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The Genetic Basis of White Tigers

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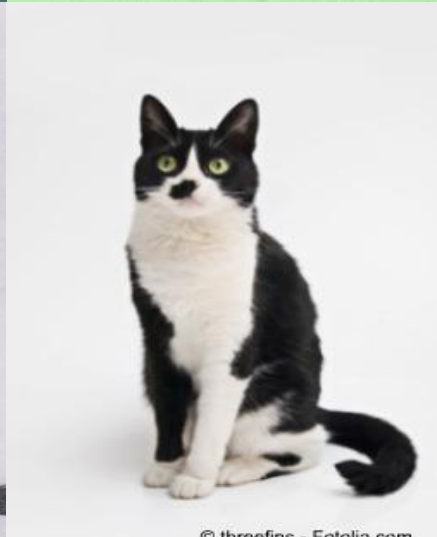
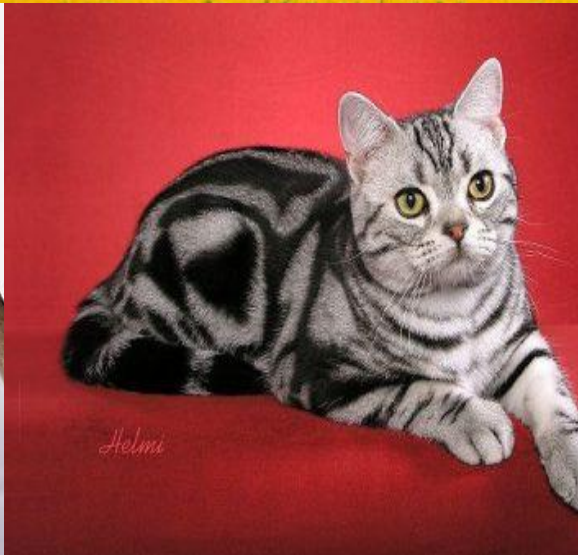
28/06/2013

History of coat color genetics

- Coat color is the most obvious phenotypic trait in mammal, and has served as an ideal model to understand how genotype determines phenotype.
- Coat color genetics has been studied for over 100 years, mainly in lab mouse, and identified more than 150 coat color genes



