Integrating QTL controlling fatness, gene expressions and lipid metabolites to genetically dissect the adiposity complex trait in a meat chicken cross

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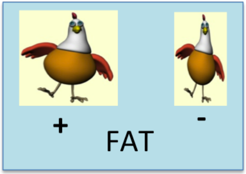
Biological context

Genetically dissect **A**bdominal **F**atness (AF) trait in meat chickens



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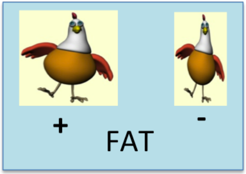
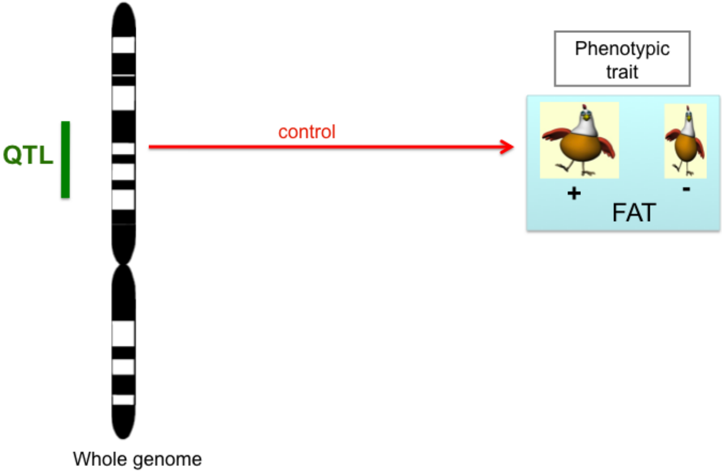


Why?

- Applied research: AF not valuable in chicken carcass
- Fundamental research: To better understand the regulation mechanisms in the lipid metabolism process

Strategy



QTL

control

Phenotypic trait

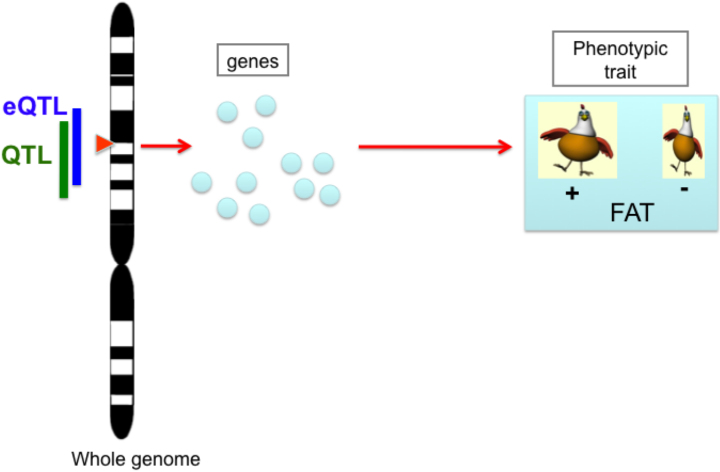
+

-

FAT

Whole genome

Strategy



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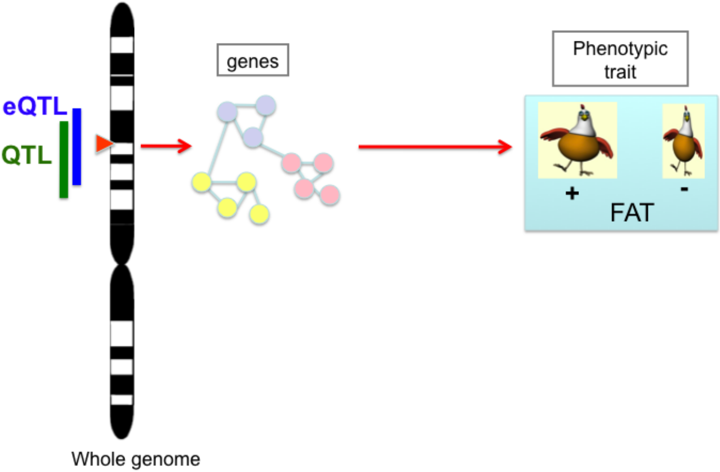

