

Role of *HOXB13* in Breast and Ovarian Cancer: Preliminary Data From a Laboratory-Based Multigene Panel Testing Cohort

Carolyn Horton, MS, CGC; Holly LaDuca, MS, CGC; Jessica Grzybowski, MS, CGC; Chia-Ling Gau, Ph.D, DABMG

BACKGROUND

- The p.G84E alteration in *HOXB13* has been associated with an increased risk for prostate cancer in male carriers.
- While the phenotypic spectrum in carriers unselected for personal or family history of prostate cancer has not been well studied, predisposition to breast or ovarian cancers in females has been suggested.
- Here we aim to evaluate the role of p.G84E in predisposition to breast and ovarian cancer using a clinical laboratory cohort.

METHODS

- De-identified molecular results and clinical histories were retrospectively reviewed for 33,146 individuals who had multigene panel testing (MGPT) that included analysis of the *HOXB13* p.G84E locus.
- The frequency of *HOXB13* p.G84E was compared between non-Finnish European (NFE) MGPT cases and NFE controls from the Exome Aggregation Consortium (ExAC).

Cohort Demographics

	Total (%)	Avg. Age at testing (range)
Gender		
Female	30,434 (91.8%)	52.4y (6-90+y)
Male	2,712 (8.2%)	54.1y (2-90+y)
Cancer Status		
Unaffected	9,256 (27.9%)	45.8y (4-90+y)
Breast	16,496 (54.2%)*	55.0y (18-90+y)*
Ovarian	2,473 (8.1%)*	61.2y (11-90+y)*
Prostate	284 (10.5%)*	61.4y (15-90+y)*
Ethnicity		
African American	2,053 (6.2%)	49.9y (14-89y)
Ashkenazi Jewish	1,978 (6%)	55.7y (6-90+y)
Asian	1,283 (3.9%)	47.7y (17-88y)
Caucasian	21,678 (65.4%)	53.6y (2-90+y)
Hispanic	1,790 (5.4%)	47.8y (4-87y)
Other/Unknown	4,364 (13.2%)	50.8y (9-90+y)

*calculations are gender-limited

RESULTS

- Eighty-nine individuals were *HOXB13* p.G84E carriers (0.27% of 33,146), including nine with a mutation in a second gene.
- The most common cancers reported in p.G84E carriers were female breast (42 of 70; 60%), ovarian (3 of 70; 4.3%), and prostate (2 of 10; 20%).
- The frequency of p.G84E was significantly higher in NFE MGPT prostate cases than the ExAC NFE controls (1.4%; OR 4.4 p=0.03), but not in NFE female breast (0.34%; OR 1.1 p=0.5) or ovarian (0.16%; OR 0.5 p=0.4) probands.
- Individuals with family history of prostate cancer were more likely to carry p.G84E than those without (OR 2.2 p=5.5E-05) and the effect was strengthened in individuals with two or more family members with prostate cancer compared to those with no family history (OR 3.1 p=0.001).
- In contrast, individuals with family history of breast or ovarian cancer were not more likely to carry p.G84E than those without family history of these cancers.

