Does the placenta and appetite hormone, GDF15, cause NVP and HG?

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No conflicts of interest to report

Why use a genetic approach?

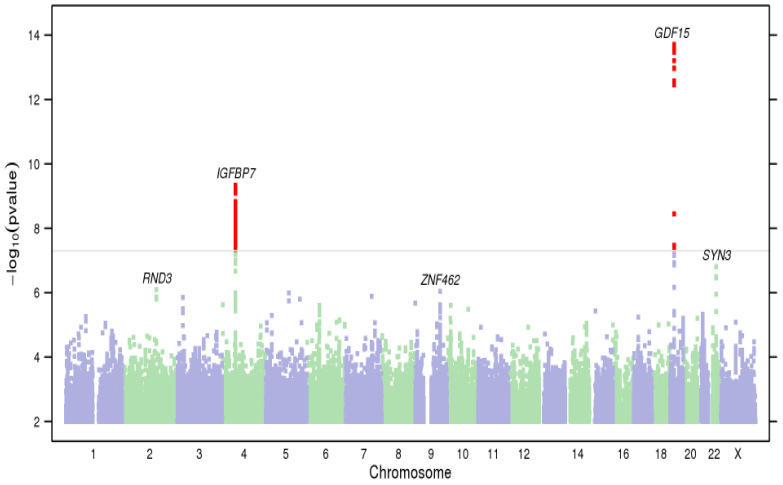
- Decades of research has failed to find a cause.
- Commonly assumed to be hCG and/or psychological with little scientific evidence.
- Heritability estimate for presence of NVP is 73% based on twin studies.
- > 50% of variation in duration and severity of NVP is heritable.
- Familial aggregation of HG
- 17-fold increased risk if sister has it
- 27-fold risk to daughter if mom has it with both daughters
- GWAS approach to etiology is unbiased with respect to which genes are involved.

Over 15 million variants scanned and NO evidence to support *hCG gene,* nor *LHCGR*

