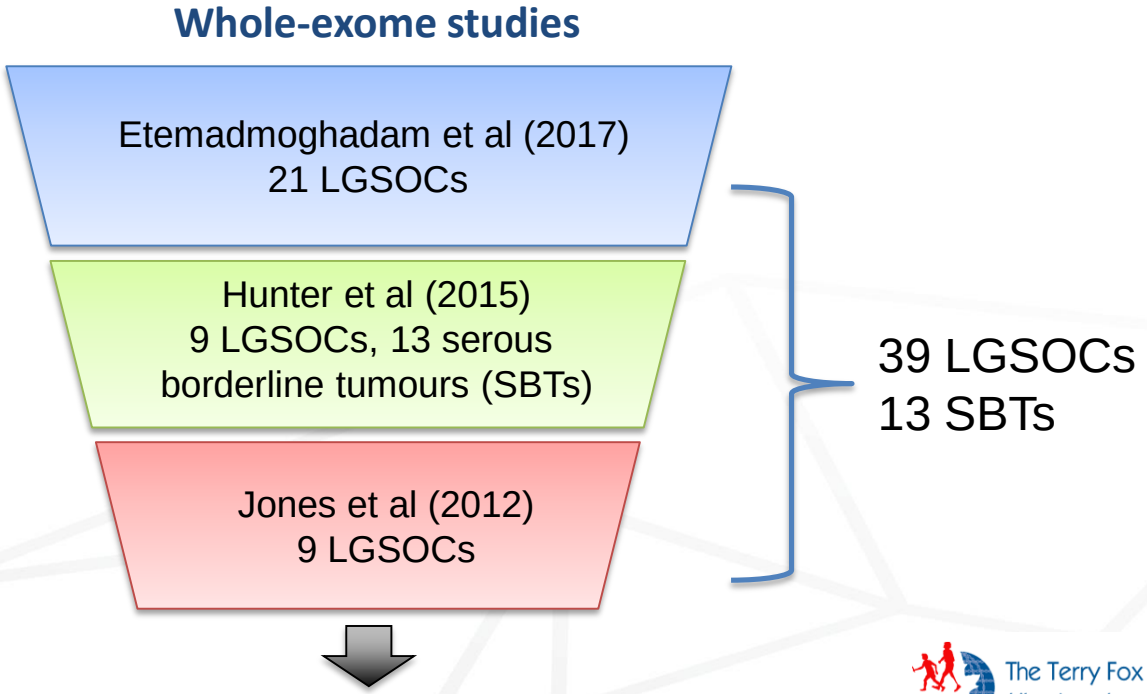
- Response in a subset of patients likely suggests that in the *RAS/RAF* mutation carriers there are other pathway alterations which can bypass the dependency of *RAS/RAF*
- Identify and functionally validate novel drivers in *RAS/RAF* negative cases

NRAS Q61K (Trametinib)



Champer *et al.* (2019)