New opportunity for coat color genetics



New opportunity for coat color genetics

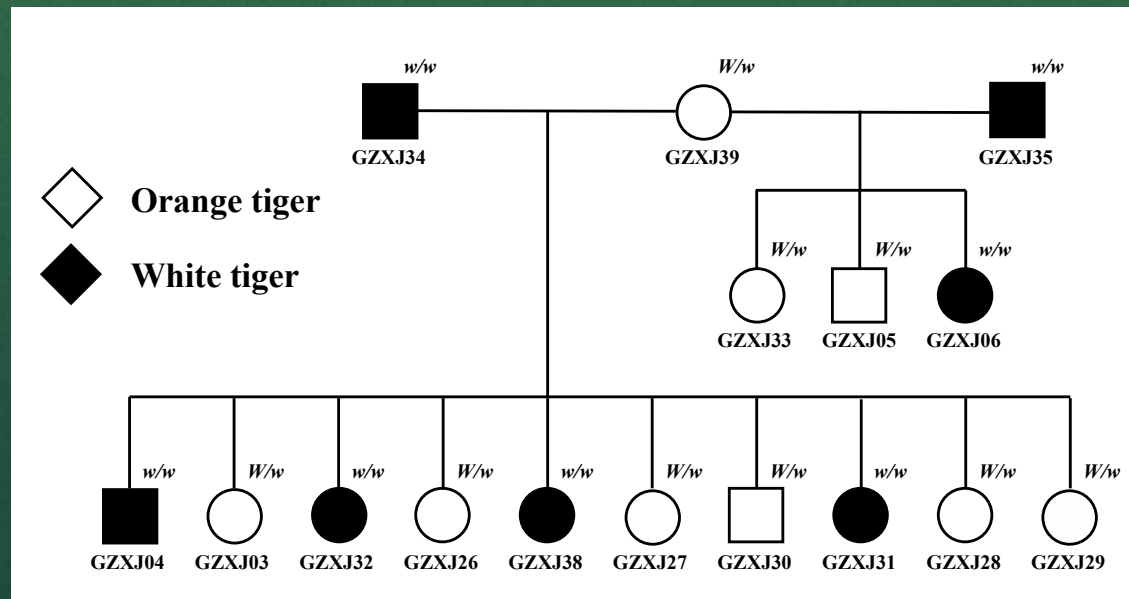


Objective of this study

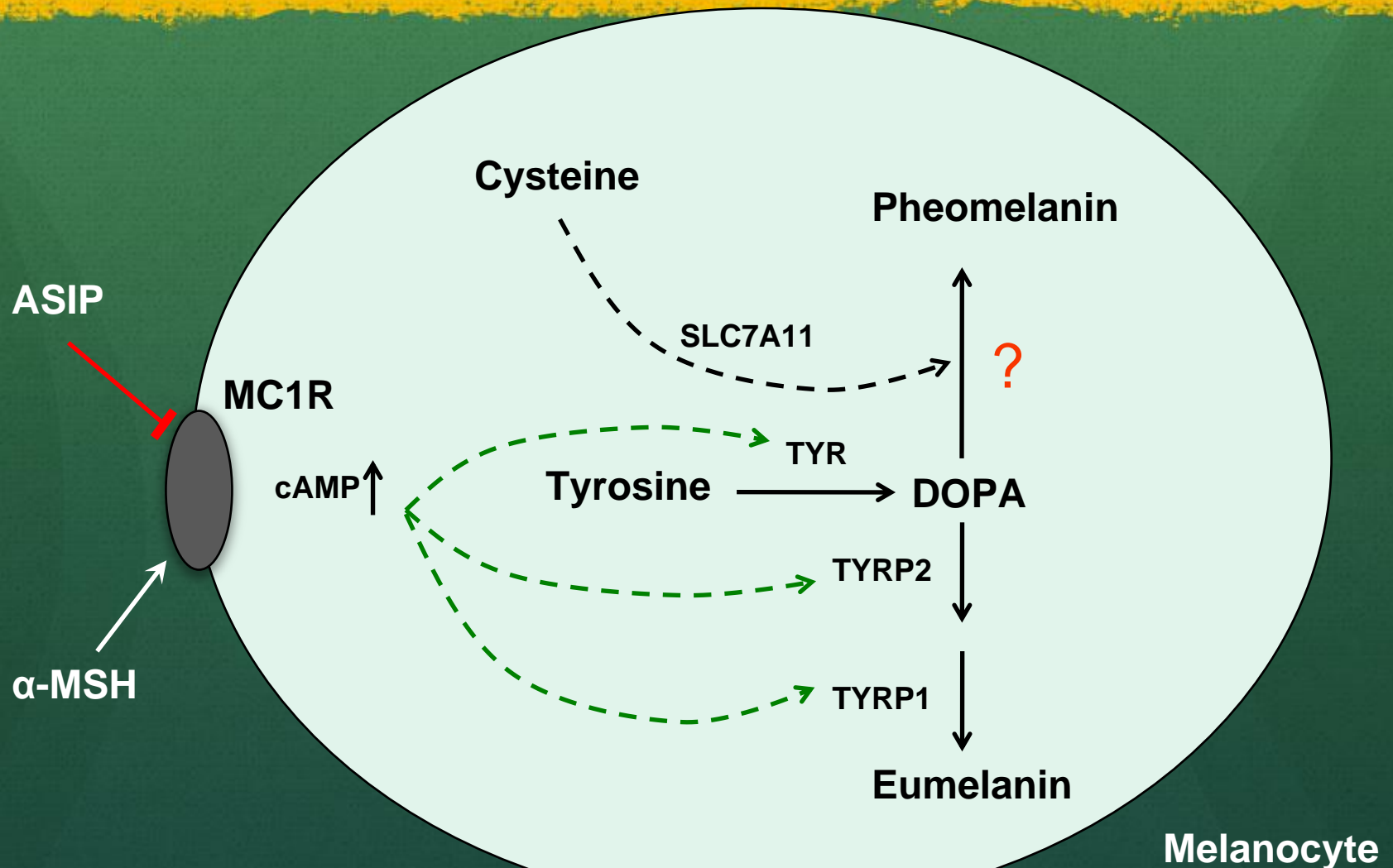


Sample collection

- Blood or tissue samples from 20 unrelated white tigers and 110 orange tigers were collected from different resources.
- Blood samples from a full tiger pedigree (7 white, 9 orange) were provided by Chimelong Safari Park, Guangzhou.



