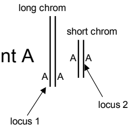
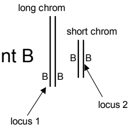
Two loci



Parent A

AA/AA x BB/BB

Parent B



↓

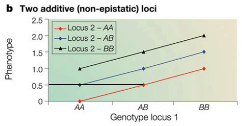
AB/AB (F1)
Locus1/Locus 2

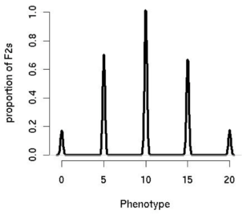
AB/AB x AB/AB

↓

16 possibilities (F2)

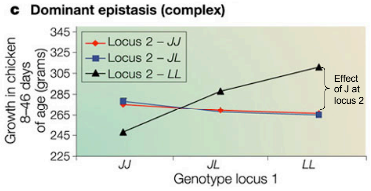
Two loci, incomplete dominance (new and improved)


b Two additive (non-epistatic) loci



2-locus interaction

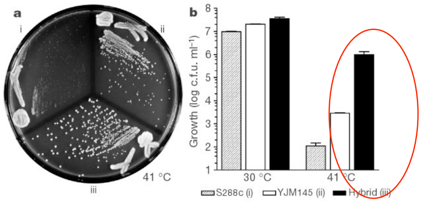
For example: locus 2 is polymorphism in a transcription factor gene that affects protein binding affinity, locus 1 is in a binding site


c Dominant epistasis (complex)

Effect of variation at locus 2 depends on genotype at locus 1: non-additive

---

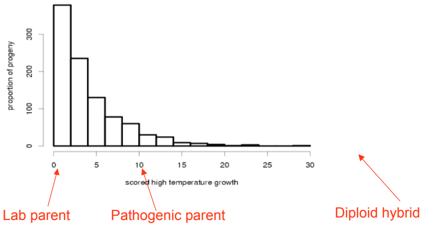
NO progeny as extreme as diploid hybrid



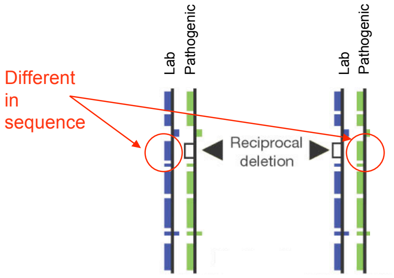
NO progeny as extreme as diploid hybrid

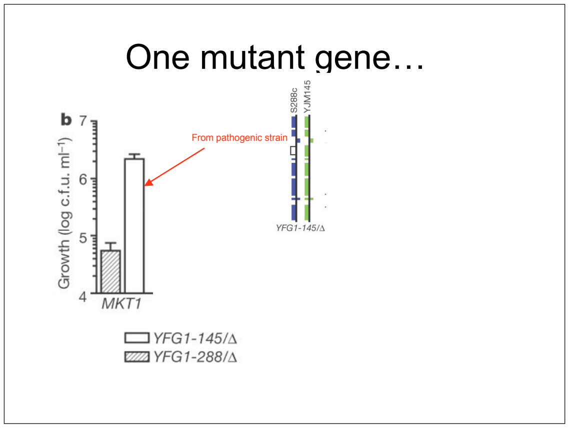

Dissecting the architecture of a quantitative trait locus in yeast

Lars M. Steinmetz*†, Himanshu Sinha‡, Dan R. Richards*, Jamie I. Spiegelman†, Peter J. Oefner†§, John H. McCusker‡ & Ronald W. Davis*†§

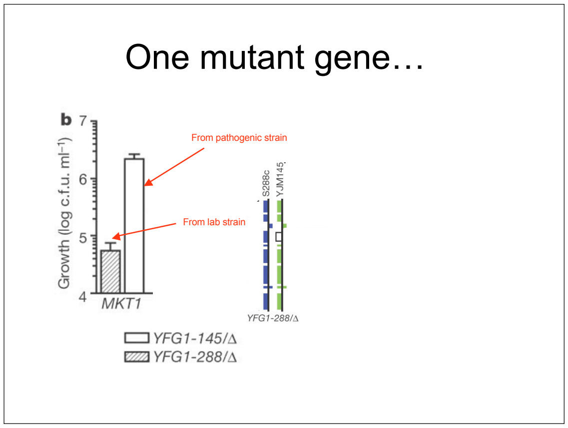


Tested in hybrid diploids





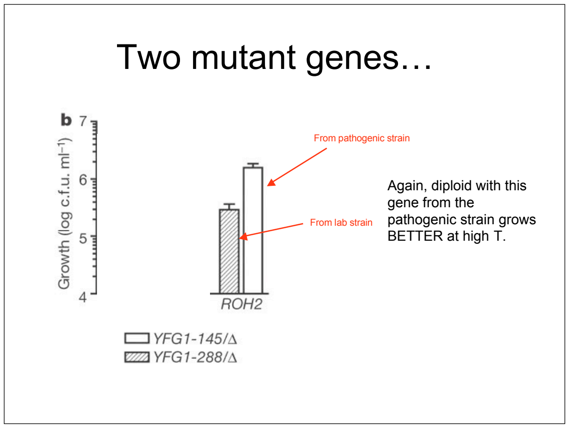
One mutant gene…



One mutant gene…

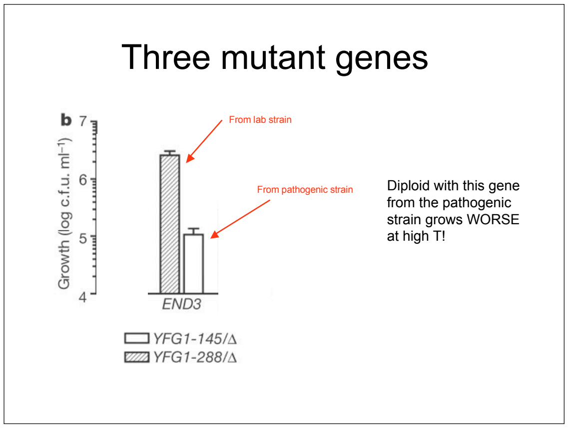
Two mutant genes.