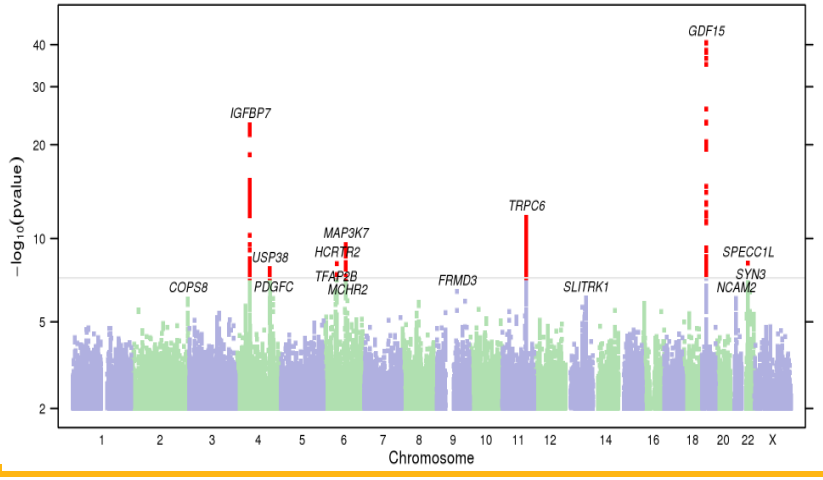
SCAN 1

- HG 1,306
- No NVP 15,756

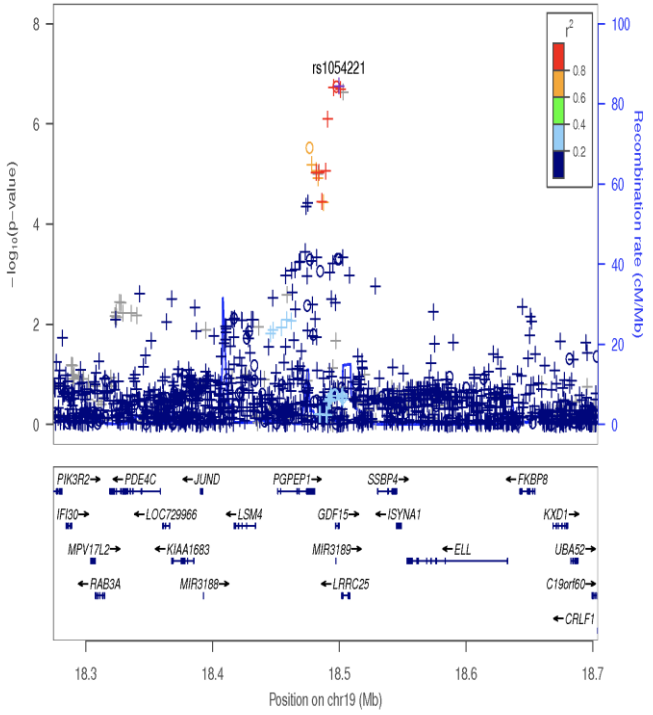
1. GDF15 P=6.8x10^{-15}



2. GFRAL P=6.2X10^{-9}, GDF15 P=2.4x10^{-41}



3. Conditional analysis identifies another GDF15 SNP



SCAN 2

- None 14,988
- Slight 14,292
- Moderate 17,786
- Severe 5,445
- Very Severe 1,220

Fejzo et al., *Nature Communications*, 2018

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Replication results

A.GDF15-rs16982345

	N	GG	AG	AA	*P*-value	OR	95% CI
HG	789	540	229	20			
CONTROL	581	330	210	41	2.80E-07	1.63	1.35-1.98
HG TPN	103	68	33	2			
NO NVP	136	75	51	10	0.04	1.61	1.01-2.60

B. GDF15 -rs1054221

	N	TT	CT	CC	*P*-value	OR	95% CI
HG	893	712	173	8			
CONTROL	635	465	155	15	1.00E-03	1.44	1.16 to 1.79
HG TPN	112	89	23	0			
NO NVP	136	105	27	4	0.37	1.29	0.74 to 2.26

C. GFRAL -rs7761177

	N	CC	CT	TT	*P*-value	OR	95% CI
HG	759	250	366	143			
CONTROL	593	143	310	140	4.00×10^{-04}	1.31	1.13 to 1.53
HG TPN	110	25	49	36			
NO NVP	140	34	71	35	0.3	1.2	0.85 to 1.72

D. IGFBP7-rs4865234

	N	AA	AG	GG	*P*-value	OR	95% CI
HG	778	404	312	62			
CONTROL	603	259	273	71	3.50E-04	1.35	1.14-1.59
HG TPN	110	64	38	8			
NO NVP	143	57	66	20	2.81E-03	1.81	1.21-2.73

E. PGR-rs7948518

	N	TT	CT	CC	*P*-value	OR	95% CI
HG	773	398	333	42			
CONTROL	606	402	178	26	7.82E-07	0.63	0.53-0.76
HG TPN	109	55	52	2			
NO NVP	139	98	37	4	9.90E-03	0.24	0.35-0.88

GENE/GWAS OVERLAP (GWAS CATALOG-4220 PUBS)

GDF15 -GDF15 protein levels, periodontitis, systemic lupus erythematosus, taste preference*

GFRAL- glomerular filtration rate, blood urea nitrogen levels, insomnia/morning person, body mass index, high IL-1beta levels in gingival crevicular fluid/periodontal inflammation, blood protein levels, heel bone mineral density/osteoporosis, HIV-1 infection

*from 23andMe blog

No evidence for association between HG-risk genes and emotional disorders in GWAS Catalog:

DISORDER	GWAS STUDIES	ASSOCIATIONS	*GDF15, GFRAL, IGFBP7, PGR*
Neurotic Disorder	16	53	0
Neurotic Measurement	15	1647	0
Neuroticism Item-level	13	743	0
Anxiety Disorder	37	176	0
Unipolar Depression	99	1307	0