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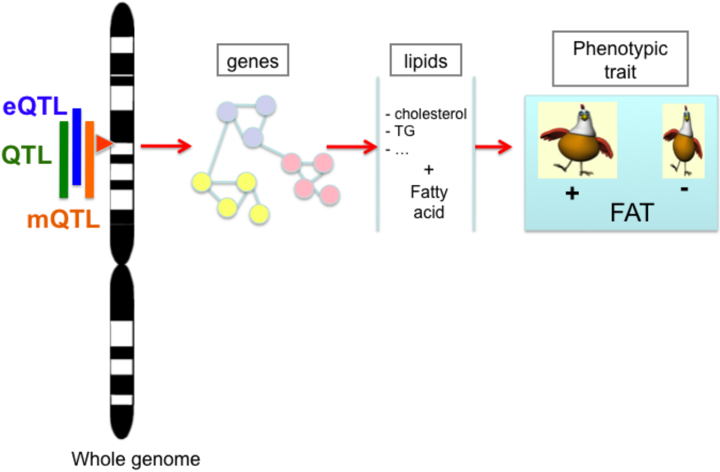
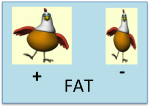
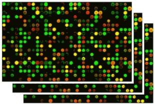

eQTL
QTL
mQTL
Whole genome
genes
lipids
- cholesterol
- TG
- ...
+
Fatty acid
Phenotypic trait
+
-
FAT

Materials

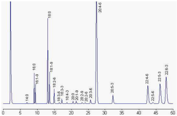
- 4 families of chickens originating from crosses between 2 lines divergently selected for AF. Total of 193 animals.



- genotyped for 1536 SNPs and 28 microsatellites covering the available genome



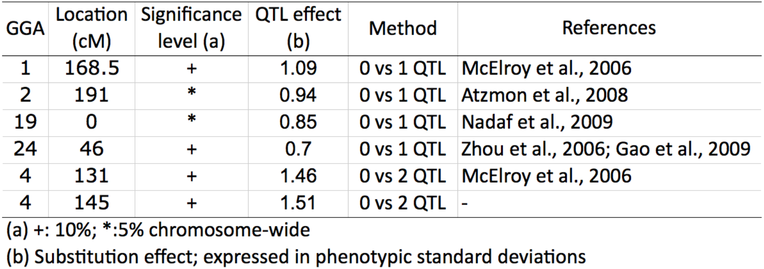
- Hepatic transcriptome profil (28743 probes) for 177 animals



- Hepatic lipids and fatty acid profil (cholesterol, triglycerides and 23 fatty acids) for 193 animals

QTL analyses

Using QTLmap software (Elsen et al, 1999)