Two mutant genes…



Two mutant genes…

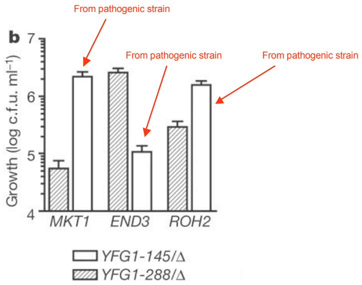
Again, diploid with this gene from the pathogenic strain grows BETTER at high T.



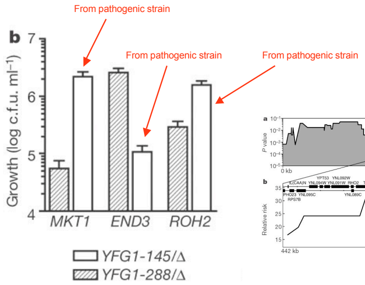
Three mutant genes

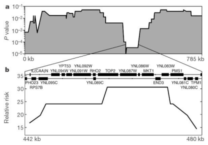
Diploid with this gene from the pathogenic strain grows WORSE at high T!

Three mutant genes

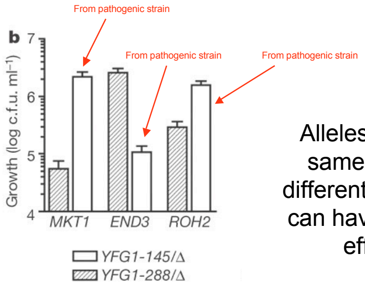


Three mutant genes



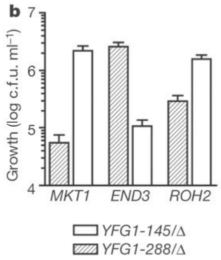


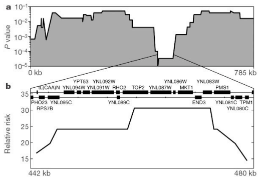
Three mutant genes



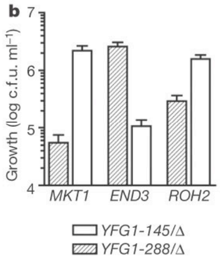
Alleles from the same strain at different genes/loci can have different effects.

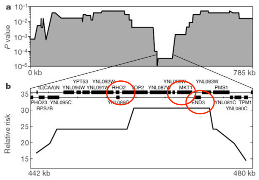
Three mutant genes in same “locus”





Three mutant genes in same “locus”

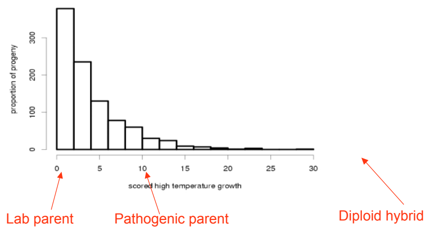




Three mutant genes

So why did 0/900 haploid progeny have a phenotype as extreme as the diploid hybrid?

NO progeny as extreme as diploid hybrid

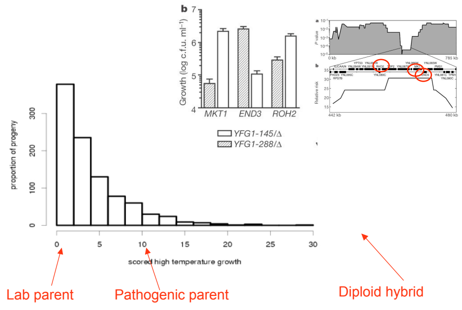


Lab parent

Pathogenic parent

Diploid hybrid

NO progeny as extreme as diploid hybrid



Lab parent

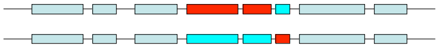
Pathogenic parent

Diploid hybrid

Linked mutations of opposite effect

Path

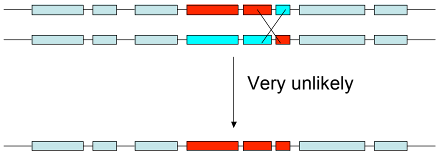
Linked mutations of opposite effect



Path

Lab

Linked mutations of opposite effect



Path

Lab

Very unlikely

“Multiple linked loci”

Model organism to human

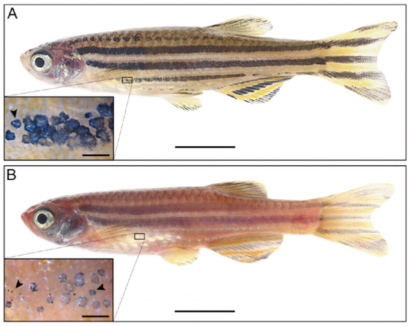
SLC24A5, a Putative Cation Exchanger, Affects Pigmentation in Zebrafish and Humans

Rebecca L. Lamason,[1*] Manzoor-Ali P.K. Mohideen,[1†]
Jason R. Mest,[1] Andrew C. Wong,[1‡] Heather L. Norton,[6]
Michele C. Aros,[1] Michael J. Jurynec,[8] Xianyun Mao,[6]
Vanessa R. Humphreville,[1§] Jasper E. Humbert,[2,9] Soniya Sinha,[2]
Jessica L. Moore,[1∥] Pudur Jagadeeswaran,[10] Wei Zhao,[3]
Gang Ning,[7] Izabela Makalowska,[7] Paul M. McKeigue,[11]
David O'Donnell,[11] Rick Kittles,[12] Esteban J. Parra,[13]
Nancy J. Mangini,[14] David J. Grunwald,[8] Mark D. Shriver,[6]
Victor A. Canfield,[4] Keith C. Cheng[1,4,5¶]

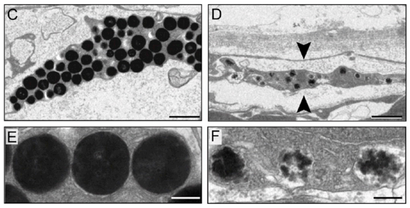
Why pigmentation?