Candidate sequencing approach

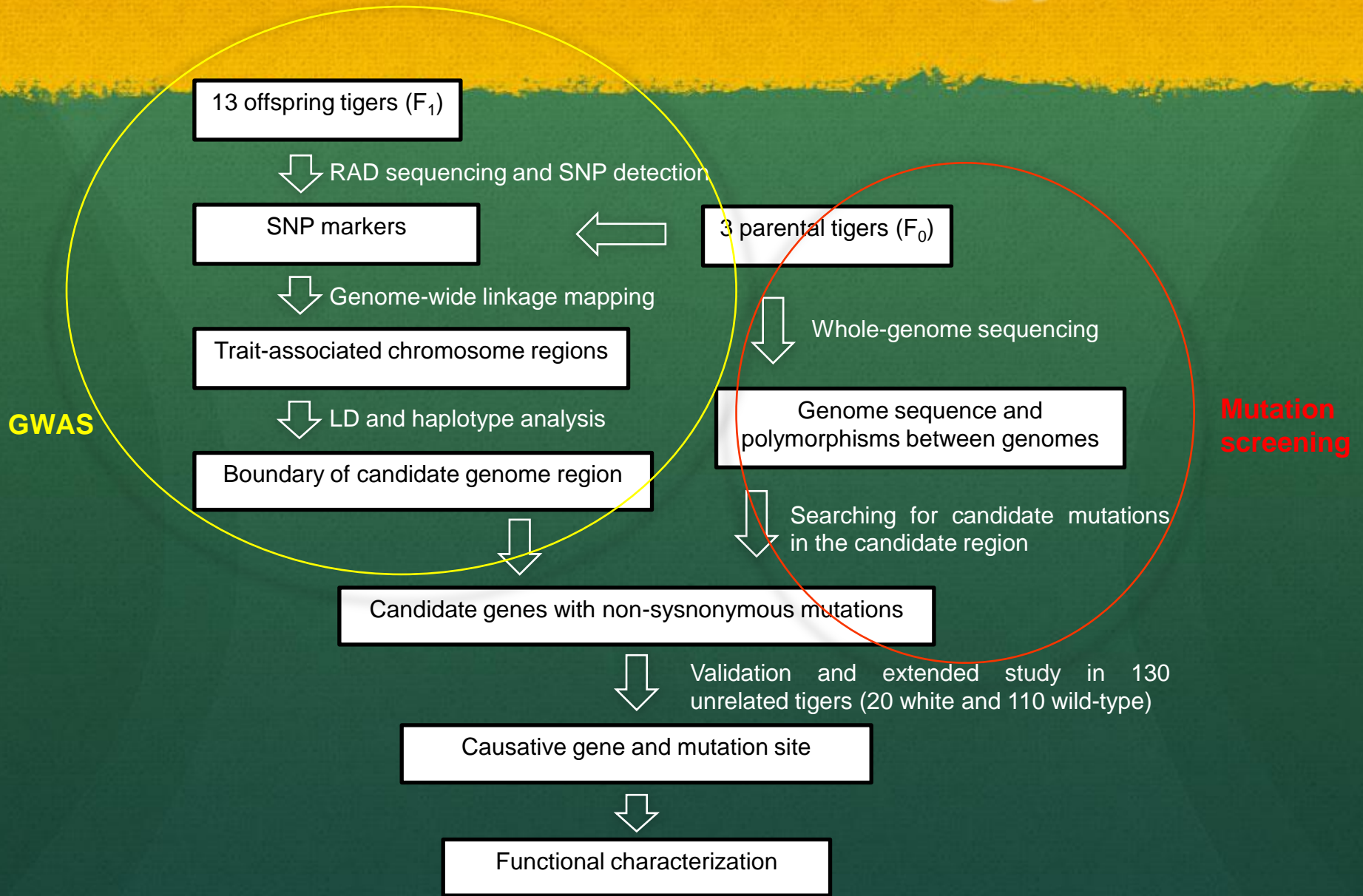


Candidate sequencing results

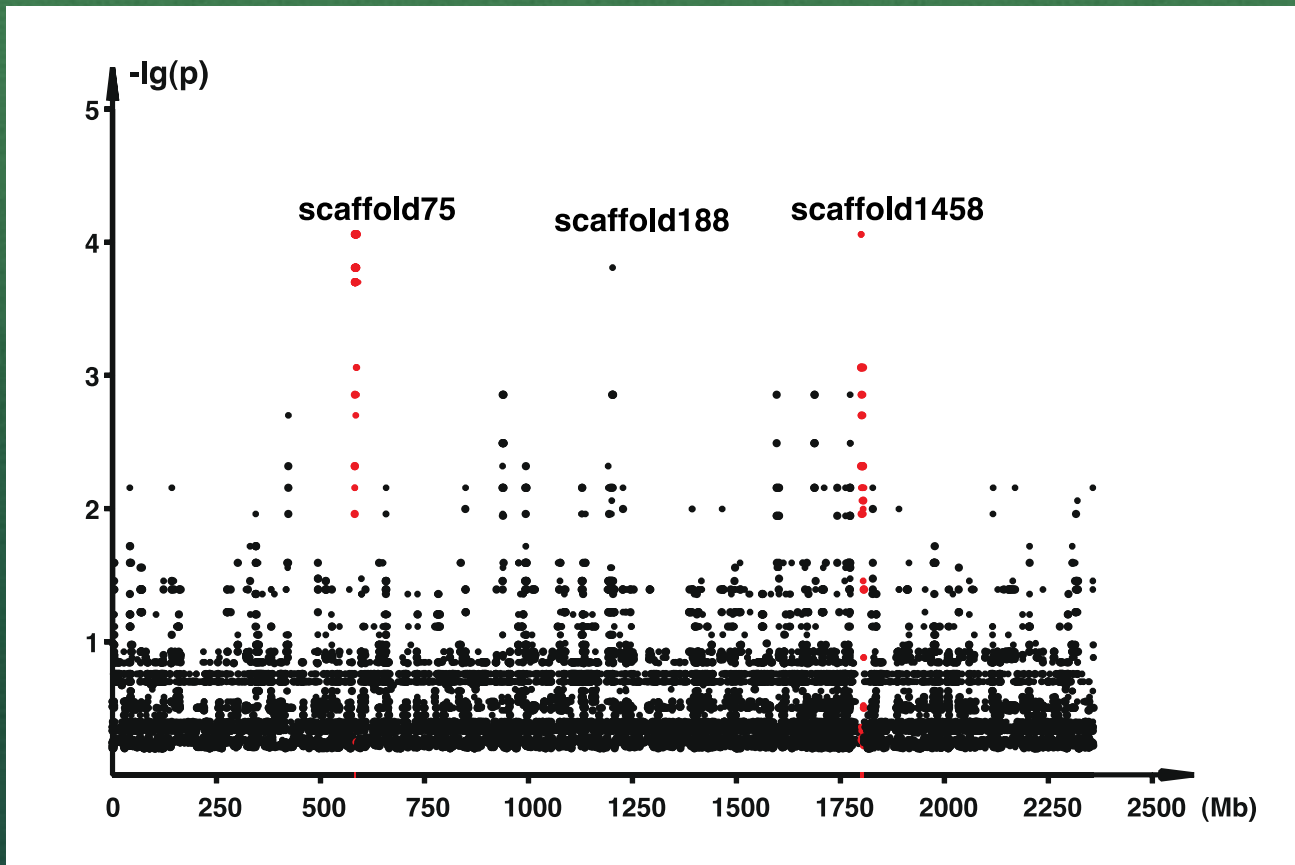
Candidate gene	Sequencing region	NO of SNPs identified	Phenotype associated SNPs
<i>MC1R</i>	CDS	1	none
<i>ASIP</i>	CDS	1	none
<i>TYR</i>	CDS, UTRs	2	none
<i>TYRP1</i>	CDS	1	none
<i>SLC7A11</i>	CDS	2	none
<i>SLC18A2</i>	CDS	0	none