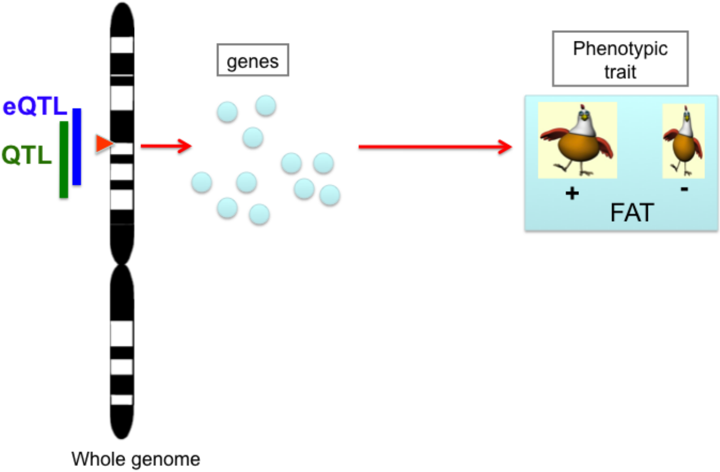


GGA	Location (cM)	Significance level (a)	QTL effect (b)	Method	References
1	168.5	+	1.09	0 vs 1 QTL	McElroy et al., 2006
2	191	*	0.94	0 vs 1 QTL	Atzmon et al., 2008
19	0	*	0.85	0 vs 1 QTL	Nadaf et al., 2009
24	46	+	0.7	0 vs 1 QTL	Zhou et al., 2006; Gao et al., 2009
4	131	+	1.46	0 vs 2 QTL	McElroy et al., 2006
4	145	+	1.51	0 vs 2 QTL	-

(a) +: 10%; *:5% chromosome-wide

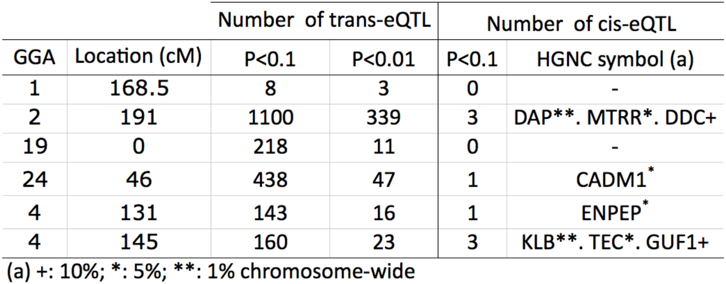
(b) Substitution effect; expressed in phenotypic standard deviations

eQTL analyses



eQTL analyses

Characterization of AF QTL through eQTL



		Number of trans-eQTL		Number of cis-eQTL	
GGA	Location (cM)	P<0.1	P<0.01	P<0.1	HGNC symbol (a)
1	168.5	8	3	0	-
2	191	1100	339	3	DAP**. MTRR*. DDC+
19	0	218	11	0	-
24	46	438	47	1	CADM1*
4	131	143	16	1	ENPEP*
4	145	160	23	3	KLB**. TEC*. GUF1+

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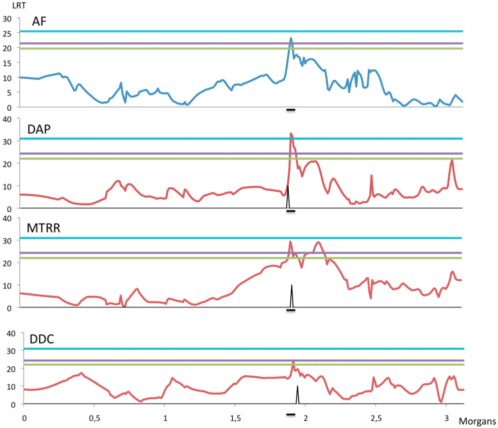
GGA2 hotspot cis-eQTL