- Camouflage
- Sexual selection
- Protection from UV
- Controlling light scatter
- (Sunlight for vitamin D)
- Accident—something else selected for nearby

Golden mutation



Golden mutation



Melanosomes, melanin-producing organelles

Golden mutation

1981: original mutant arose spontaneously in the lab.

Showed mendelian segregation (1 locus), and is recessive.

Golden mutation

1981: original mutant arose spontaneously in the lab.

Showed mendelian segregation (1 locus), and is recessive.

Dramatic, single-locus differences not common in the wild. Why not?

Linkage analysis with sparse markers mapped *golden* to markers on chromosome 18, but high-resolution position of markers unknown.

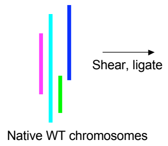
Linkage analysis with sparse markers mapped *golden* to markers on chromosome 18, but high-resolution position of markers unknown.

Genome sequence not completed…

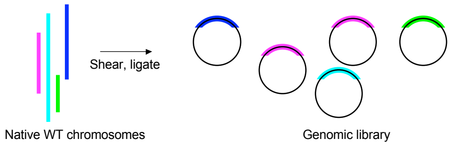
Linkage analysis with sparse markers mapped *golden* to markers on chromosome 18, but high-resolution position of markers unknown.

Genome sequence not completed…
Hybrid cell lines not available…

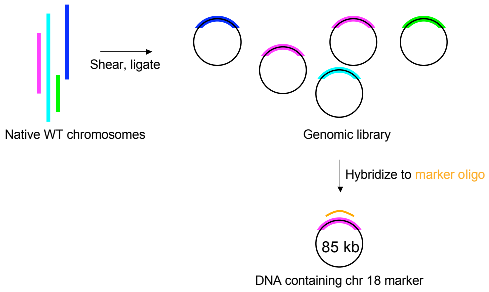
Library screen

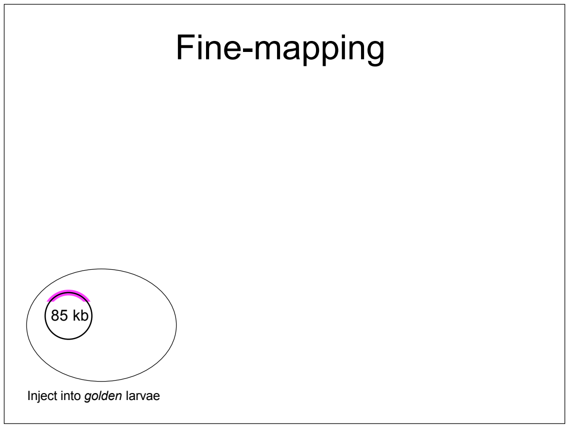


Library screen



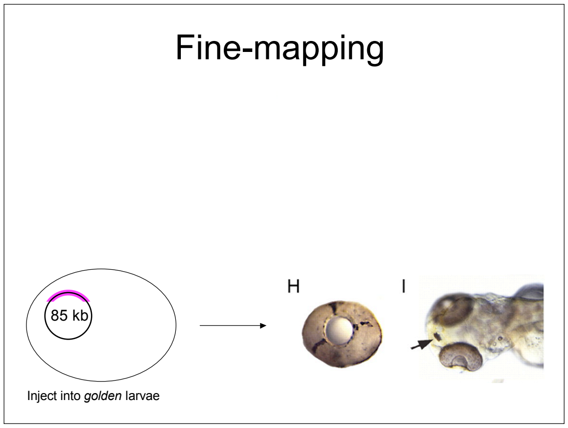
Library screen





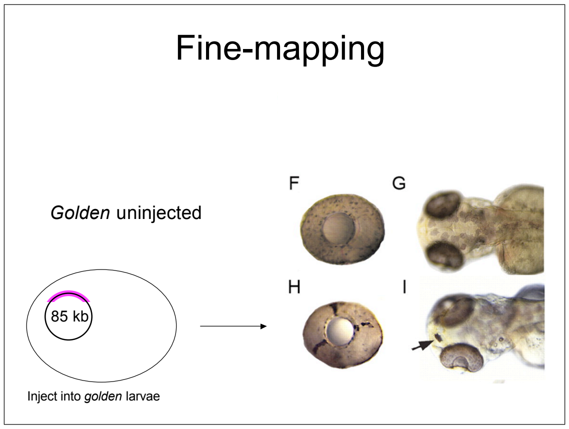
Fine-mapping

Inject into *golden* larvae



Fine-mapping

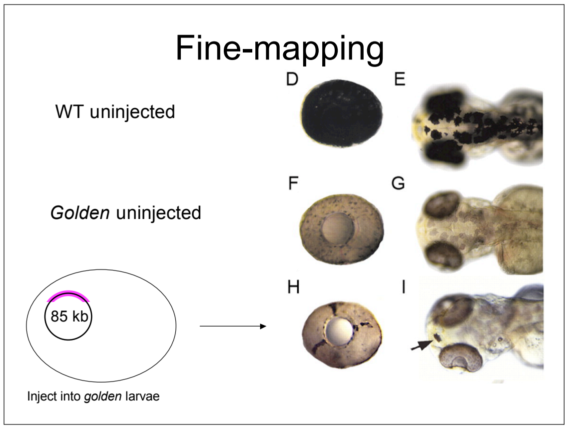
Inject into *golden* larvae



Fine-mapping

Golden uninjected

Inject into *golden* larvae

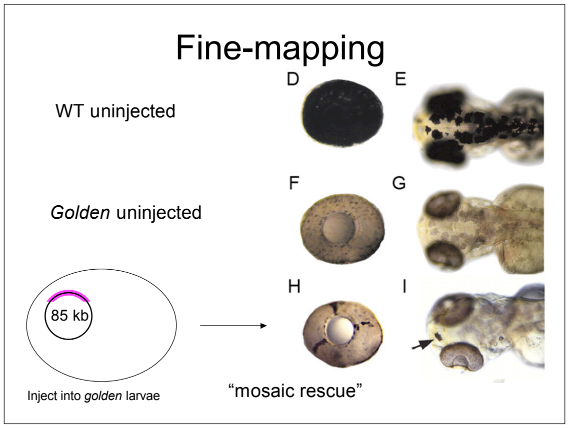


Fine-mapping

WT uninjected

Golden uninjected

Inject into *golden* larvae



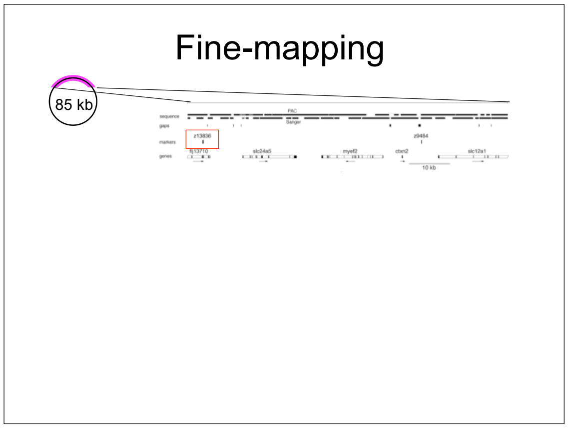
Fine-mapping

WT uninjected

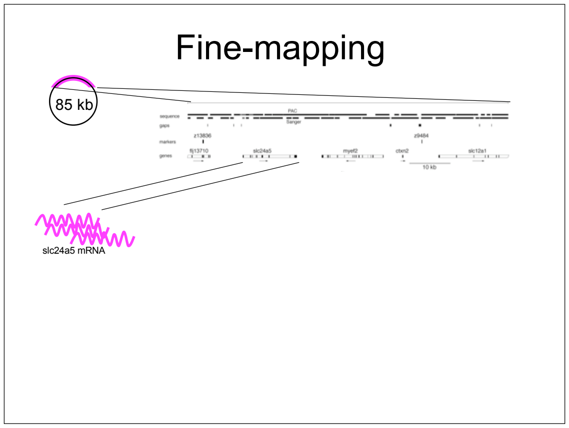
Golden uninjected

Inject into *golden* larvae

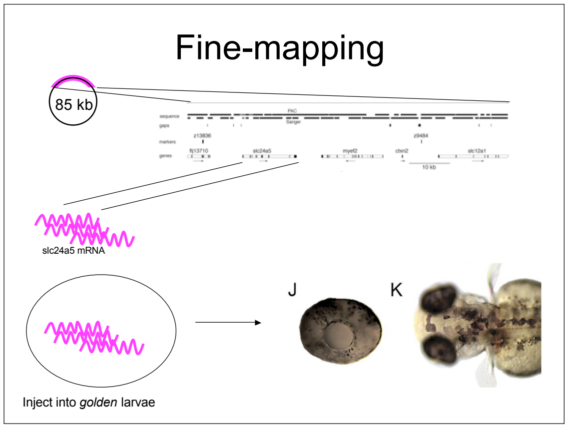
“mosaic rescue”



