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Prevalence of *HOXB13* G84E germline mutation and prostate cancer risk in the UK

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Disclosure slide

- Research funded by CRUK
- The Ronald and Rita McAulay Foundation

HOXB13 gene

- The *HOX* genes are a subfamily of the homeobox superfamily of transcription factors
- There are *HOX* clusters on chromosomes 7 (HOXA), 17 (HOXB), 12 (HOXC), and 2 (HOXD)
- The genes within each *HOX* cluster are essential for the pattern formation of the human body
- *HOX* genes in paralogue group 13 are involved in the developing of the urogenital system in vertebrates
- *HOXB13* maintains a high expression level into adulthood in normal prostate

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Germline Mutations in *HOXB13* and Prostate-Cancer Risk

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- Prostate cancer region of linkage17q21-22

- Non-synonymous mutation in *HOXB13,* a change of adenosine for guanine (transition, c.251G→A) in the second position of codon 84 (GGA→GAA) resulting in a non-conservative substitution of glycine for glutamic acid (G84E).

- European men with prostate cancer more likely to carry the *HOXB13* G84E allele (carrier frequency, 1.4%) than healthy controls (carrier frequency, 0.1%) (odds ratio in families, 20.1; 95% CI 3.5 to 803.3)

- Carrier frequency in men with early-onset prostate cancer (3.1%)

MADRID 2014 ESMO congress

International Consortium for Prostate Cancer Genetics (ICPCG)

Hum Genet (2013) 132:5–14
DOI 10.1007/s00439-012-1229-4

ORIGINAL INVESTIGATION

***HOXB13* is a susceptibility gene for prostate cancer: results from the International Consortium for Prostate Cancer Genetics (ICPCG)**

Jianfeng Xu · Ethan M. Lange · Lingyi Lu · Siqun L. Zheng · Zhong Wang · Stephen N. Thibodeau · Lisa A. Cannon-Albright · Craig C. Teerlink · Nicola J. Camp · Anna M. Johnson · Kimberly A. Zuhlke · Janet L. Stanford · Elaine A. Ostrander · Kathleen E. Wiley · Sarah D. Isaacs · Patrick C. Walsh · Christiane Maier · Manuel Luedeke · Walther Vogel · Johanna Schleutker · Tiina Wahlfors · Teuvo Tammela · Daniel Schaid · Shannon K. McDonnell · Melissa S. DeRycke · Geraldine Cancel-Tassin · Olivier Cussenot · Fredrik Wiklund · Henrik Grönberg · Ros Eeles · Doug Easton · Zsofia Kote-Jarai · Alice S. Whittemore · Chih-Lin Hsieh · Graham G. Giles · John L. Hopper · Gianluca Severi · William J. Catalona · Diptasri Mandal · Elisa Ledet · William D. Foulkes · Nancy Hamel · Lovise Mahle · Pal Moller · Isaac Powell · Joan E. Bailey-Wilson · John D. Carpten · Daniela Seminara · Kathleen A. Cooney · William B. Isaacs · International Consortium for Prostate Cancer Genetics

Received: 13 July 2012 / Accepted: 15 September 2012 / Published online: 12 October 2012

- In this study of 2443 prostate cancer families of European descent the G84E mutation was found in 4.6% of families.
- The proportion was highest in families from the Nordic countries of Finland (22.4 %) and Sweden (8.2 %) and lower in North America (0–6.1 %) and Australia (2.6 %).
- The odds ratio (OR) for prostate cancer was 4.4 for the G84E mutation carriers.
- The mean age at diagnosis of carriers was 62.8 years compared with patients without the mutation (64.4 years)