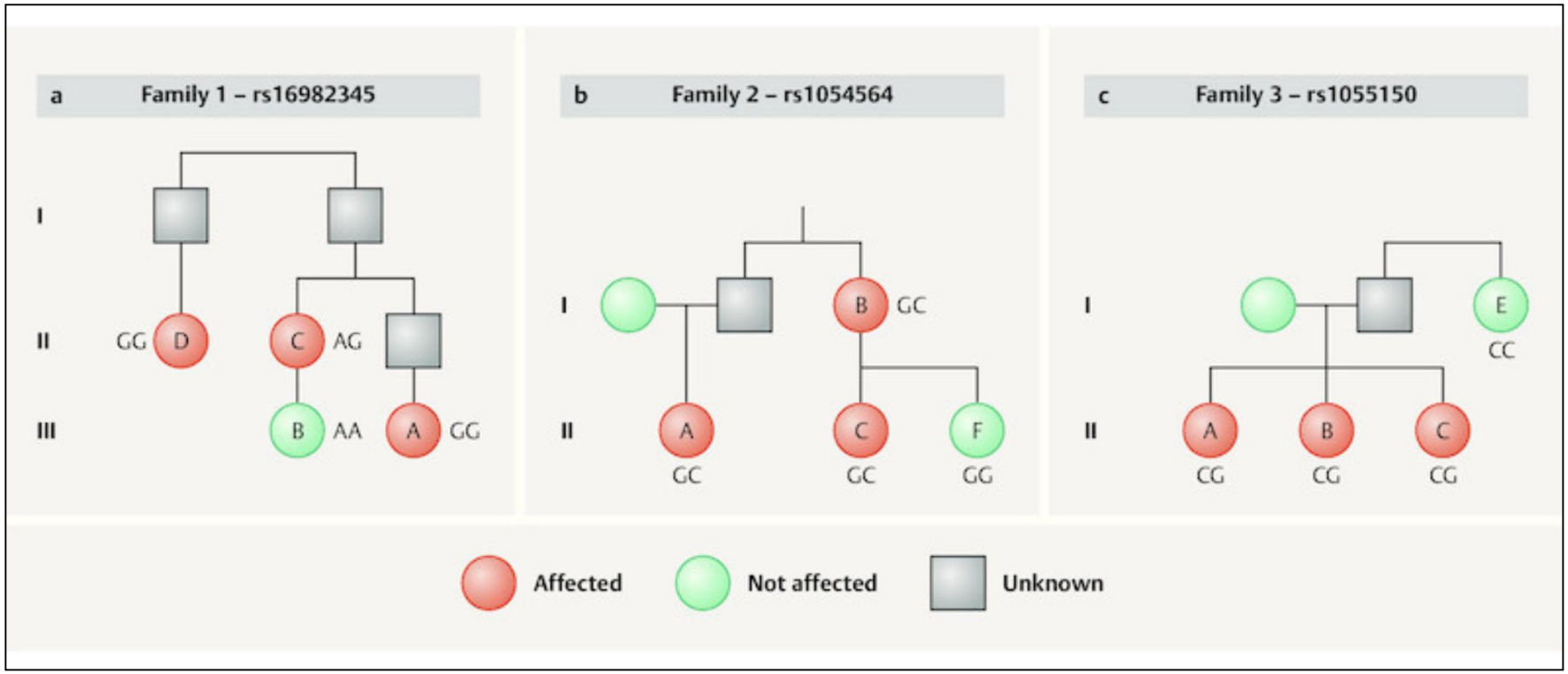
8-fold increased odds of NO recurrence for GDF15 rs16982345 A/A

- 84% RECUR (HG with iv P1 and >5% weight loss in P2)
- 16% NO RECUR (HG with iv P1 and ≤5% weight loss in P2)

rs16982345	Recur	No recur
	N=119	N=25
A/A	2 (1.7 %)	3 (12%)
A/G	34 (28.6%)	4 (16%)
G/G	83 (69.7%)	18 (72%)

AA: (P=0.03, OR=7.98, 95%CI=1.26-50.55)

GDF15 variants associated with altered blood levels segregate with HG in 3/5 families



*Gene combinations with lowest/highest risk of HG (TPN)

1. Comparing 136 women with NO NVP to 102 women with TPN
For either homozygous GDF15 rs16982345-AA or rs1054221-TT

NO NVP	HG TPN	P-value	OR	CI
14 (10%)	1 (1%)	0.02	11.59	1.50 to 89.66

~12X more likely to have no NVP than HG(TPN)