Fine-mapping

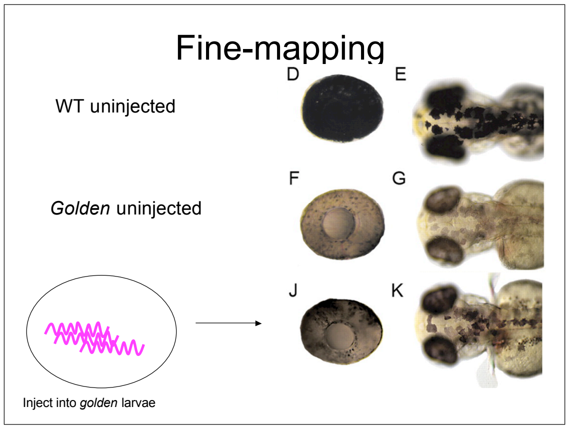


Fine-mapping



Fine-mapping

Inject into *golden* larvae



Fine-mapping

WT uninjected

Golden uninjected

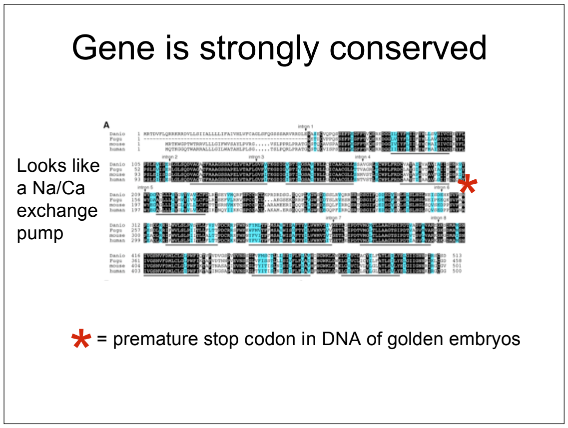
Inject into *golden* larvae

Gene is strongly conserved

Looks like a Na/Ca exchange pump

Gene is strongly conserved

Looks like a Na/Ca exchange pump



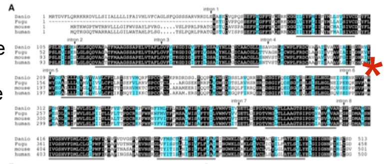
Gene is strongly conserved

Looks like a Na/Ca exchange pump

* = premature stop codon in DNA of golden embryos

Gene is strongly conserved

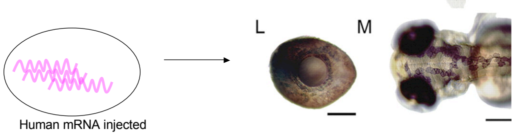
Looks like a Na/Ca exchange pump



* = premature stop codon in DNA of golden embryos

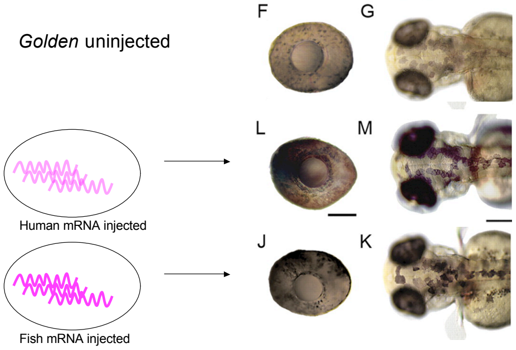
(Don’t usually see such dramatic mutations in the wild)

Human can rescue fish!

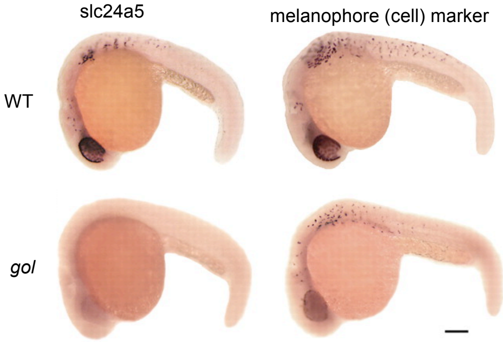


Human can rescue fish!

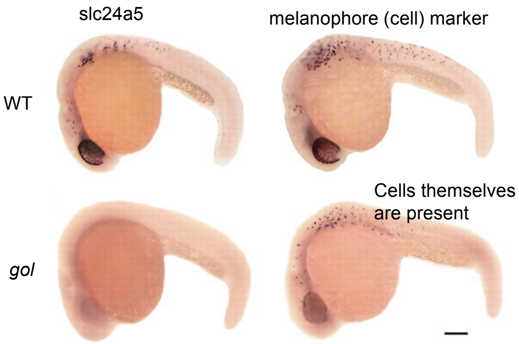
Golden uninjected



What is this gene?



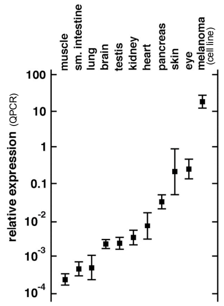
What is this gene?

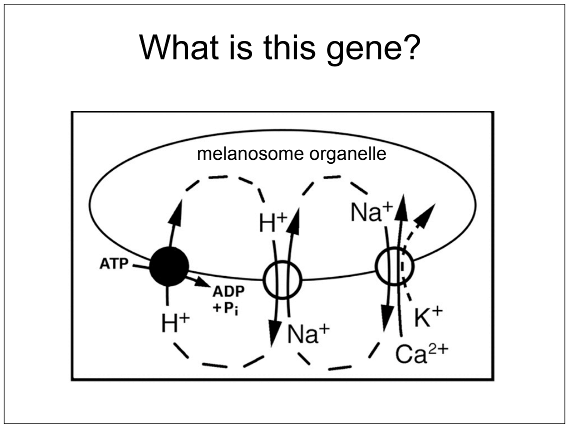


Cells themselves are present

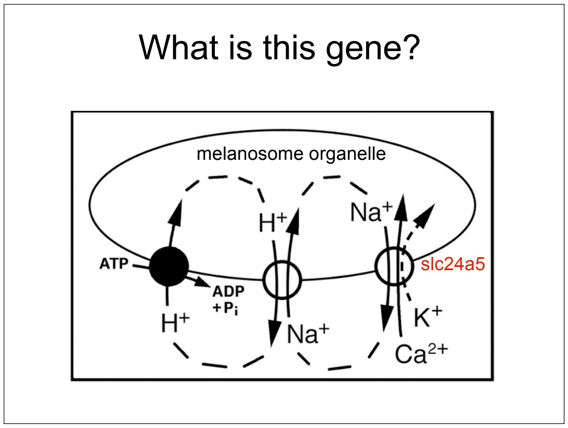
What is this gene?

in mouse

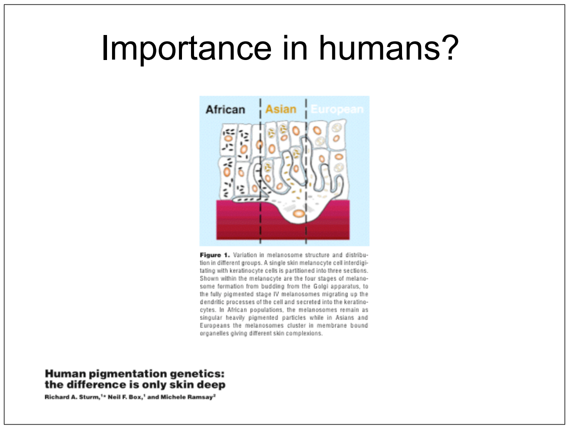




What is this gene?



What is this gene?