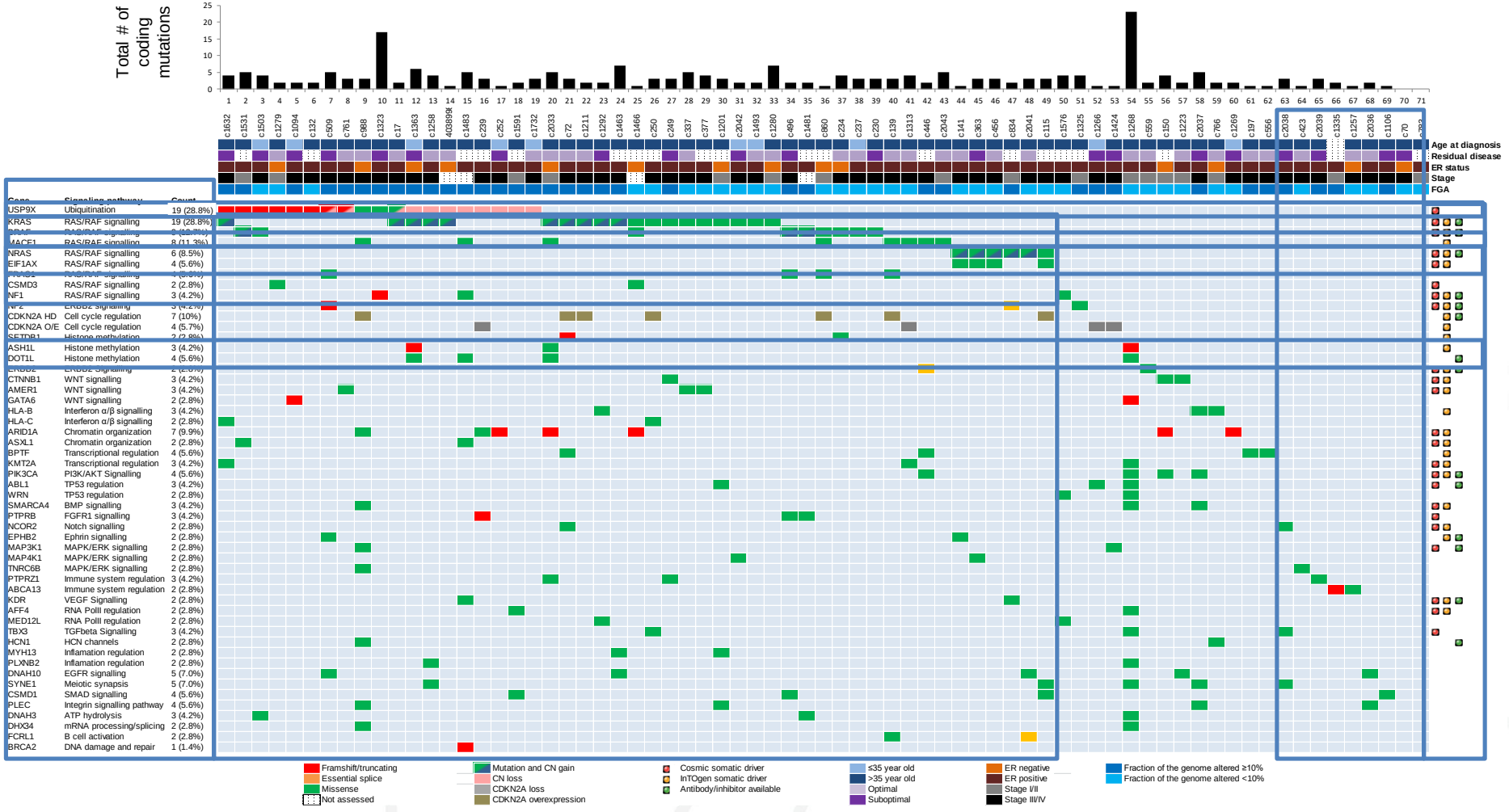
Generation of the candidate LGSOC targeted gene panel