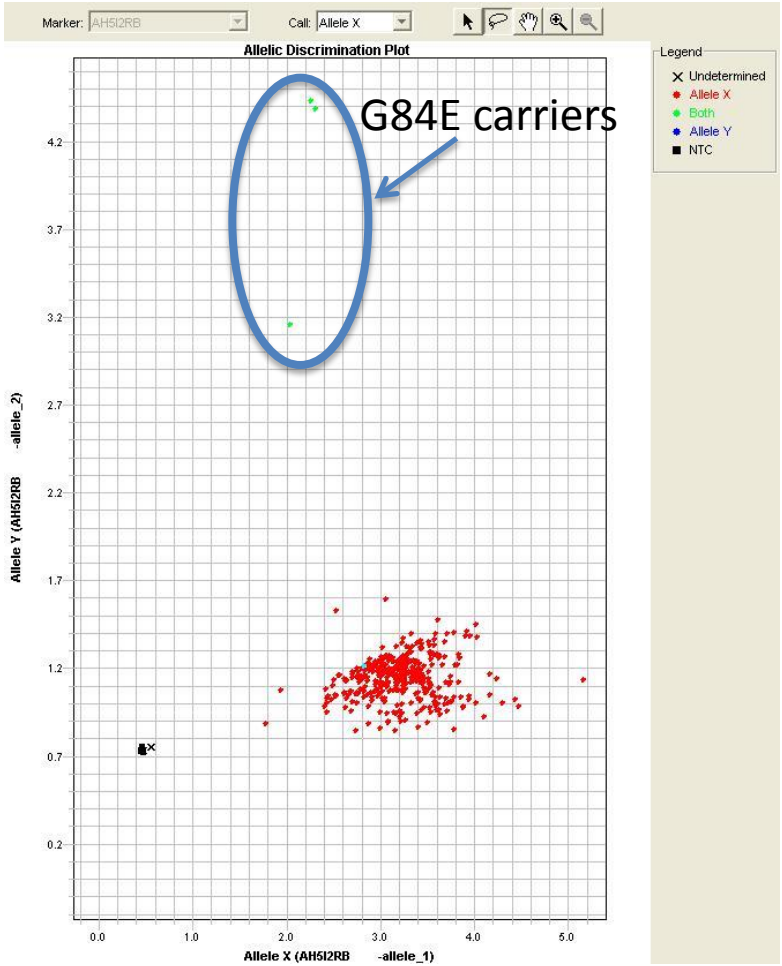
UK Study Results

TaqMan assay

(Applied Biosystem/Life Technologies)

- genotyping data for 8652 PrCa cases (UKGPCS)and 5252 controls (ProtecT)

- 2 duplicate samples and 4 positive and 4 negative controls were included on each 384 well plate



Results – the UK

- *HOXB13* G84E identified in 0.5% of healthy controls *vs.* 1.5% of prostate cancer (PrCa) cases.
- OR=2.93 (95%CI: 1.94-4.59) relative risk of PrCa
- OR=4.53 (95%CI:2.86-7.34) relative risk of familial PrCa
- OR=3.11(95%CI:1.98-5) relative risk of early-onset PrCa (under 55 years)

There was no significant association of HOXB13G84E with:

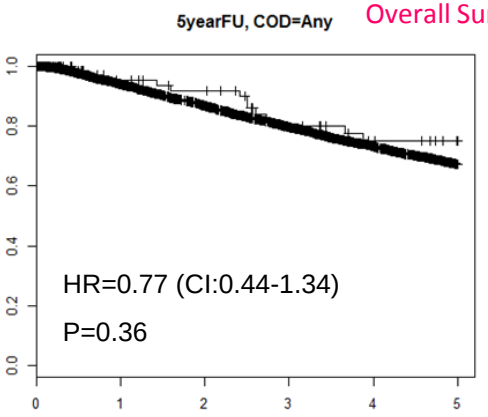
1.Gleason Score
2. Presenting PSA
3. TNM stage
4. NCCN risk

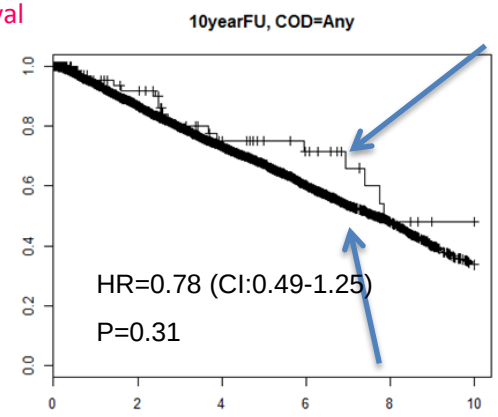
Characteristic	Carriers N	Carriers %	Noncarriers N	Noncarriers %	P(carriers vs noncarriers
Age					
Median	59		59		0.735
Range	37-79		36-89		
Median PSA	8.625		8.3		0.363
FH					
No	60	47.6	4847	64.1	<0.001
Yes	66	52.4	2718	35.9	
Unknown	8	6	953	11.2	
TStage					
T1	26	23.4	1845	27.3	0.836
T2	49	44.1	2608	38.6	
T3	32	28.8	2008	29.8	
T4	4	3.6	287	4.3	
Unknown	23	17.2	1770	20.8	
NStage					
N0	76	91.6	4444	90.2	0.826
N1	7	8.4	481	9.8	
Unknown	51	38.1	3593	42.2	
MStage					
M0	70	92.1	4222	86.4	0.206
M1	6	7.9	662	13.6	
Unknown	58	43.3	3634	42.7	
NCCN					
Low	24	19.8	1428	19.6	0.079
Intermediate	51	42.1	2420	33.2	
High	30	24.8	2013	27.6	
VeryHigh	5	4.1	466	6.4	
Metastatic	11	9.1	966	13.2	
Unknown	13	9.7	1225	14.4	