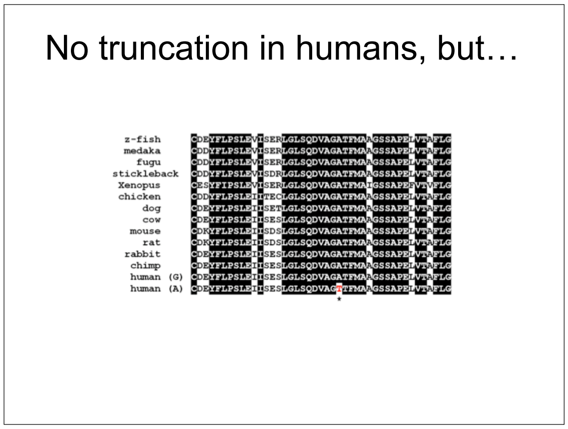


Importance in humans?

Figure 1. Variation in melanosome structure and distribution in different groups. A single skin melanocyte cell interdigitating with keratinocyte cells is partitioned into three sections. Shown within the melanocyte are the four stages of melanosome formation from budding from the Golgi apparatus, to the fully pigmented stage IV melanosomes migrating up the dendritic processes of the cell and secreted into the keratinocytes. In African populations, the melanosomes remain as singular heavily pigmented particles while in Asians and Europeans the melanosomes cluster in membrane bound organelles giving different skin complexions.

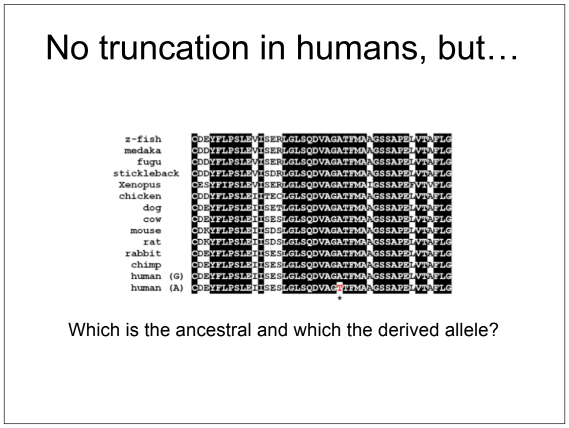
Human pigmentation genetics: the difference is only skin deep

Richard A. Sturm,[1]* Neil F. Box,[1] and Michele Ramsay[2]



No truncation in humans, but…

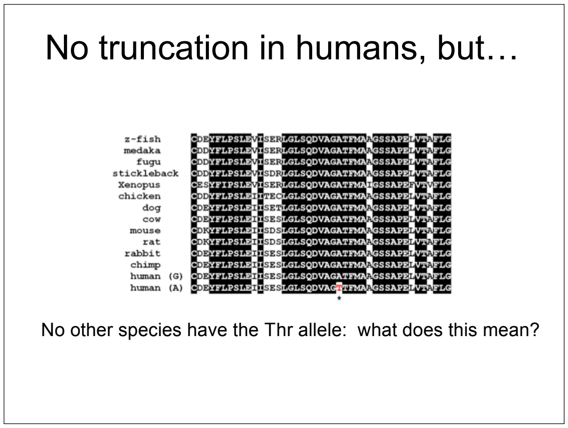
```
     z-fish   CDEYFLPSLEVISERLGLSQDVAGATFMAAGSSAPELVTAFLG
     medaka   CDDYFLPSLEVISERLGLSQDVAGATFMAAGSSAPELVTAFLG
       fugu   CDDYFLPSLEVISERLGLSQDVAGATFMAAGSSAPELVTAFLG
stickleback   CDDYFLPSLEVISDRLGLSQDVAGATFMAAGSSAPELVTAFLG
    Xenopus   CESYFIPSLEVISERLGLSQDVAGATFMAIGSSAPEFVTVFLG
    chicken   CDDYFLPSLEIITECLGLSQDVAGATFMAAGSSAPELVTAFLG
        dog   CDEYFLPSLEIISETLGLSQDVAGATFMAAGSSAPELVTAFLG
        cow   CDEYFLPSLEIISESLGLSQDVAGATFMAAGSSAPELVTAFLG
      mouse   CDKYFLPSLEIISDSLGLSQDVAGATFMAAGSSAPELVTAFLG
        rat   CDKYFLPSLEIISDSLGLSQDVAGATFMAAGSSAPELVTAFLG
     rabbit   CDEYFLPSLEIISESLGLSQDVAGATFMAAGSSAPELVTAFLG
      chimp   CDEYFLPSLEIISESLGLSQDVAGATFMAAGSSAPELVTAFLG
  human (G)   CDEYFLPSLEIISESLGLSQDVAGATFMAAGSSAPELVTAFLG
  human (A)   CDEYFLPSLEIISESLGLSQDVAGTTFMAAGSSAPELVTAFLG
                                      *
```



No truncation in humans, but…

```
     z-fish   CDEYFLPSLEVISERLGLSQDVAGATFMAAGSSAPELVTAFLG
     medaka   CDDYFLPSLEVISERLGLSQDVAGATFMAAGSSAPELVTAFLG
       fugu   CDDYFLPSLEVISERLGLSQDVAGATFMAAGSSAPELVTAFLG
stickleback   CDDYFLPSLEVISDRLGLSQDVAGATFMAAGSSAPELVTAFLG
    Xenopus   CESYFIPSLEVISERLGLSQDVAGATFMAIGSSAPEFVTVFLG
    chicken   CDDYFLPSLEIITECLGLSQDVAGATFMAAGSSAPELVTAFLG
        dog   CDEYFLPSLEIISETLGLSQDVAGATFMAAGSSAPELVTAFLG
        cow   CDEYFLPSLEIISESLGLSQDVAGATFMAAGSSAPELVTAFLG
      mouse   CDKYFLPSLEIISDSLGLSQDVAGATFMAAGSSAPELVTAFLG
        rat   CDKYFLPSLEIISDSLGLSQDVAGATFMAAGSSAPELVTAFLG
     rabbit   CDEYFLPSLEIISESLGLSQDVAGATFMAAGSSAPELVTAFLG
      chimp   CDEYFLPSLEIISESLGLSQDVAGATFMAAGSSAPELVTAFLG
  human (G)   CDEYFLPSLEIISESLGLSQDVAGATFMAAGSSAPELVTAFLG
  human (A)   CDEYFLPSLEIISESLGLSQDVAGTTFMAAGSSAPELVTAFLG
                                      *
```

Which is the ancestral and which the derived allele?