2. Comparing 134 women with NO NVP to 106 women with TPN
(*GDF15-rs16982345-GG*, *IGFBP7-AA*, *PGR-CT*)

NO NVP	HG TPN	P-value	OR	CI
7 (5.2%)	22 (20.8%)	0.0006	4.75	1.94 to 11.62

~5X more likely to have HG(TPN) than no NVP

3. Comparing 132 women with NO NVP to 106 women with TPN
(*GDF15-rs16982345-GG, GFRAL-TT, PGR-CT*)

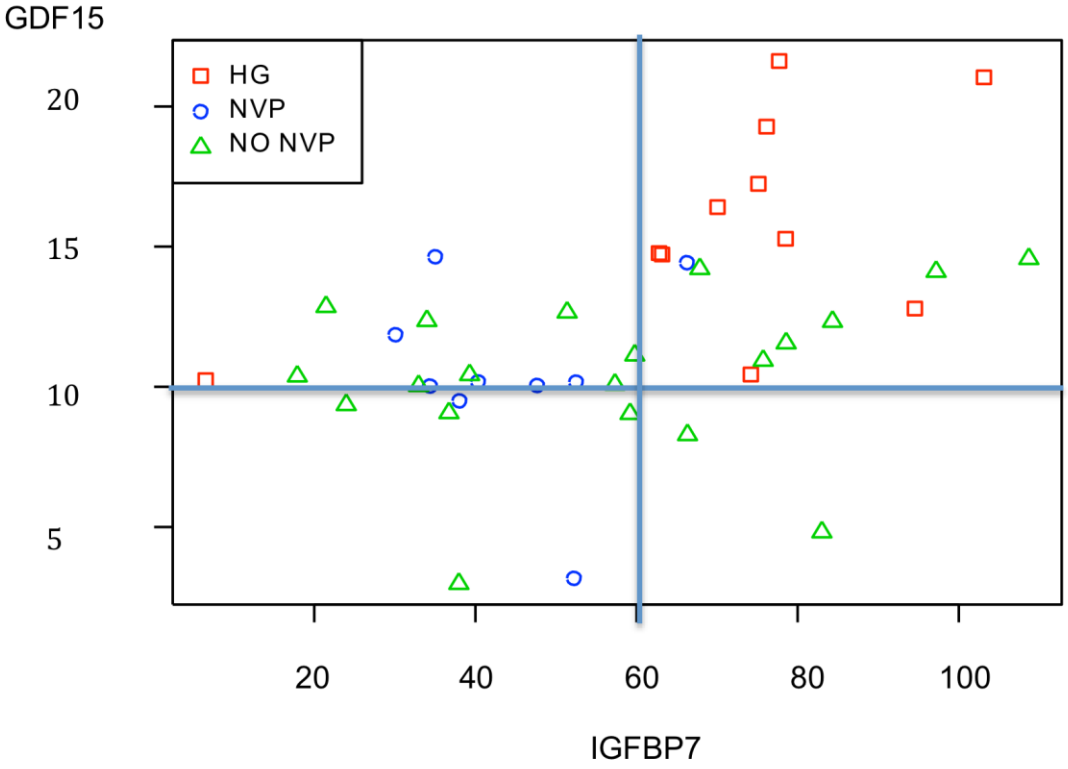
NO NVP	HG TPN	P-value	OR	CI
4 (3.0%)	15 (14.2%)	0.0041	5.27	1.70 to 16.41

~5X more likely to have HG(TPN) than no NVP

*must be verified in other cohorts

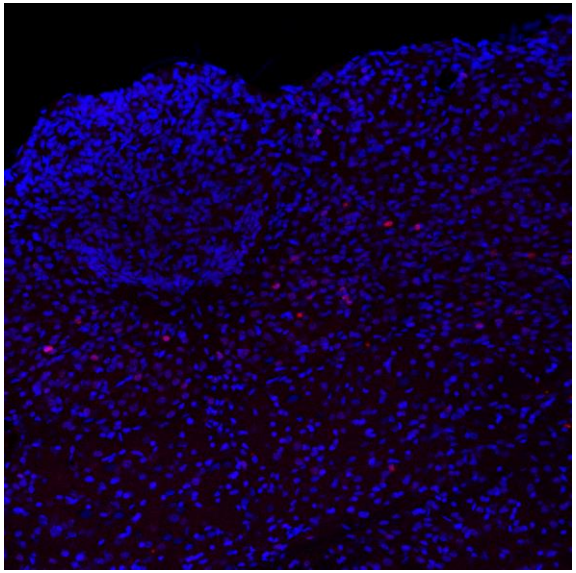
Can GDF15 and IGFBP7 blood levels be used to predict/diagnose HG?