- 5 white tigers and 5 orange tigers

Alternative Strategy

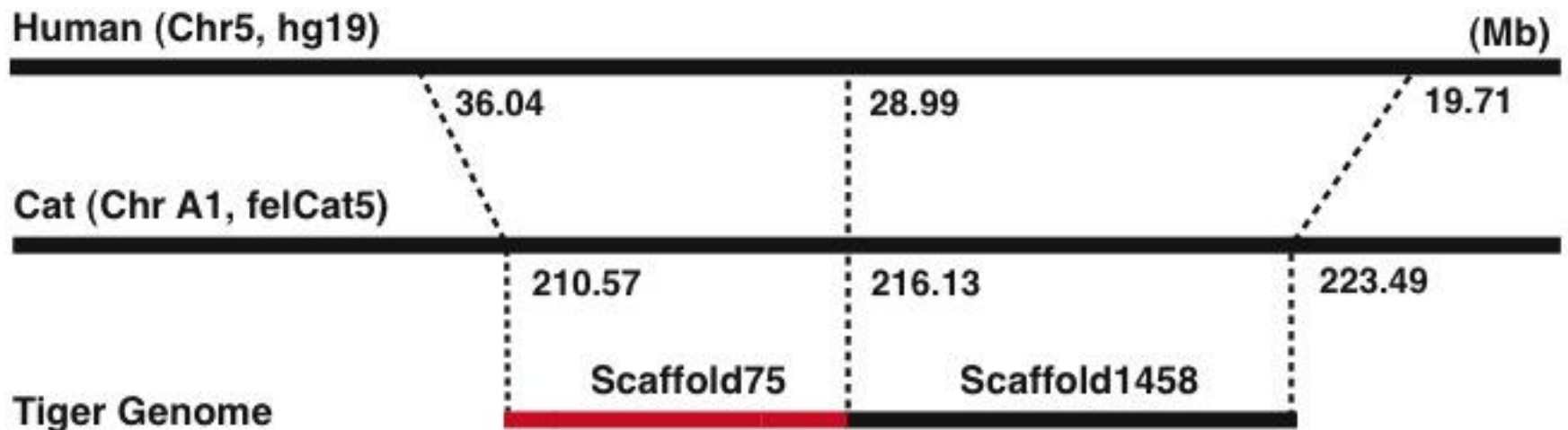


Result of family-based GWAS

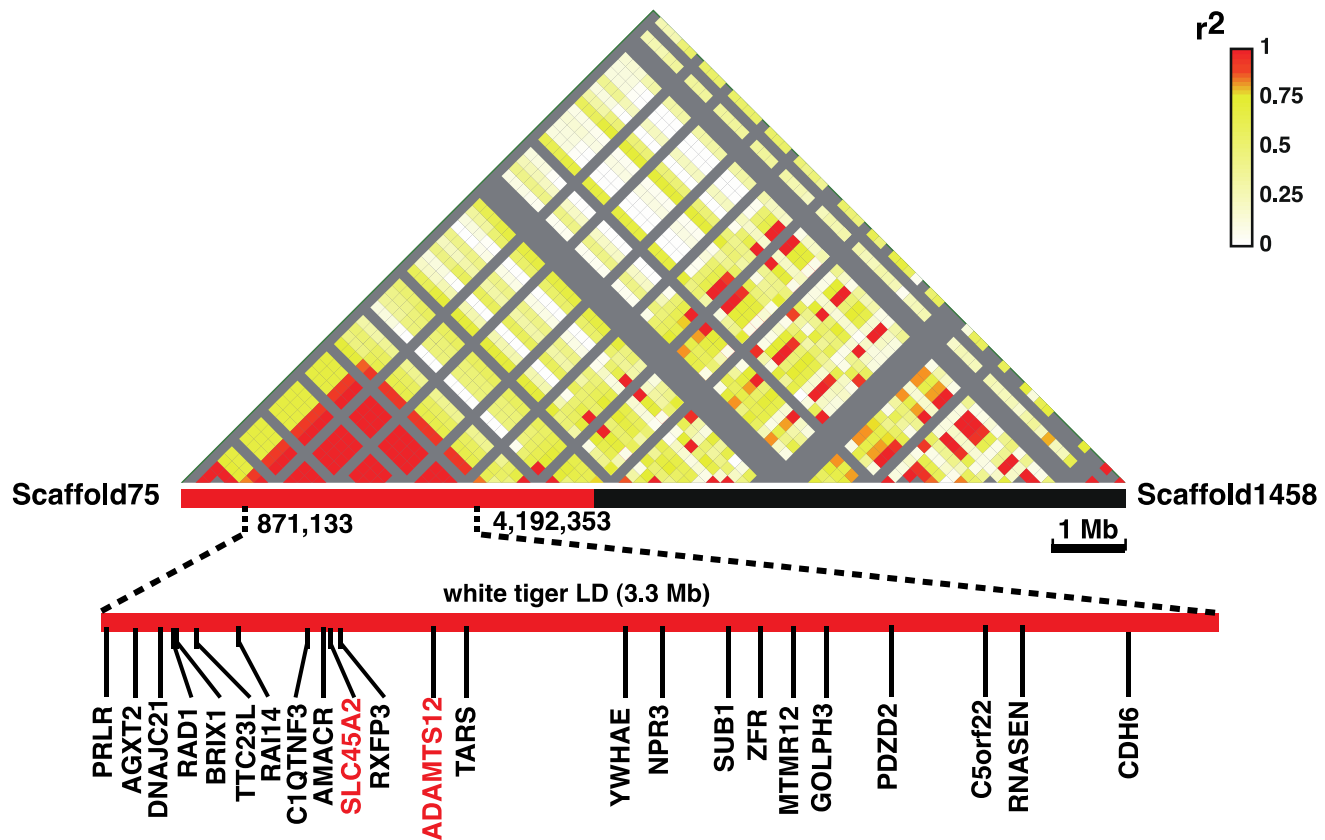


172,554 SNPs were used for GWAS analysis

Homology of Scaffold75 and 1458



Critical region for white trait



Causal mutation screening

Gene	CDS SNP NO	AA change	Gene description
<i>DNAJC21</i>	2	N/A	DnaJ (Hsp40) homolog, subfamily C, member 21
<i>SLC45A2</i>	1	A477V	solute carrier family 45, member 2
<i>ADAMTS12</i>	4	D1125A	ADAM metalloproteinase with thrombospondin type 1 motif, 12
<i>TARS</i>	2	N/A	threonyl-tRNA synthetase
<i>YWHAE</i>	1	N/A	14-3-3 protein epsilon
<i>PTIG0011772</i>	1	N/A	PDZD2 PDZ domain containing 2
<i>RNASEN</i>	3	N/A	ribonuclease 3

SLC45A2 is a known pigmentation gene, whose mutations cause hypopigmentation in human, lab mouse, horse, chicken and fish.

