CORRESPONDENCE

doi: 10.1093/jnci/djw143 First published online July 14, 2016 Correspondence

# RE: HABP2 G534E Mutation in Familial Nonmedullary Thyroid Cancer

# Pasquale Simeone, Saverio Alberti

Affiliations of authors: Unit of Cytomorphology, Center of Excellence on Aging and Translational Medicine (CeSI-MeT) and Department of Medicine and Aging Sciences, School of Medicine and Health Sciences, University "G. d'Annunzio", Chieti, Italy (PS); Unit of Cancer Pathology, Center of Excellence on Aging and Translational Medicine (CeSI-MeT) and Department of Neuroscience, Imaging and Clinical Sciences, Unit of Physiology and Physiopathology, University 'G. d'Annunzio,' Chieti, Italy (SA)

Correspondence to: Saverio Alberti, MD, PhD, Unit of Cancer Pathology, CeSI-MeT, University "G. D' Annunzio," via L. Polacchi 11, 66100 Chieti Scalo, Chieti, Italy (e-mail: s.alberti@unich.it).

In a recent report, Zhang et al. (1) investigated families affected by nonmedullary thyroid cancer (FNMTC) and detected G534E mutations in the Hyaluronan-Binding Protein 2 (HABP2) in 13.8% of the kindreds. None of the normal subjects or patients with benign thyroid neoplasms were found to carry the G534E mutation. Germline HABP2 mutations were previously identified in hereditary FNMTC (2). Such HABP2 polymorphism was indicated to cause loss of function and higher transforming capacity. These studies were met with criticism as HABP2 G534E prevalence in control populations was found to be close to that in affected individuals. Moreover, frequency variation across human populations (cancergenome.nih.gov) appeared just as large as that across experimental subgroups (1,2). It should also be pointed out that even in kindreds where HABP2 G534E appeared associated to FNMTC (1,2) only a fraction of patients carried the mutation. Taken together, these findings indicated that factors other than the HABP2 G534E mutation played a role in FNMTC.

We argue that the impact of HABP2 on cancer does not depend on protein sequence mutations.

Disregulation of expression of HABP2, ie, downregulation or upregulation vs normal tissue levels, is associated with several cancer histotypes (www.proteinatlas.org/ENSG00000148702-HABP2/cancer) (Figure 1). Both deletion and amplification of the HABP2 gene were found in pancreatic cancer (3). Nextgeneration transcriptome sequencing defined a core set of 12 cellular signaling pathways, which were altered in 67% to 100% of the tumors. Convergent evidence indicated highest impact of HABP2 on PI3K-driven networks (3). HABP2 was downregulated by miRNA in colon cancer. Similar findings were obtained in non-small cell lung cancer (4). Either up or downregulation in cancer vs normal tissues is found in breast, endometrium, ovary, pancreas, testis, and thyroid (Figure 1). The Cancer Genome Atlas investigators found a three-fold lower expression of HABP2 in gliomas (cancergenome.nih.gov). High levels of HABP2 are most frequently observed in ovarian, prostate, gastric, and pancreatic cancer (Figure 1).

Wild-type HABP2 expression in cancer is altered through multiple distinct mechanisms. HABP2 mRNA levels were found divergently regulated vs corresponding protein levels (Figure 1, left), suggesting post-transcriptional and post-translational regulation. HABP2 transcripts were shown to take part to mRNA chimeras in tumors (5). Most such chimeras possess transforming activity (6,7). mRNA chimeras cause altered mRNA stability and protein translation capacity. This is key to acquisition of transforming ability and is not related to oncogene-like protein mutations (6). Further, HABP2 was found to be epigenetically disregulated by H3K27Me3 and H3K4Me3 (cancergenome.nih.gov). Mutations in HABP2 intron 7 were then found in breast cancer (cancergenome.nih.gov), consistent with a transformation ability beyond protein coding sequence mutations. Notably, the very same protein codon mutations can lead to reduced mRNA half-life ([6] and references therein).

In summary, disregulation of HABP2 expression is heavily associated with cancer whereas the HABP2 G534E mutation is not. We argue that investigation of the functional impact of HABP2 disregulation in cancer and of the control mechanisms identified above may provide key insights on the role of HABP2 in FNMTC and in other solid tumors.

## Funding

This work was supported by the Italian Association for Cancer Research (AIRC, Italy), the Ministry of the University

Received: March 31, 2016; Accepted: April 26, 2016

<sup>©</sup> The Author 2016. Published by Oxford University Press. All rights reserved. For Permissions, please e-mail: journals.permissions@oup.com.