The Terry Fox Research Institute
L'Institut de recherche Terry Fox

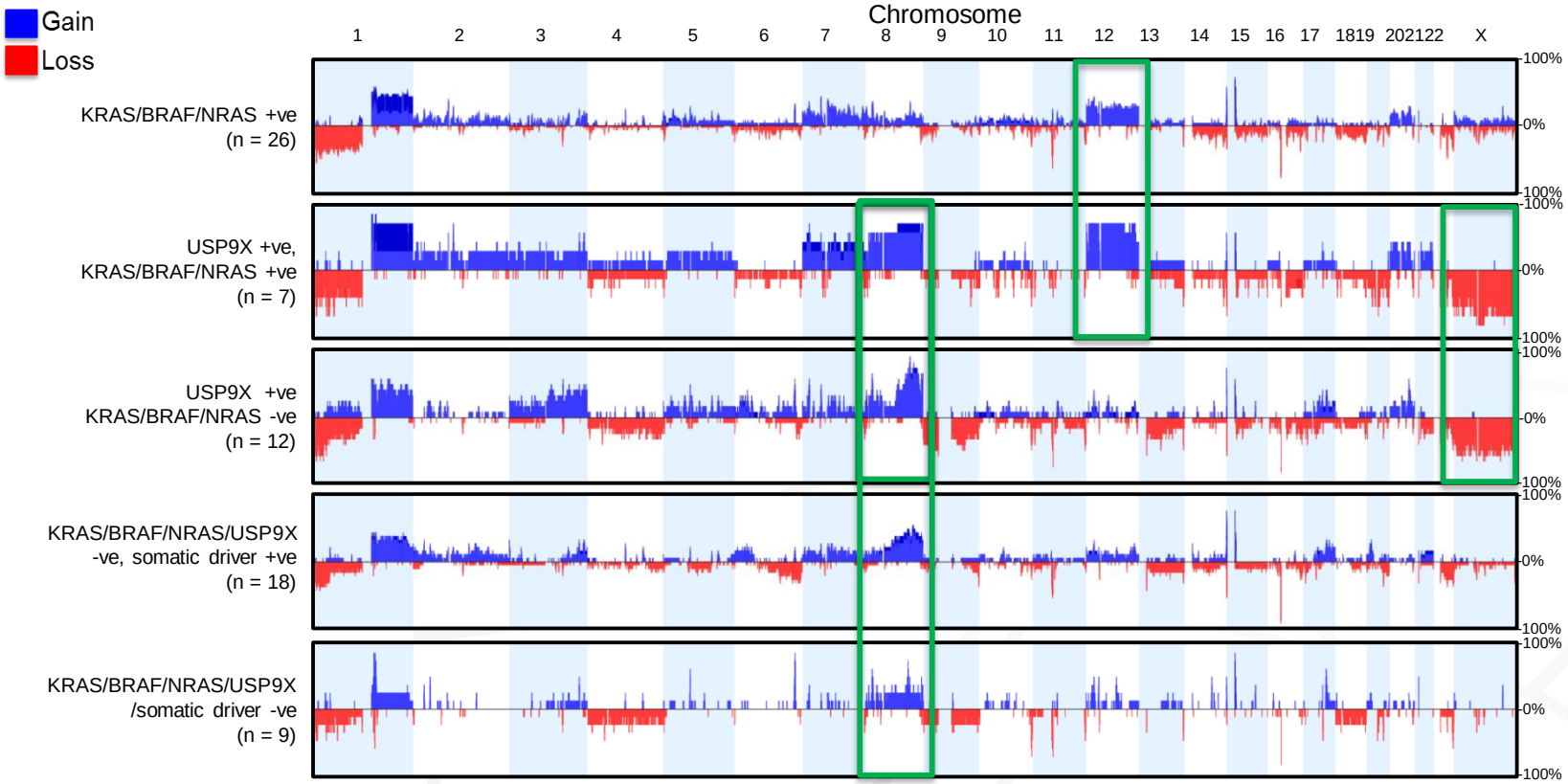
AOCS
Australian Ovarian Cancer Study

Somatic mutation profile of the low-grade serous ovarian cancer cohort

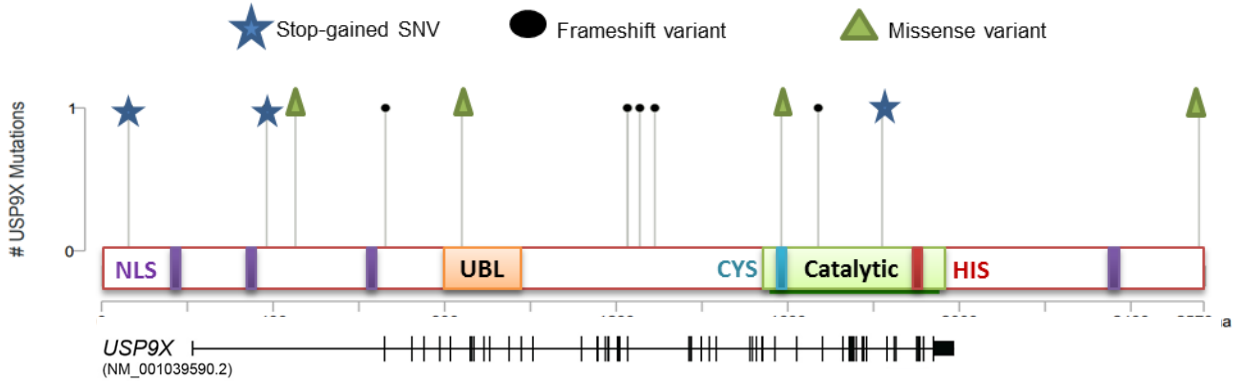


Gene	Signaling pathway	Count
USP9X	Ubiquitination	19 (28.8%)
KRAS	RAS/RAF signalling	19 (28.8%)
[illegible]	RAS/RAF signalling	9 (13.8%)
MACF1	RAS/RAF signalling	8 (11.3%)
NRAS	RAS/RAF signalling	6 (8.5%)
EIF1AX	RAS/RAF signalling	4 (5.6%)
[illegible]	RAS/RAF signalling	1 (1.5%)
CSMD3	RAS/RAF signalling	2 (2.8%)
NF1	RAS/RAF signalling	3 (4.2%)
[illegible]	ERBB2 signalling	3 (4.2%)
CDKN2A HD	Cell cycle regulation	7 (10%)
CDKN2A O/E	Cell cycle regulation	4 (5.7%)
[illegible]	Histone methylation	2 (2.8%)
ASH1L	Histone methylation	3 (4.2%)
DOT1L	Histone methylation	4 (5.6%)
[illegible]	ERBB2 signalling	2 (2.8%)
CTNNB1	WNT signalling	3 (4.2%)
AMER1	WNT signalling	3 (4.2%)
GATA6	WNT signalling	2 (2.8%)
HLA-B	Interferon α/β signalling	3 (4.2%)
HLA-C	Interferon α/β signalling	2 (2.8%)
ARID1A	Chromatin organization	7 (9.9%)