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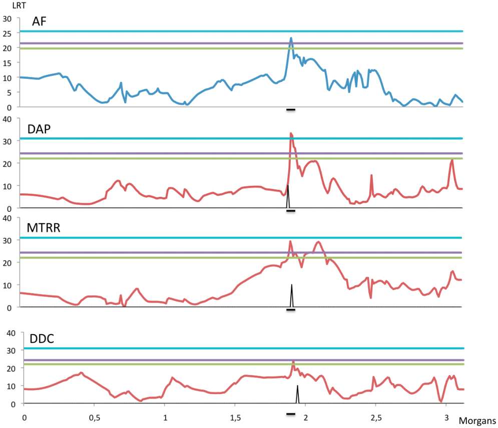
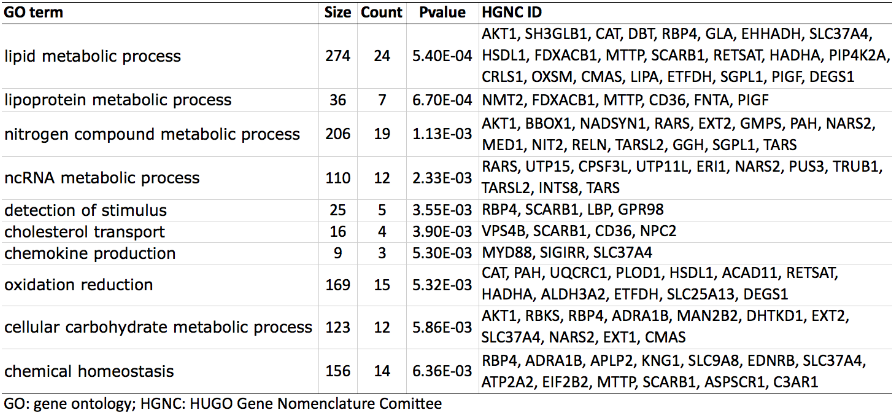


- DAP: death associated protein
- MTRR: methyltransferase involved in methionine and folate metabolism
- DDC: L-DOPA decarboxilase

GGA2 hotspot functional characterization

Biological process enrichment tests for the GGA2 cis- and trans-eQTL

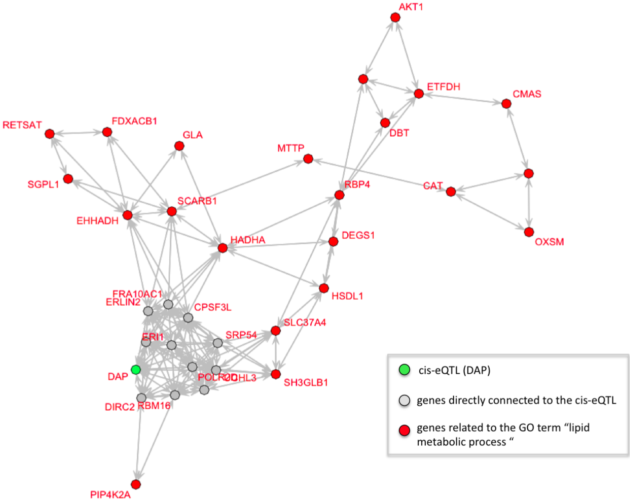


GO term	Size	Count	Pvalue	HGNC ID
lipid metabolic process	274	24	5.40E-04	AKT1, SH3GLB1, CAT, DBT, RBP4, GLA, EHHADH, SLC37A4, HSDL1, FDXACB1, MTTP, SCARB1, RETSAT, HADHA, PIP4K2A, CRLS1, OXSM, CMAS, LIPA, ETFDH, SGPL1, PIGF, DEGS1
lipoprotein metabolic process	36	7	6.70E-04	NMT2, FDXACB1, MTTP, CD36, FNTA, PIGF
nitrogen compound metabolic process	206	19	1.13E-03	AKT1, BBOX1, NADSYN1, RARS, EXT2, GMPS, PAH, NARS2, MED1, NIT2, RELN, TARSL2, GGH, SGPL1, TARS
ncRNA metabolic process	110	12	2.33E-03	RARS, UTP15, CPSF3L, UTP11L, ERI1, NARS2, PUS3, TRUB1, TARSL2, INTS8, TARS
detection of stimulus	25	5	3.55E-03	RBP4, SCARB1, LBP, GPR98
cholesterol transport	16	4	3.90E-03	VPS4B, SCARB1, CD36, NPC2
chemokine production	9	3	5.30E-03	MYD88, SIGIRR, SLC37A4
oxidation reduction	169	15	5.32E-03	CAT, PAH, UQCRC1, PLOD1, HSDL1, ACAD11, RETSAT, HADHA, ALDH3A2, ETFDH, SLC25A13, DEGS1
cellular carbohydrate metabolic process	123	12	5.86E-03	AKT1, RBKS, RBP4, ADRA1B, MAN2B2, DHTKD1, EXT2, SLC37A4, NARS2, EXT1, CMAS
chemical homeostasis	156	14	6.36E-03	RBP4, ADRA1B, APLP2, KNG1, SLC9A8, EDNRB, SLC37A4, ATP2A2, EIF2B2, MTTP, SCARB1, ASPSCR1, C3AR1