Survival Data

- No impact on overall and prostate cancer specific survival

Overall Survival

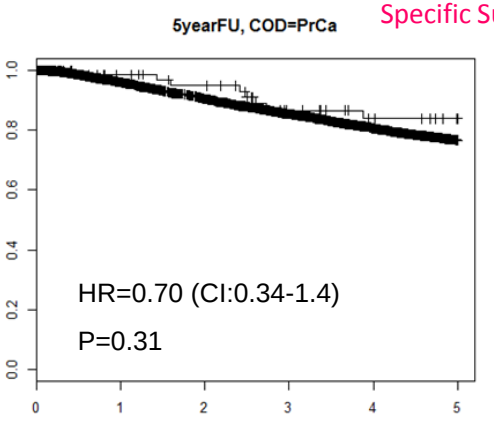


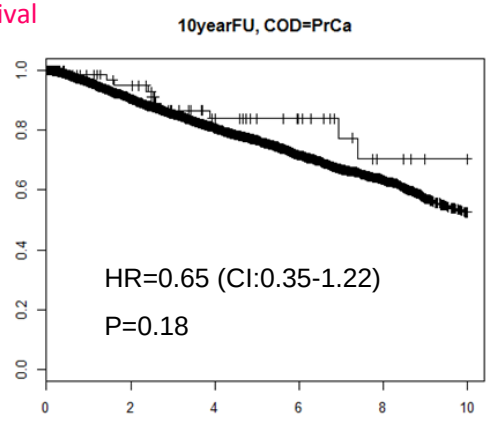


G84E carrier

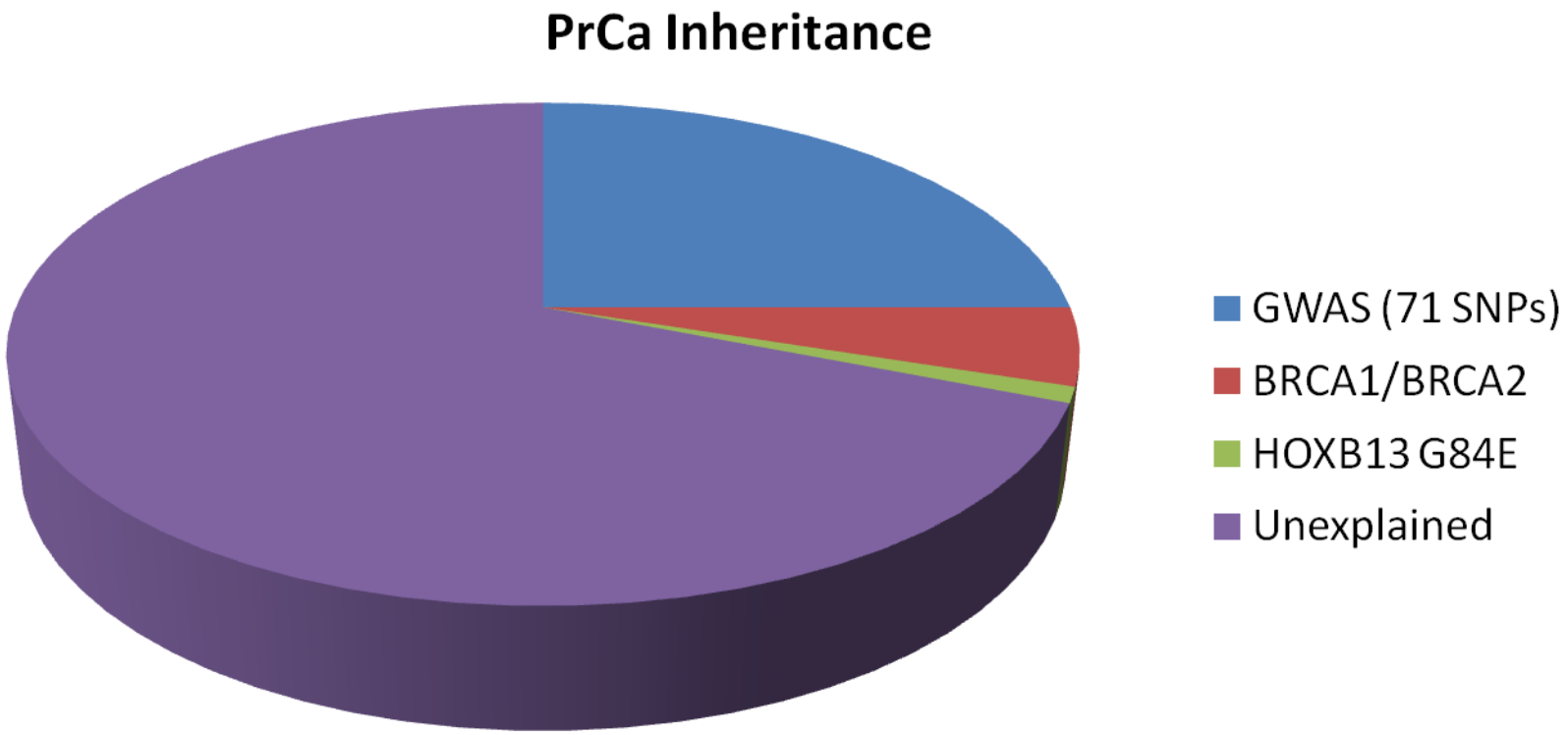
control

Prostate Cancer Specific Survival

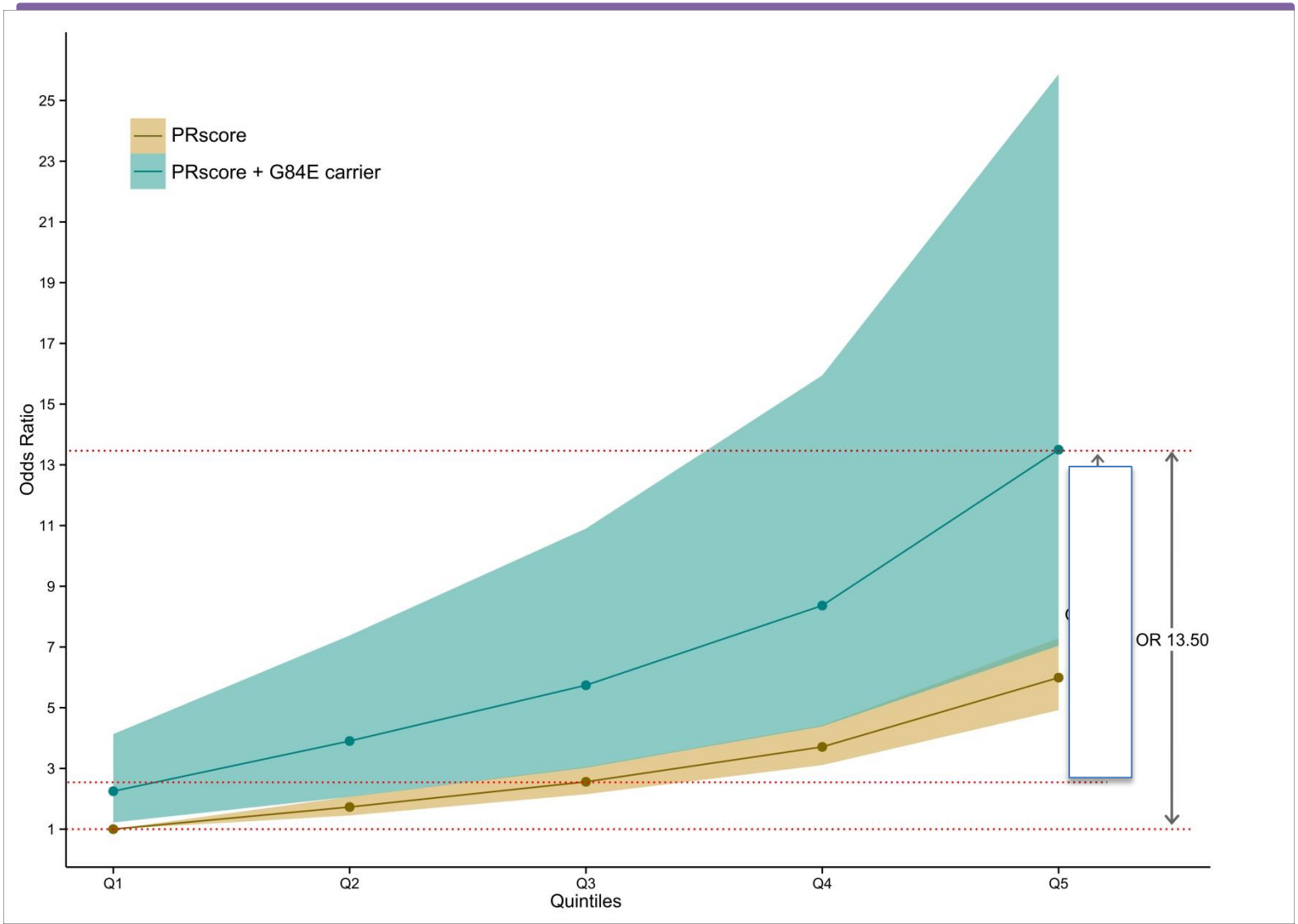




HOXB13 G84E impact on PrCa genetic risk



Polygenic Risk Score



Conclusions

- 1.5% of PrCa cases in the UK harbour G84E mutations
- In men with a high polygenic risk score who also have a G84E mutation, their PrCa relative risk is 13.5
- Testing more applicable to Nordic Countries in families with PrCa cases
- Associated with early onset and familial PrCa
- No obvious phenotypic association
- No impact on survival

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Making the discoveries that defeat cancer