ASXL1	Chromatin organization	2 (2.8%)
BPTF	Transcriptional regulation	4 (5.6%)
KMT2A	Transcriptional regulation	3 (4.2%)
PIK3CA	PI3K/AKT Signalling	4 (5.6%)
ABL1	TP53 regulation	3 (4.2%)
WRN	TP53 regulation	2 (2.8%)
SMARCA4	BMP signalling	3 (4.2%)
PTPRB	FGFR1 signalling	3 (4.2%)
NCOR2	Notch signalling	2 (2.8%)
EPHB2	Ephrin signalling	2 (2.8%)
MAP3K1	MAPK/ERK signalling	2 (2.8%)
MAP4K1	MAPK/ERK signalling	2 (2.8%)
TNRC6B	MAPK/ERK signalling	2 (2.8%)
PTPRZ1	Immune system regulation	3 (4.2%)
ABCA13	Immune system regulation	2 (2.8%)
KDR	VEGF Signalling	2 (2.8%)
AFF4	RNA PolII regulation	2 (2.8%)
MED12L	RNA PolII regulation	2 (2.8%)
TBX3	TGFbeta Signalling	3 (4.2%)
HCN1	HCN channels	2 (2.8%)
MYH13	Inflamation regulation	2 (2.8%)
PLXNB2	Inflamation regulation	2 (2.8%)
DNAH10	EGFR signalling	5 (7.0%)
SYNE1	Meiotic synapsis	5 (7.0%)
CSMD1	SMAD signalling	4 (5.6%)
PLEC	Integrin signalling pathway	4 (5.6%)
DNAH3	ATP hydrolysis	3 (4.2%)
DHX34	mRNA processing/splicing	2 (2.8%)
FCRL1	B cell activation	2 (2.8%)
BRCA2	DNA damage and repair	1 (1.4%)