No truncation in humans, but…

```
     z-fish   CDEYFLPSLEVISERLGLSQDVAGATFMAAGSSAPELVTAFLG
     medaka   CDDYFLPSLEVISERLGLSQDVAGATFMAAGSSAPELVTAFLG
       fugu   CDDYFLPSLEVISERLGLSQDVAGATFMAAGSSAPELVTAFLG
stickleback   CDDYFLPSLEVISDRLGLSQDVAGATFMAAGSSAPELVTAFLG
    Xenopus   CESYFIPSLEVISERLGLSQDVAGATFMAIGSSAPEFVTVFLG
    chicken   CDDYFLPSLEIITECLGLSQDVAGATFMAAGSSAPELVTAFLG
        dog   CDEYFLPSLEIISETLGLSQDVAGATFMAAGSSAPELVTAFLG
        cow   CDEYFLPSLEIISESLGLSQDVAGATFMAAGSSAPELVTAFLG
      mouse   CDKYFLPSLEIISDSLGLSQDVAGATFMAAGSSAPELVTAFLG
        rat   CDKYFLPSLEIISDSLGLSQDVAGATFMAAGSSAPELVTAFLG
     rabbit   CDEYFLPSLEIISESLGLSQDVAGATFMAAGSSAPELVTAFLG
      chimp   CDEYFLPSLEIISESLGLSQDVAGATFMAAGSSAPELVTAFLG
  human (G)   CDEYFLPSLEIISESLGLSQDVAGATFMAAGSSAPELVTAFLG
  human (A)   CDEYFLPSLEIISESLGLSQDVAGTTFMAAGSSAPELVTAFLG
                                      *
```

No other species have the Thr allele: what does this mean?

No truncation in humans, but…

No other species have the Thr allele: what does this mean?
Could be deleterious, just an accidental mutation.

No truncation in humans, but…

No other species have the Thr allele: what does this mean?
Could be deleterious, just an accidental mutation.
Could be advantageous for some humans, no other species.

Population genetics

Survey multiple European-Americans in Utah: >99% Thr.

Population genetics

Survey multiple European-Americans in Utah: >99% Thr.
Survey multiple Han Chinese in Beijing: >93% Ala.
Survey multiple Japanese in Tokyo: >93% Ala.
Survey multiple Yoruba in Ibadan, Nigeria: >93% Ala.

Population genetics

Survey multiple European-Americans in Utah: >99% Thr.
Survey multiple Han Chinese in Beijing: >93% Ala.
Survey multiple Japanese in Tokyo: >93% Ala.
Survey multiple Yoruba in Ibadan, Nigeria: >93% Ala.

So this allele is NOT definining race.

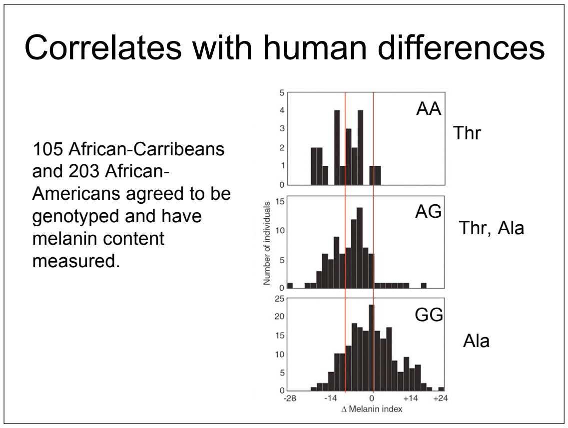
Population genetics

Survey multiple European-Americans in Utah: >99% Thr.
Survey multiple Han Chinese in Beijing: >93% Ala.
Survey multiple Japanese in Tokyo: >93% Ala.
Survey multiple Yoruba in Ibadan, Nigeria: >93% Ala.

So this allele is NOT definining race.
Does it explain differences in skin color in humans?

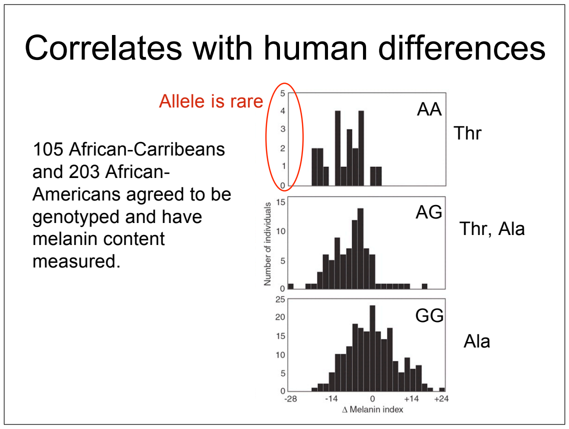
Correlates with human differences

105 African-Carribeans and 203 African-Americans agreed to be genotyped and have melanin content measured.



Correlates with human differences

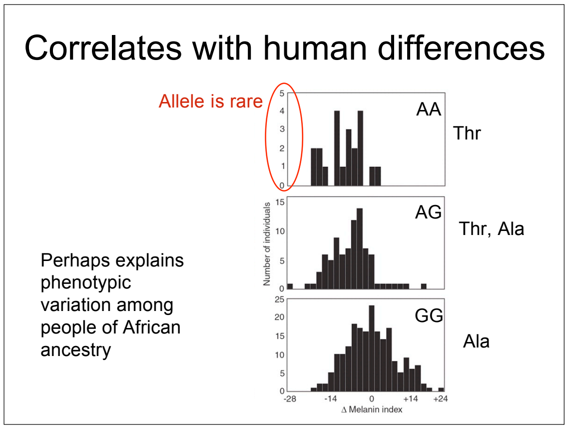
105 African-Carribeans and 203 African-Americans agreed to be genotyped and have melanin content measured.