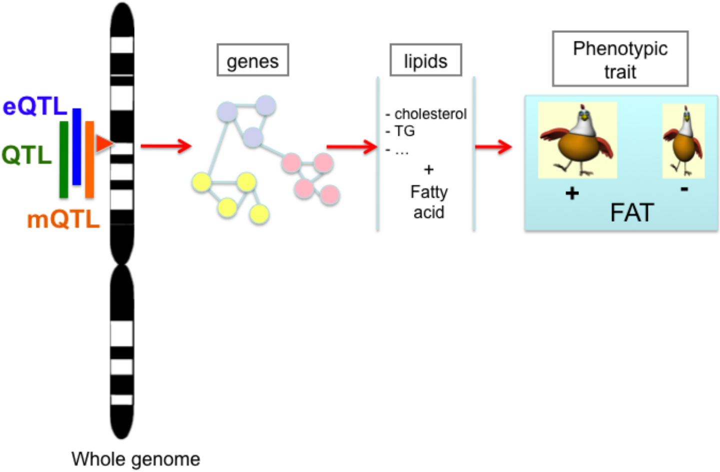
GO: gene ontology; HGNC: HUGO Gene Nomenclature Comittee

GGA2 eQTL sub-network

Network of the cis-eQTL DAP, its connection and the genes related to the lipid metabolic process GO term



Lipid and fatty acid QTL



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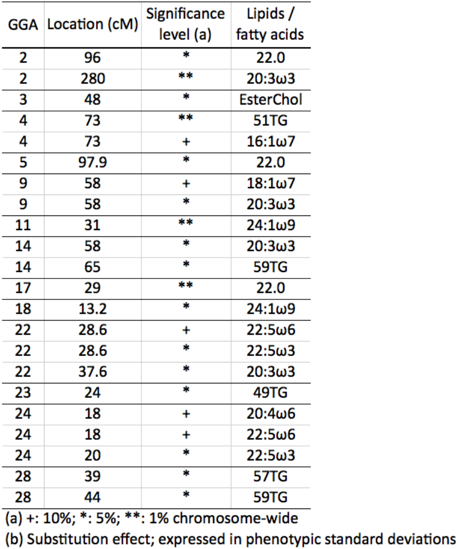
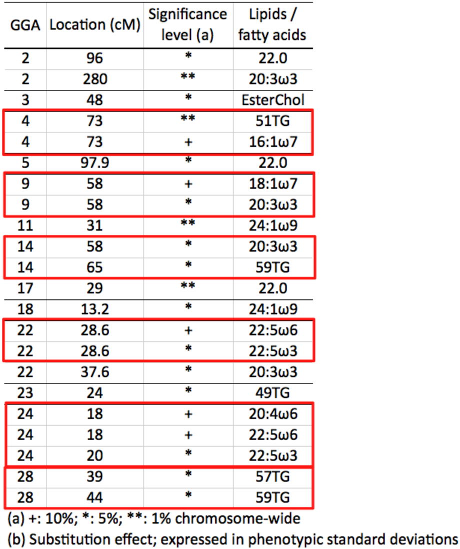