Copy number analysis of low-grade serous ovarian carcinomas



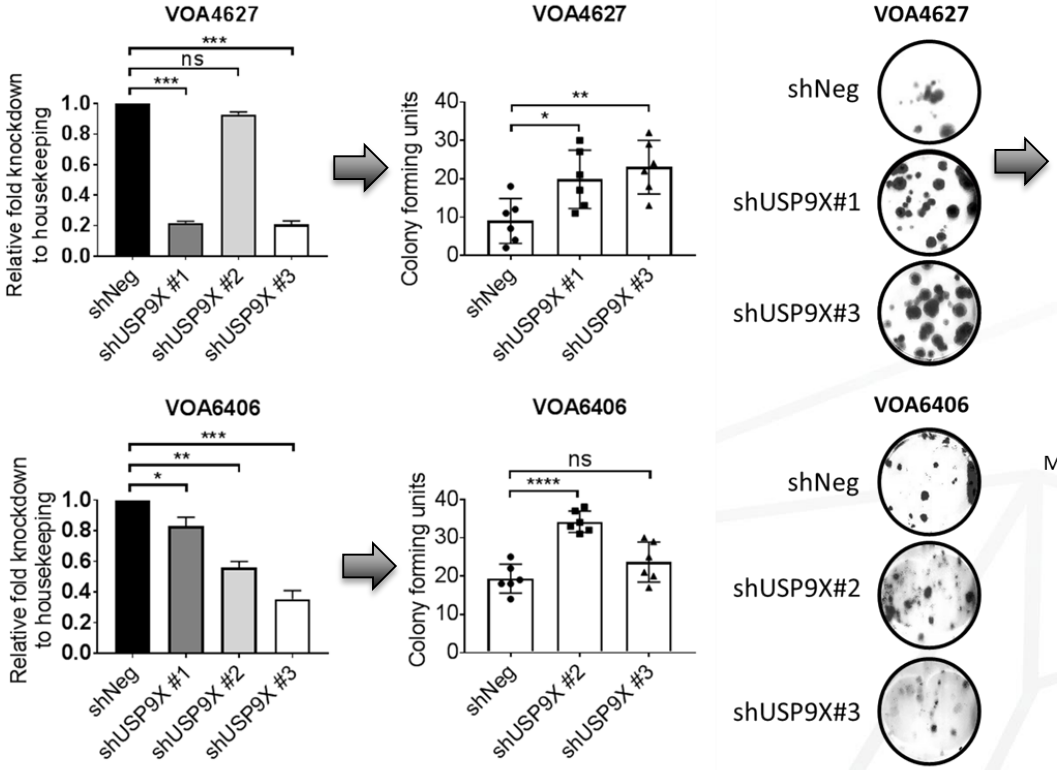
USP9X appears to act as a haploinsufficient tumor suppressor gene