GDF15 ng/ml vs IGFBP7 ng/ml scatterplot. Dividing serum values into high (GDF15>10 ng/ml and IGFBP7>60 ng/ml) vs low (GDF15< 10 ng/ml and IGFBP7< 60 ng/ml respectively), p-value is 0.000199, thus there is a significant difference for HG vs. no HG in the categories high and low serum values.

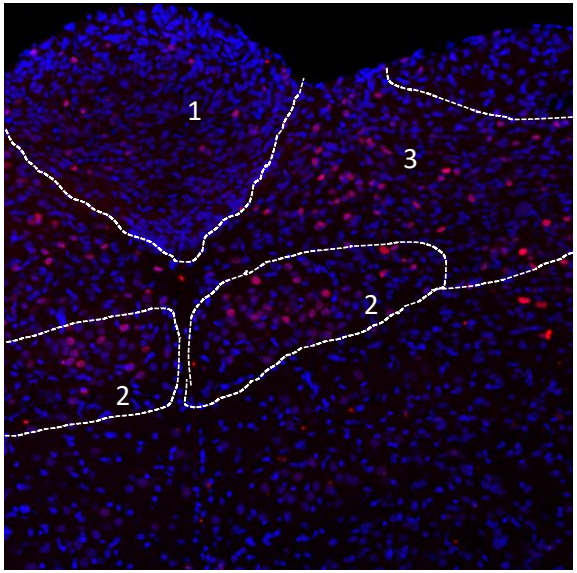


rGDF15 ACTIVATES VOMITING CENTER, BUT NO INCREASE IN VOMITING

Control

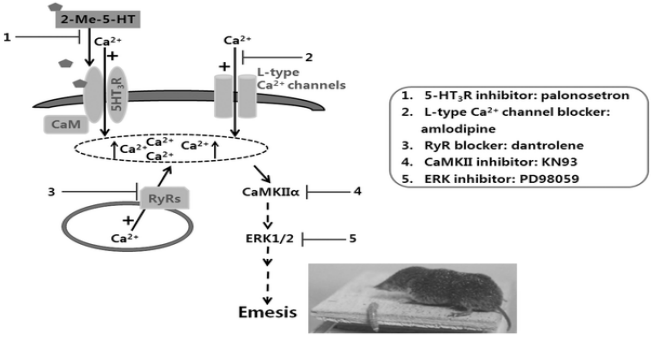


rGDF15 (0.08 mg/kg., i.p. 90 min)



C-fos (red)
Dapi (blue)