ADAMTS12 is a gene responsible for the inflammatory response.

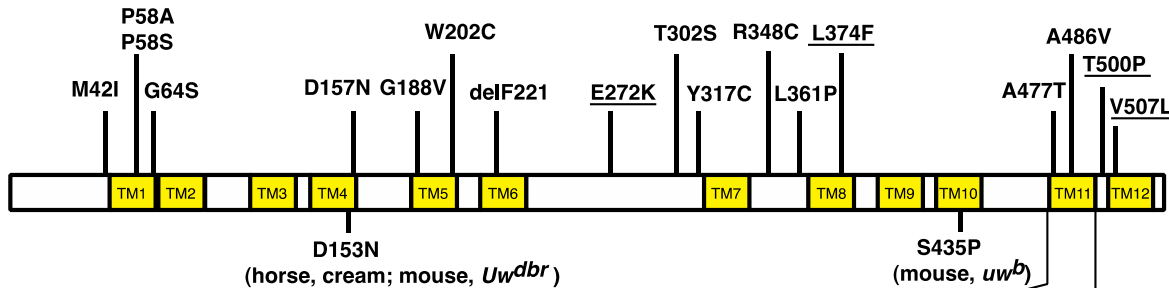
Mutation Validation

Table 1. Correlation between Tiger Coat Color Phenotypes and *SLC45A2* Genotypes

Gene	Genotype	Phenotype	
		White	Wild-Type
<i>SLC45A2</i>	A477V/A477V	20 (7)	0
	A477V/+	0	1 (9)
	+/+	0	109
<i>ADAMTS12</i>	D1125A/D1125A	20 (7)	19
	D1125A/+	0	30 (9)
	+/+	0	60
	missing data	0	1
Total		20 (7)	110 (9)

Prediction of A477V impact

(Human, OCA4 mutations and normal pigmentation polymorphisms)



tiger A477

tiger
white tiger
cat
dog
panda
cattle
pig
horse
elephant
human
chimpanzee
mouse
chicken
clawed frog
zebrafish