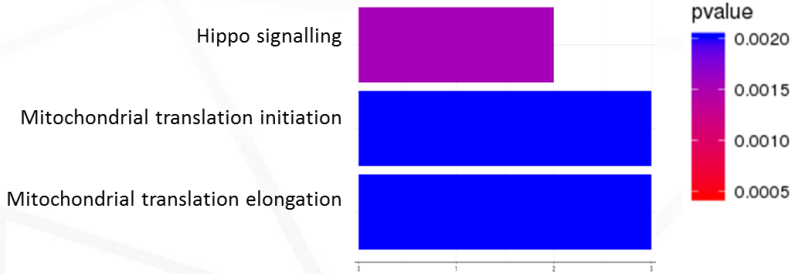
Sample ID	USP9X nucleotide position	USP9X protein change	Mutation type	Read depth	USP9X allele frequency	USP9X CN loss	Predicted allelic status USP9X	Mutation within domain	Condel	PolyPhen	SIFT	REVEL	CADD
c1632	c.187G>T	p.E63*	Stop-gained	340	0.56	No	Heterozygous	No					
c1279	c.1981_1982insT	p.R662*	Frameshift	202	0.43	No	Heterozygous	No					
c988a	c.2518G>A	p.V840I	Missense	871	0.37	No	Heterozygous	UBL	N	N	N	N	N
c1094	c.3679delG	p.D1227fs*12	Frameshift	216	0.50	No	Heterozygous	No					
c132	c.3867delG	p.E1290fs*2	Frameshift	863	0.48	No	Heterozygous	No					
c1323	c.4755T>G	p.I1585M	Missense	260	0.47	No	Heterozygous	Catalytic CYS	Y	Y	N	N	N
c1503	c.5013delC	p.F1671Ffs*17	Frameshift	441	0.50	No	Heterozygous	Catalytic					
c1531	c.5458C>T	p.R1820*	Stop-gained	1238	0.38	No	Heterozygous	Catalytic					
c988b	c.7675A>G	p.S2559G	Missense	831	0.53	No	Heterozygous	No	N	N	N	N	N
c509	c.1153C>T	p.R385*	Stop-gained	228	0.83	Yes	Loss wildtype	No					
c17	c.1355T>G	p.L452R	Missense	330	0.80	Yes	Loss wildtype	No	N	N	Y	Y	N
c761	c.3761_3762insA	p.Q1255Tfs*5	Frameshift	283	0.92	Yes	Loss wildtype	No					

- USP9X appears to escapes promoter methylation
- + 8 samples with USP9X copy loss
- USP9X haploinsufficienty has been documented

Functional validation of USP9X knockdown



Proteins down-regulated in VOA4627 cells following knockdown



Article | OPEN | Published: 29 March 2016

Deubiquitylating enzyme USP9x regulates hippo pathway activity by controlling angiomotin protein turnover

Hung Thanh Nguyen, Diana Andrejeva, Rajat Gupta, Chunaram Choudhary, Xin Hong, Pieter J A Eichhorn, Anand C Loya & Stephen M Cohen

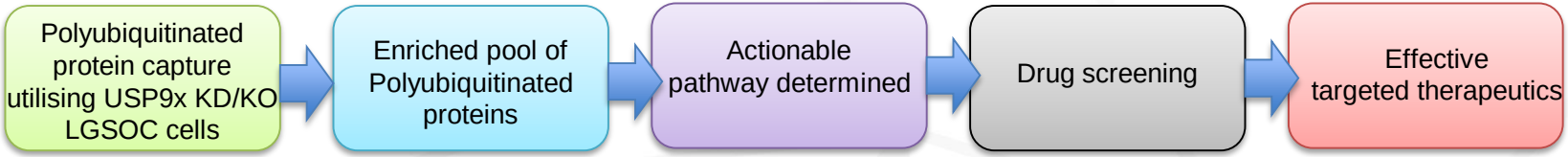
Cell Discovery **2**, Article number: 16001 (2016) | Download Citation

renal clear cell carcinomas

Abhimanyu Nigam

Future directions for the study

- ~40 additional LGSOC samples to sequence
- phosphor MAPKp44/p48, ERK1/2 IHC on TMA – Dr Martin Koebel
- Identify the molecular context of USP9X-regulated processes across our LGSOC cell line panel



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Faculty Disclosure

✓	No, nothing to disclose
	Yes, please specify:

	Honoraria/ Expenses	*Consulting/ Advisory Board*	*Funded Research*	*Royalties/ Patent*	*Stock Options*	*Ownership / Equity Position*	*Employee*	*Other (please specify)*

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- Tim Semple

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- Canadian Ovarian Experimental Unified Resource (COEUR, Cécile Lepage)
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AUSTRALIAN GYNAECOLOGICAL CANCER FOUNDATION

The Way-In Network