Α			В					
			Tissue	Cancer staining	Protein expression of normal tissue	Tissue	Cancer staining	Protein expression of normal tissue
			Breast cancer		normal tissue	Melanoma		
			Carcinoid			Ovarian cancer		
RNA		Protein	Cervical cancer			Pancreatic cancer		
Expression	Organ system	Localization (score)	Colorectal cancer			Prostate cancer		
	Uver and pantoress Uver		Endometrial cancer			Renal cancer		
<del></del> _	Galibladder		Glioma			Skin cancer		
	Pancreas Digestive tract (G&tract)		Head and neck cancer			Stomach cancer		
NA	Oral mucosa Salivary gland		Liver cancer			Testis cancer		
	Esophagus		Lung cancer			Thyroid cancer		
	Stomach Duodenum		-					
	Small intestine		Lymphoma			Urothelial cancer		
	Appendix							
	Colon Rectum							
	Uninery tract (Kidney and bladder)		Undetectable			High		
1	Kidney	_	•					
	Urinary bladder Male reproductive system (Male tissues)		С					
	Tests			and the second second	1. 199	9 18 6 8 11 24		15 1 1
NA	Epididymis	_	ALL IN M	S. Ander				Frank MAR
NA	Prostate Seminal vesicle		and the second second	1-96 Land 1 1	1. 1. 1. 1.	Carl Bank Bank	SEAL AND AND A	100
S.	Breast and female reproductive system		Philip Philipping	ALCON TRUE	11.00	Statistics .	STELL SHOWER	A 10 51
NIA	Breast	_	Store The Asia	AP CONTRACTOR	Net and	and the parties	ALL AND ALLAND	1 Stalle
NA NA	Vagina Cervix, uterine		Per and all	A Charles and the		State Shill	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	1 1 1 1 1 1
	Endometrium		1 2 1 1 5 B	Contain and the se	1	1000 121	115 4 7 1 23	Berlin
1	Fallopian tube		B. C. C. In Brile	still - in any to	31 - 3	COCHI 13	<b>同于任此在于在4月</b> 月	10/18-38
	Ovary		St. St. Ash	In Edit Cart & Martin		Dette state	A State of State	219 200
	Placenta Shin and soft tasses			and the second state of the second	1.4	1200	THE REAL PROPERTY AND	R. R.
	Skin and soft testures Skin		a Starting and	a man a life wall	110 200	and the day		D-200 02
	Adipose tissue	_	the second	11	1.710-2	11 San 11	ST PROVIDE	Set Harrs
	Skeletal muscle		Carl Starting			Sector Sector	Not the second s	11 10 10 10 10 10 10 10 10 10 10 10 10 1
	Smooth muscle			Lung can	cer 🚪	Strange St.	Prostate	cancer 🚪
NA	Soft tissue Nood and knowine system (Nextstopoletic)			C. C. State Street Street Street Street	1000		State of the second	51 5 Stor 1
	Bone marrow		1 2 1 1 1 1 4 1 K	A STATE AND A S	Sec. 136.30			and the state
	Lymph node		15 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	用空間的 建复加分子	BEN SA			MAN STR
	Tonsil Spieen		and the state of the		1. 19 7. 8	A PROPERTY AND A PROP		AND AND AND
	Central nervous system (Brain)			and the second second	M.W.B	N		TE ET
	Cerebral cortex		Same Section for	and the states of the states	a harris	Contraction of	C) X	128.184
NA	Hippocampus Lateral ventricle		<b>的公共</b> 会计算机	Personal States of the States		14 10 107		THE TOP C
NA	Cerebellum		A Contractor and	Man - AN RALLING	A. 16 19	0	the state of the s	18 2 30
	Endocrine glands			in the set of the	12 11 102	and the second		and the first
NA	Thyroid gland Parathyroid gland		品。····································	A TRACK STATISTICS	N 1 3 1	The Se MAL	TO PART	A STOR
	Adrenal gland	-	a start and a start of	State & Contractory	-11 m to		189 1 St 1 1	Se of a
	Respiratory system (Lung)		State Reading	M. W. C. P. M. B. AV.	130 350	I That is	CHARLES AND	
N/A N/A	Nasopharynx Bronchus		1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1	and the strength of the	部是代	A JAK SE		Contration of
	Lung	_	And the second s	Wig. Statist of		KE STORE	0	
	Cardiovascular system		and aller and a	Glio	ma 📲	AND NO C	Ovarian	cancer 🚦
	Heart muscle		and a sale of	The second of the second	all and all		Service -	2 22 20 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0

Figure 1. HAPB2 expression in normal and transformed tissues (www.proteinatlas.org/ENSG00000148702-HABP2/cancer). A) Expression in normal tissues at the mRNA (left bars) and protein levels (right bars). Bars: 15 µm. B) Comparative levels of expression of the HABP2 protein in normal organs and corresponding cancers. Expression levels were color-coded as indicated. C) HABP2 protein expression in lung, prostate, brain, and ovary tumors, as detected by immunohistochemistry (www.proteinat las.org/ENSG00000148702-HABP2/antibody). Bars: 30 µm.

and Research (MIUR, Italy) (SCN\_00558), and the Ministry of Development (MISE, Italy) (MI01\_00424).

### Notes

The study sponsor had no role in the design of the study, in the collection, analysis, or interpretation of the data, in the writing of the manuscript, or in the decision to submit the manuscript for publication. The authors declare no conflicts of interest.

### References

1. Zhang T, Xing M. HABP2 G534E Mutation in Familial Nonmedullary Thyroid Cancer. J Natl Cancer Inst. 2016;108(6):djw108.

- Gara SK, Jia L, Merino MJ, et al. Germline HABP2 Mutation Causing Familial Nonmedullary Thyroid Cancer. N Engl J Med. 2015;373(5):448–455.
- Jones S, Zhang X, Parsons DW, et al. Core signaling pathways in human pancreatic cancers revealed by global genomic analyses. *Science*. 2008;321(5897): 1801–1806.
- Mirzapoiazova T, Mambetsariev N, Lennon FE, et al. HABP2 is a Novel Regulator of Hyaluronan-Mediated Human Lung Cancer Progression. Front Oncol. 2015;5:164.
- McPherson A, Hormozdiari F, Zayed A, et al. deFuse: an algorithm for gene fusion discovery in tumor RNA-Seq data. PLoS Comput Biol. 2011;7(5): e1001138.
- Guerra E, Trerotola M, Dell' Arciprete R, et al. A bi-cistronic CYCLIN D1-TROP2 mRNA chimera demonstrates a novel oncogenic mechanism in human cancer. *Cancer Res.* 2008;68(19):8113–8121.
- Plebani R, Oliver GR, Trerotola M, et al. Long-range transcriptome sequencing reveals cancer cell growth regulatory chimeric mRNA. Neoplasia. 2012;14(11): 1087–1096.