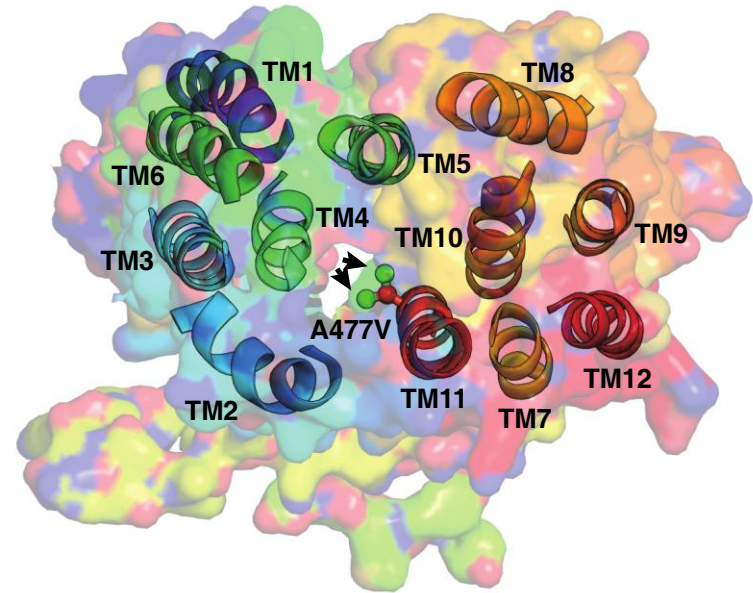
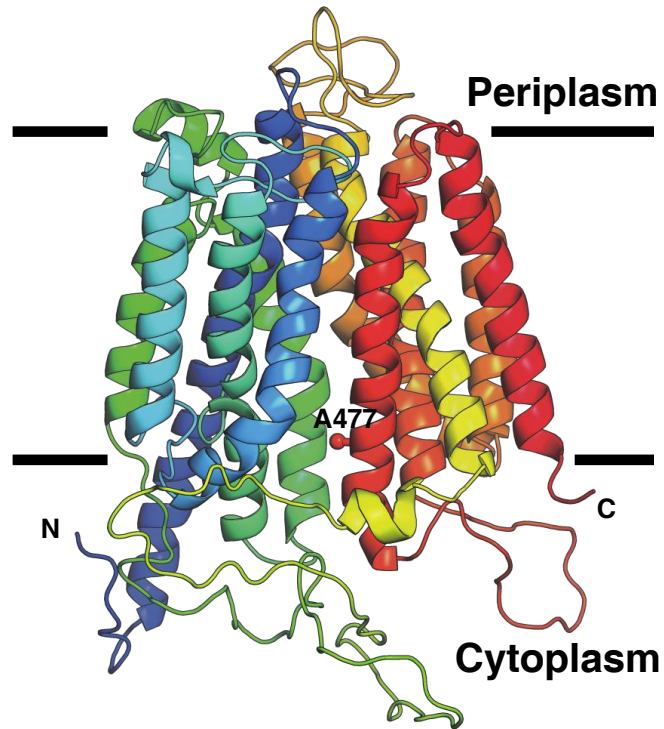
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R-QQAPGGSLDGSERGGQGLDCAVLTCMVQLAQILVGGGLGFLV NKAGS-VIVVIT
-.....V.....
-.....V.....
-...R...SG.....
-H.....GG..DG.....
K-.R.L..GP...S.....A..S.....L...T...V.V...
-...Q..G..S.R.....A.....VV..V.V...
-R..Q..DV.S.G.....A.....I...V.V...
-.ALSE.-P.S...K.V..A..S.....L...T...VIV...
-.....DP.N.V..K.M..T.....T..TV.V...
-.....DP.NNV..K.M..T.....T..TV.V...
KG.E....-P.NQG..K.V..A.....M...V.V...
L-..KEQ.TEH.--..K.I..A.....IL.V...L..SV...-AVT..S
M-.PNGKTPTPSDN..K.I..A.....I.....SL...V.V...S
-.KLG-.DGVAPPEG..T.M..A.....VI..A..A..L...VIV...LS
    
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Newton et al (2001) and Fukamachi et al (2001) predicted SLC45A2 is a 12 transmembrane transporter protein.

The MAPP score of A477V is 35.49, suggesting significant impact to SLC45A2

SLC45A2 structure prediction



How does SLC45A2 determine pigmentation ?

- SLC45A2 locates on the membrane of melanosome in melanocyte.
- SLC45A2 shares similar structure and the signature domain of sucrose/proton co-transporter in plants.
- SCRT, the *Drosophila melanogaster* homology of SLC45A2, is proved to be a sucrose/proton co-transporter.
- The activity of tyrosinase (TYR) is regulated by the melanosomal pH.

How does SLC45A2 determine pigmentation ?

- The activity of SLC45A2 in *underwhite* mouse was only about 20% of that found in wild type mouse.
- Premature melanosome was secreted in *underwhite* mouse.
- Crenated melanosome was found in the melanocyte of *underwhite* mouse.

How does SLC45A2 determine pigmentation ?

We proposed: SLC45A2 is a sucrose/proton co-transporter and mediate melanin synthesis by regulating melanosomal pH and/or osmotic balancing.



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Xu X., Dong G. X., Hu X. S., Miao L., Zhang X. L., Zhang D. L., Yang H. D., Zhang T. Y., Zou Z. T., Zhang T. T., Zhuang Y., Bhak J., Cho Y. S., Dai W. T., Jiang T. J., Xie C., Li R., Luo S. J. (2013) The genetic basis of white tigers. *Curr. Biol.* 23: 1031-1035.

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