Correlates with human differences

Allele is rare

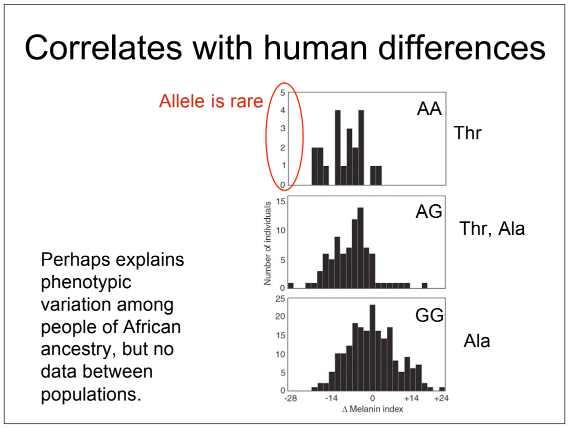
105 African-Carribeans and 203 African-Americans agreed to be genotyped and have melanin content measured.



Correlates with human differences

Allele is rare

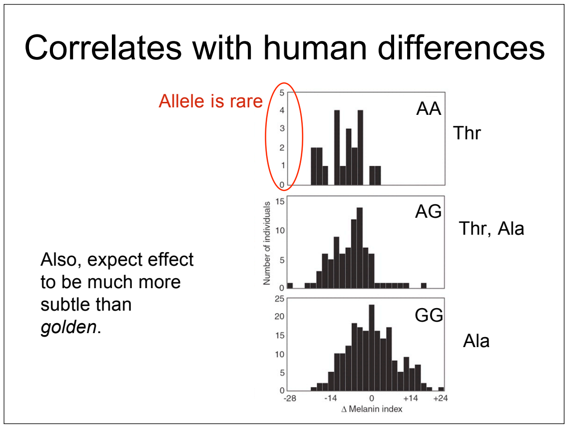
Perhaps explains phenotypic variation among people of African ancestry



Correlates with human differences

Allele is rare

Perhaps explains phenotypic variation among people of African ancestry, but no data between populations.



Correlates with human differences

Allele is rare

Also, expect effect to be much more subtle than *golden*.

The contrast with albinism

Gene	Phenotype	Mendelian inheritance in man accession
Tyrosinase gene (TYR)	oculocutaneous albinism type 1 (OCA1;)	MIM *203100
P gene	oculocutaneous albinism type 2 (OCA2)	MIM *203200
Tyrosinase related protein-1 gene (TYRP1)	oculocutaneous albinism type 3 (OCA3)	MIM #203290
Membrane-associated transporter protein (MATP)	oculocutaneous albinism type 4 (OCA4)	MIM #606574
HPS1 gene	Hermansky–Pudlak syndrome type 1 (HPS1)	MIM #604982
Beta-3 A-adaptin gene (ADTB3A)	Hermansky–Pudlak syndrome type 2 (HPS2)	MIM *603401
HPS3 gene	Hermansky–Pudlak syndrome type 3 (HPS3)	MIM *606118
HPS4 gene	Hermansky–Pudlak syndrome type 4 (HPS4)	MIM *606682
HPS5 gene	Hermansky–Pudlak syndrome type 5 (HPS5)	MIM *607521
HPS6 gene	Hermansky–Pudlak syndrome type 6 (HPS6)	MIM *607522
CHS1 gene	Chediak–Higashi syndrome (CHS)	MIM *214500
OA1 gene	X-linked ocular albinism (OA)	MIM *300500

Oculocutaneous Albinism Type 1: The Last 100 Years

WILLIAM S. OETTING, JAMES P. FRYER, SABITHA SHRIRAM and RICHARD A. KING

The contrast with albinism

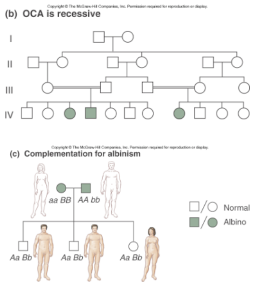


Fig. 3.19

(One such mutation usually sufficient = Mendelian)

"Normal" skin color variation is genetically complex

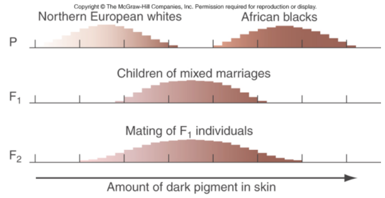
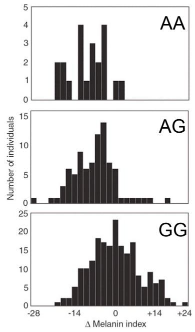


Fig. 3.21

Correlates with human differences



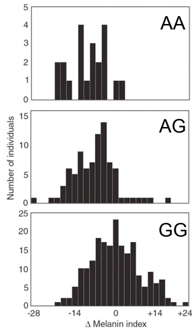
Thr

Thr, Ala

Ala

Correlates with human differences

Note that this is not linkage analysis. Individuals are unrelated. More details on Monday.



Thr

Thr, Ala

Ala