p.G84E frequency in general population vs. affected cohort

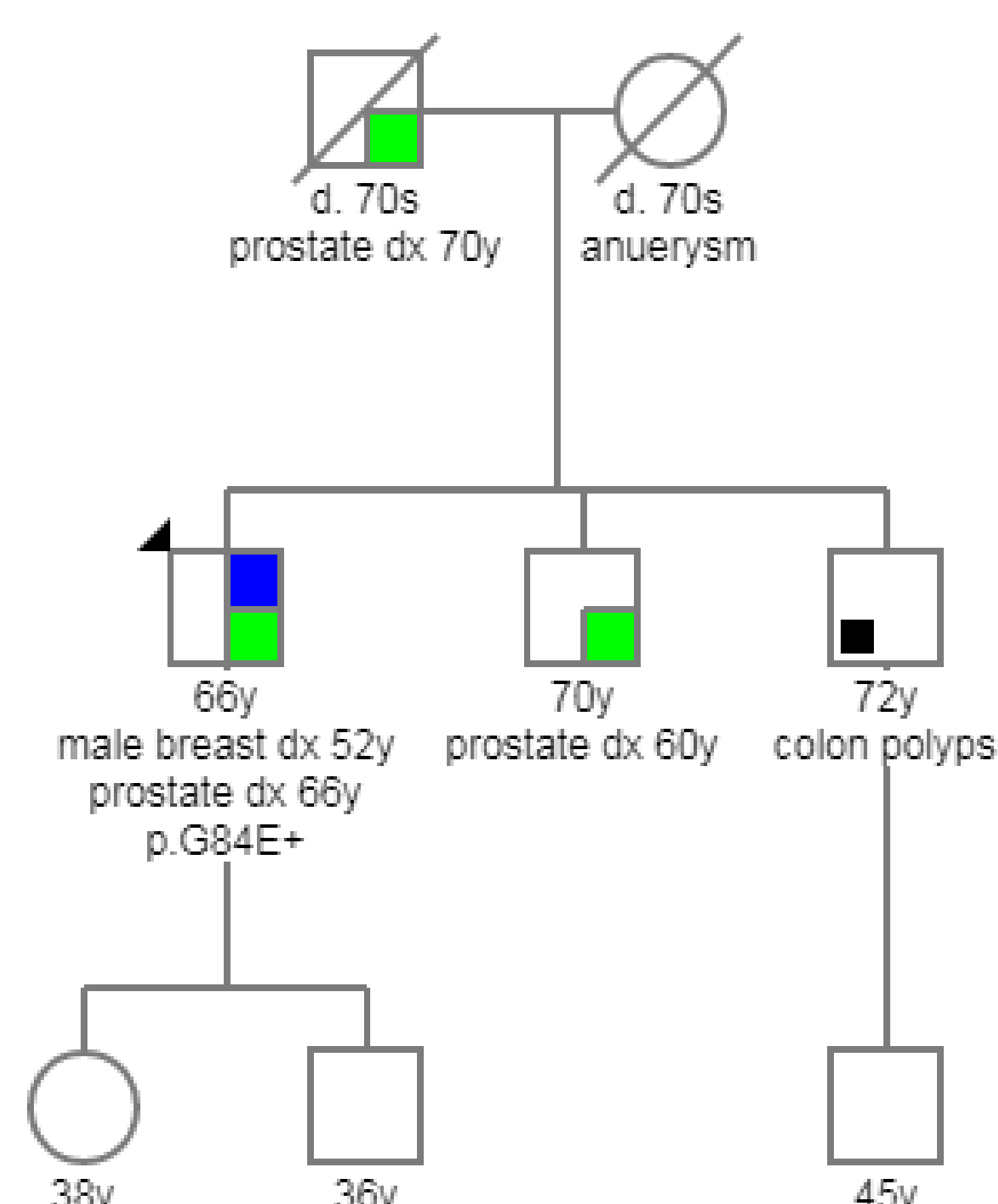
General Population vs. Study Cohort	Total	p.G84E (%)	OR [‡] (95% CI)	p-value
Exac NFE	65,068	202 (0.31%)	n/a	n/a
Breast NFE	11,747	43 (0.36%)	1.2 (0.8-1.6)	0.3
Female Breast NFE	11,605	40 (0.34%)	1.1 (0.8-1.6)	0.5
Male Breast NFE	142	3 (2.1%)	6.9 (1.4-20.9)	0.01
Ovarian NFE	1,861	3 (0.16%)	0.5 (0.1-1.5)	0.4
Prostate NFE	222	3 (1.4%)	4.4 (0.8-13.2)	0.03