GGA	Location (cM)	Significance level (a)	Lipids / fatty acids
2	96	*	22.0
2	280	**	20:3ω3
3	48	*	EsterChol
4	73	**	51TG
4	73	+	16:1ω7
5	97.9	*	22.0
9	58	+	18:1ω7
9	58	*	20:3ω3
11	31	**	24:1ω9
14	58	*	20:3ω3
14	65	*	59TG
17	29	**	22.0
18	13.2	*	24:1ω9
22	28.6	+	22:5ω6
22	28.6	*	22:5ω3
22	37.6	*	20:3ω3
23	24	*	49TG
24	18	+	20:4ω6
24	18	+	22:5ω6
24	20	*	22:5ω3
28	39	*	57TG
28	44	*	59TG

(a) +: 10%; *: 5%; **: 1% chromosome-wide

(b) Substitution effect; expressed in phenotypic standard deviations

Lipid and fatty acid QTL



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18	13.2	*	24:1ω9
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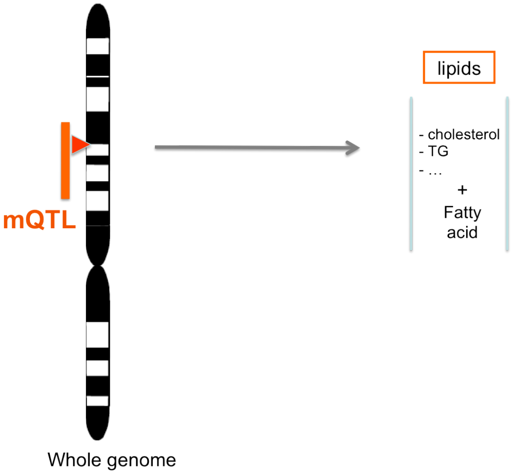
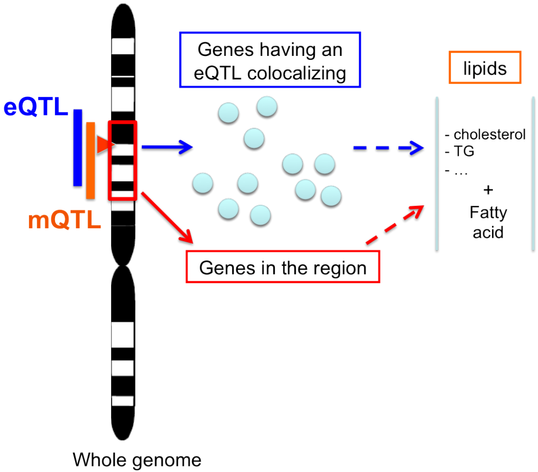


Lipid and fatty acid QTL



Genes having an eQTL colocalizing

lipids

- cholesterol
- TG
- …

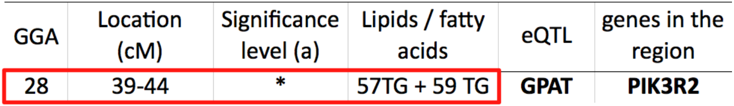
\+

Fatty acid

Genes in the region

Whole genome

Lipid and fatty acid QTL



GGA	Location (cM)	Significance level (a)	Lipids / fatty acids	eQTL	genes in the region
28	39-44	*	57TG + 59 TG	**GPAT**	**PIK3R2**

- GPAT: enzyme involved in the triglyceride biosynthesis
- PIK3R2: regulates XBP1 (Park et al., 2010, Nature Medicine) which is a transcription factor regulating hepatic lipogenesis (Lee, et al., 2008, Science)

Concluding comments

- Detection and functional characterization of genomic regions controlling abdominal fatness

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  ⇒ In progress: gene regulatory networks underlying each of the 6 AF QTL

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- No direct link between hepatic lipid / fatty acid concentrations and abdominal fatness

  ⇒ In progress: gene regulatory networks underlying each of the 15 lipid- and/or fatty acid-QTL

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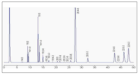

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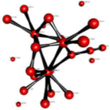

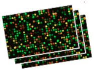

Fonctional genomic plateform
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UE PEAT INRA(Nouzilly)

URA INRA (Nouzilly)
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