1. Area Postrema
2. DMNV
3. NTS

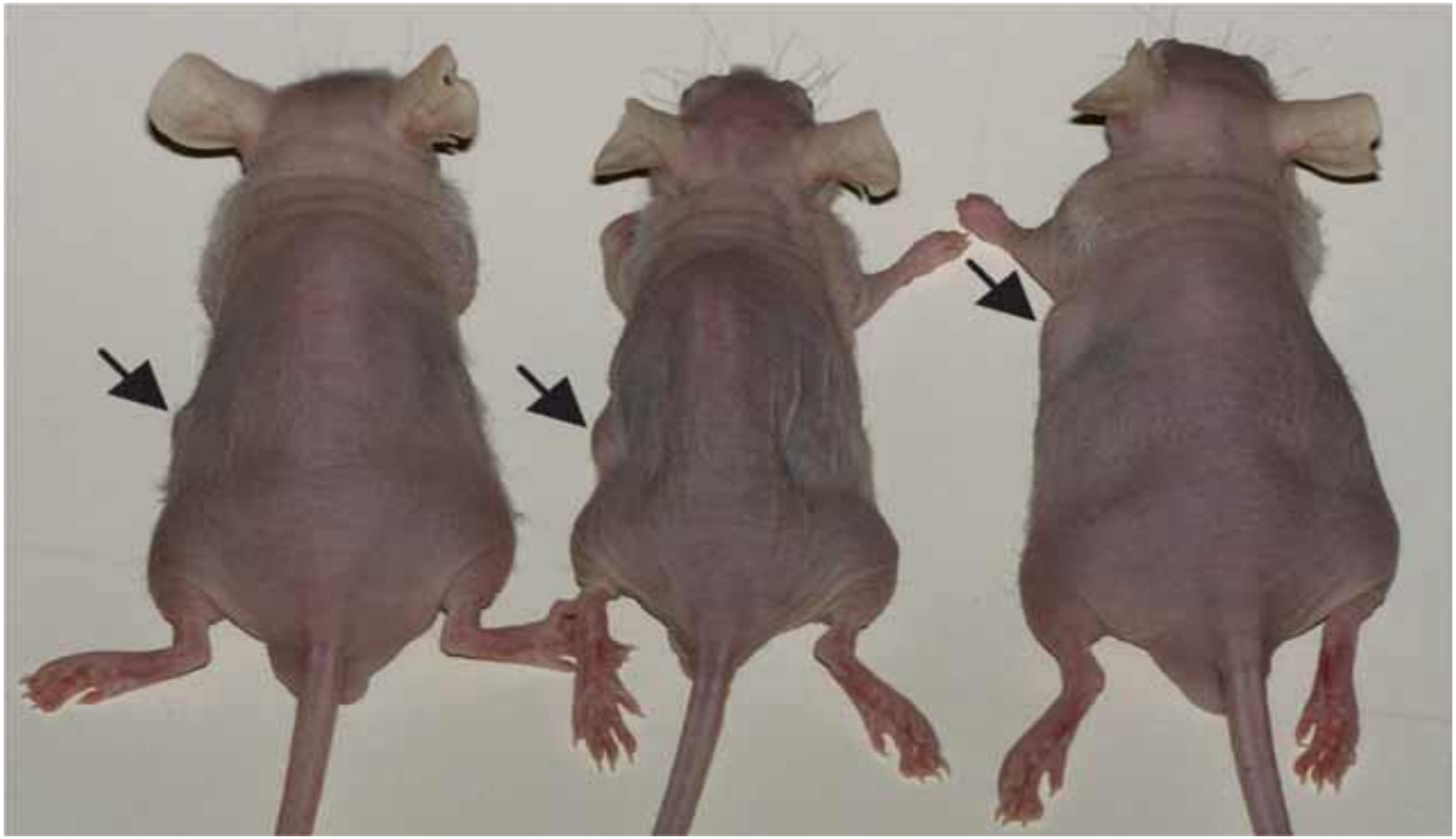


Zhong et al, 2014

The vomiting **center** is comprised of two major groups of **brain**-stem nuclei known as the nucleus tractus solitarius (NTS) and the dorsal motor nucleus of the vagus (DMNV).

DU145 Prostate Cancer Cells transfected with:

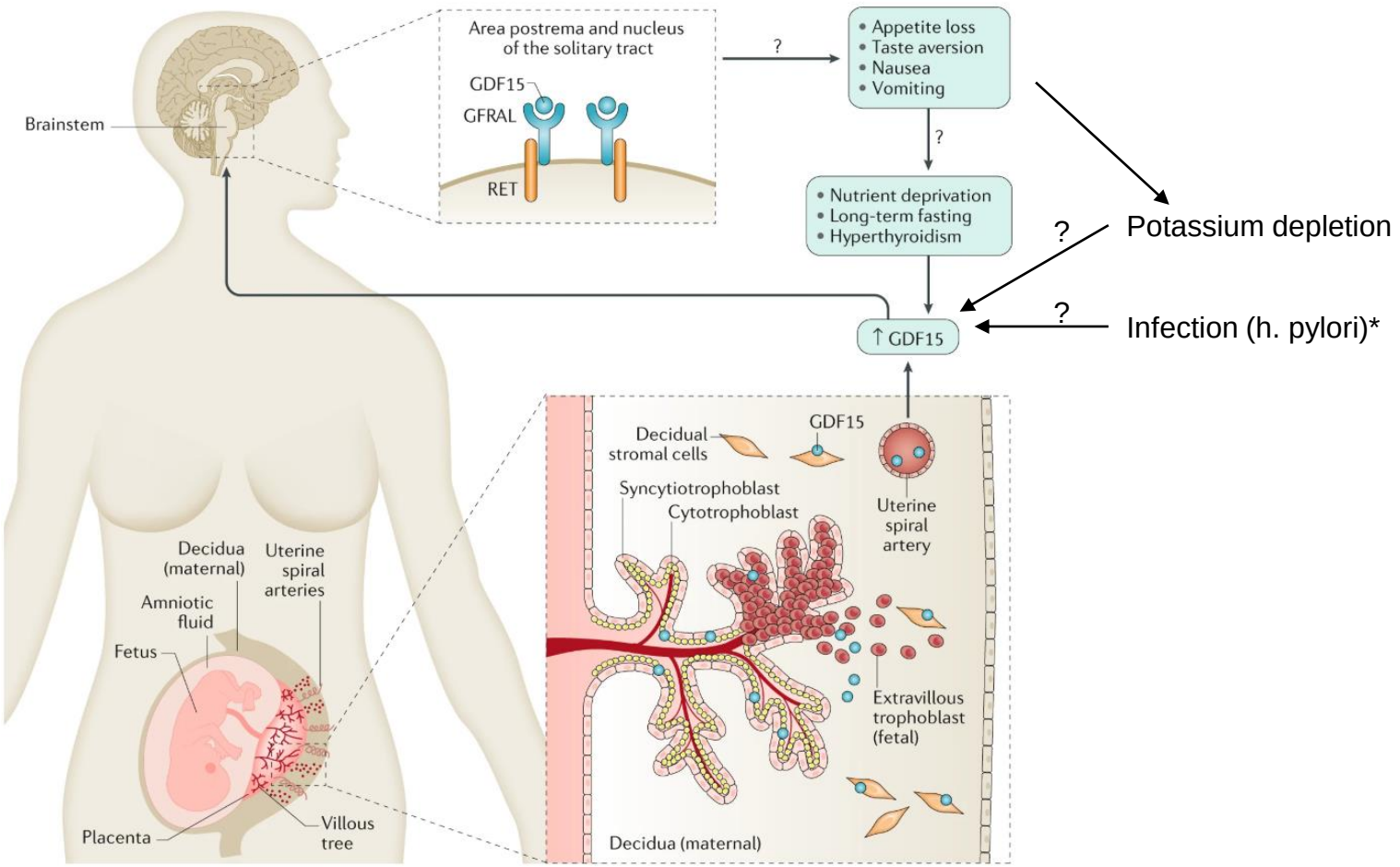
A. empty vector B. overexpressing GDF15 14 d post xenograft C. B+ 1 mg GDF15-mAb i.p. 9 d earlier



Nature Medicine, 2007: Tumor Induced anorexia and weight loss mediated by GDF15
And rescued by anti-GDF15!!!

Possible model for the role of GDF15 in HG pregnancies

Nature Reviews Disease Primers **volume 5**, Article number: 62 (2019), *added after publication



Summary

1. 2 unlinked variants in GDF15 and 1 in GFRAL are associated with HG
2. No variants in hCG nor LHCGR are associated with HG
3. GDF15 associated with levels, periodontitis, lupus, taste preference GWASes
4. GDF15 does NOT show up in neuroticism/anxiety/depression GWASes
5. GDF15 is associated with recurrence risk defined by >5% weight loss
6. GDF15 variants segregate with disease in HG families
7. We are starting to tease out how genes and combinations may be used in the future to predict risk, but these studies must be replicated.
8. Preliminary evidence suggests GDF15 hormone levels may be increased in HG pregnancies, but more work must be done in larger cohorts at different GA
8. rGDF15 activates the brainstem, but does not increase vomiting in the least shrew
9. GDF15/GFRAL therapeutics developed for cachexia are promising.
10. Other factors that increase GDF15 levels in addition to genetics may explain HG.

Conclusion: there is a larger body of evidence to support a role for GDF15 in HG than for any other theory at this time.

What is next?

- Are the findings replicated in other populations?
- What else contributes to HG (ie rare variants, fetal DNA)?
- Can serum levels of GDF15, IGFBP7 be used to predict, diagnose, and eventually treat HG?
- Can a GDF15/GFRAL inhibitor work as a drug for HG?

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