‡ based on Fisher's exact test

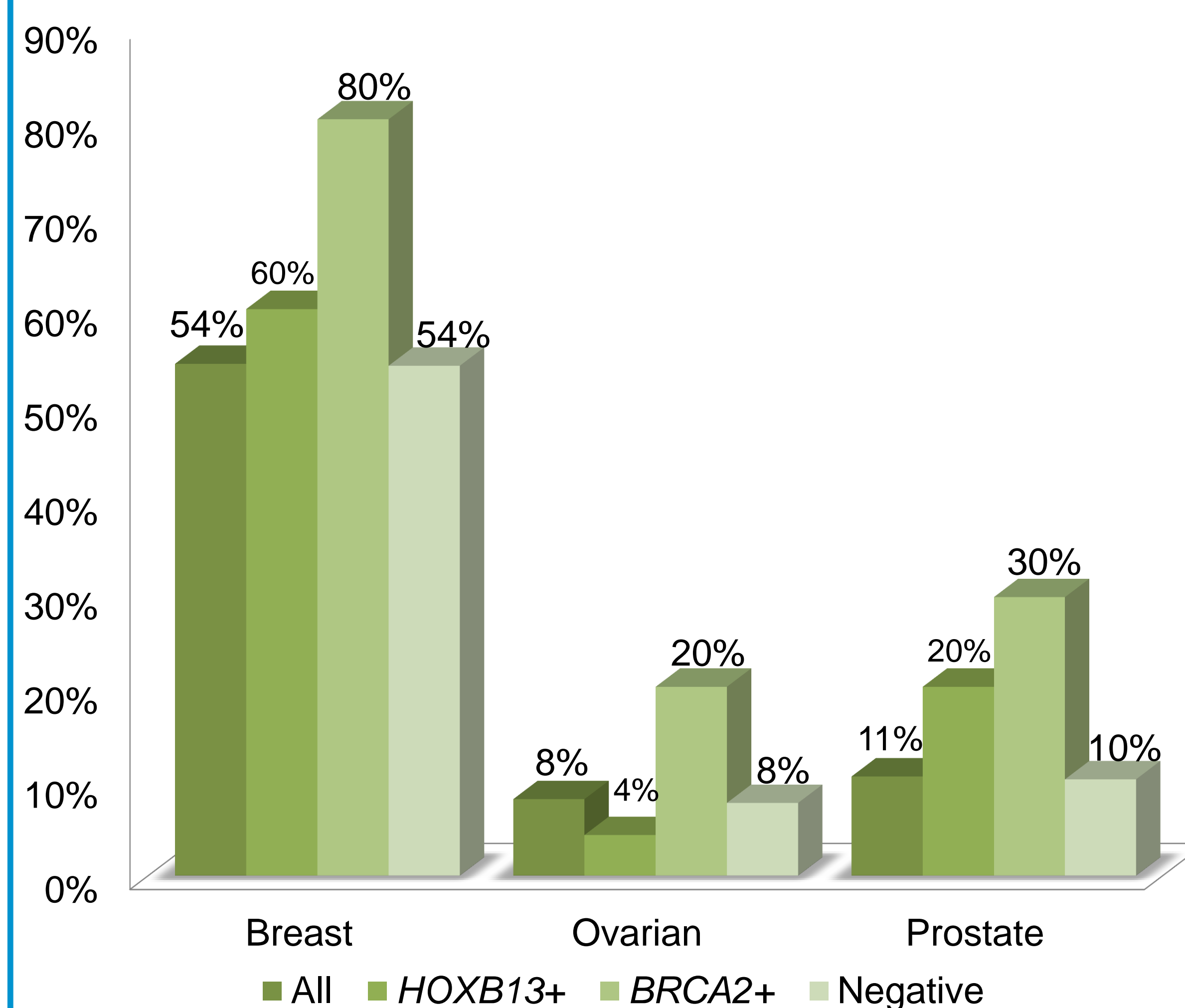
p.G84E frequency in affected cohort based on fhx

Family Hx in Study Cohort	Total	p.G84E (%)	OR [‡] (95% CI)	p-value
No fhx breast	12,498	31 (0.2%)	n/a	n/a
Fhx breast	20,648	58 (0.3%)	1.1 (0.7-1.8)	0.7
No fhx ovarian	27,201	68 (0.3%)	n/a	n/a
Fhx ovarian	5,945	21 (0.4%)	1.4 (0.8-2.3)	0.2
No fhx prostate	26,231	56 (0.2%)	n/a	n/a
1+ fhx prostate	6,915	33 (0.5%)	2.2 (1.4-3.5)	5.5E-05
2+ fhx prostate	1,813	12 (0.7%)	3.1 (1.5-5.9)	0.001

Pedigree of p.G84E carrier



Frequency of Cancer Type by Result



BRCA2+ individuals selected for comparison due to known association with breast, ovarian, and prostate cancer

TAKE-HOME POINTS

- Although breast and ovarian cancer were among the most common cancers in p.G84E carriers, the mutation rate in these probands was not increased compared to the general population.
- The preponderance of breast and ovarian cancer likely reflects the nature of this laboratory cohort rather than a risk association.
- The novel finding that p.G84E is enriched in male breast cancer probands warrants further study.
- The results of this study reinforce the association between *HOXB13* and prostate cancer; however, more data is needed to determine if female carriers are at increased risk to develop cancer.

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