Compound heterozygosity

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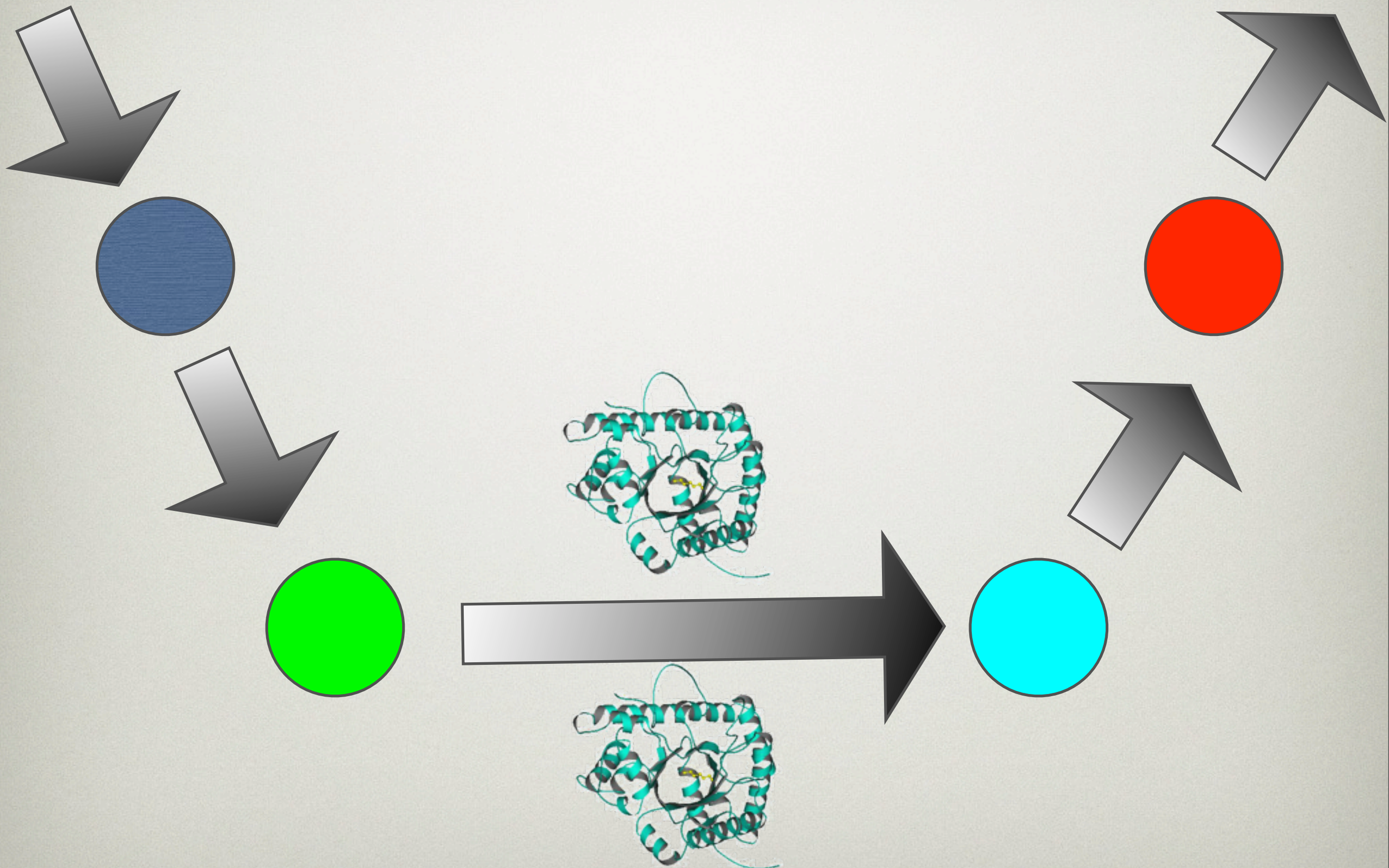
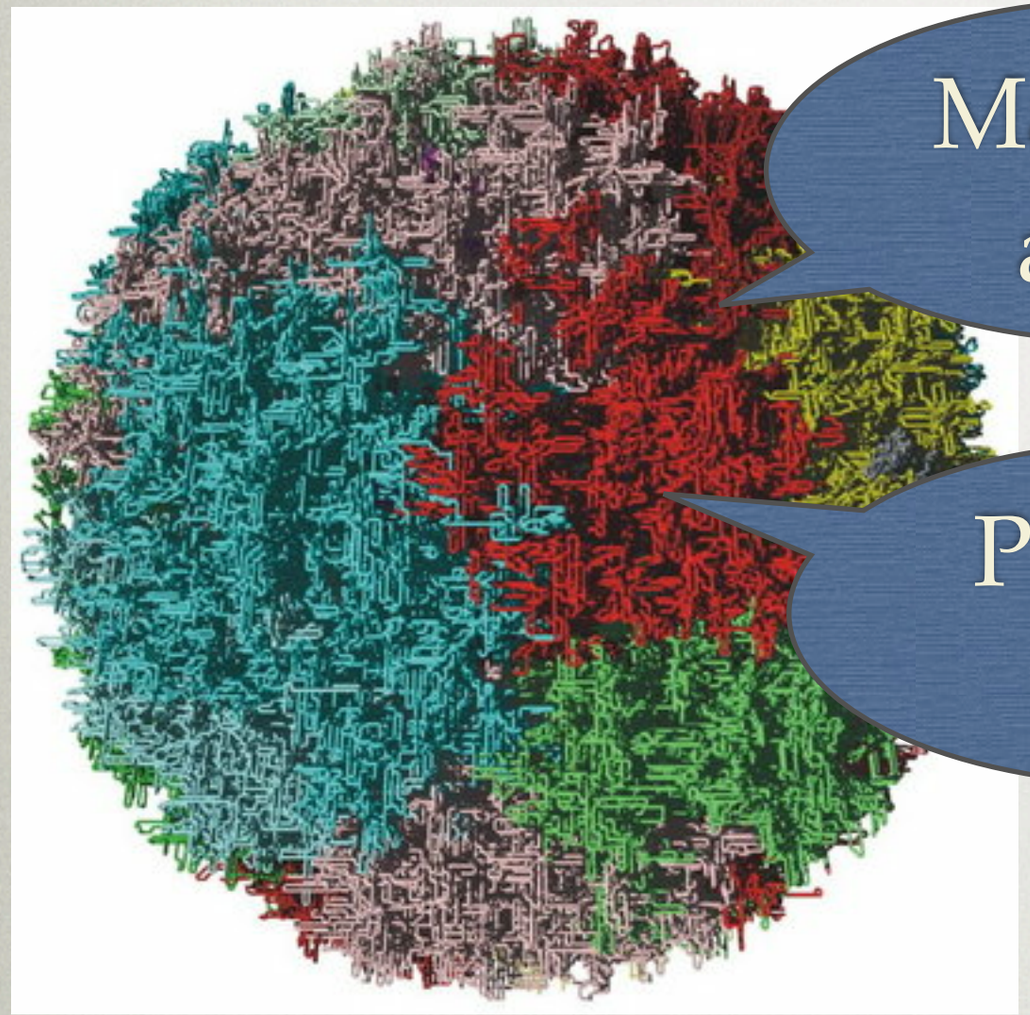
Outline

- Recessive model
- Examples of Compound Heterozygosity
- Compound Double Heterozygosity (CDH) test

Recessive model

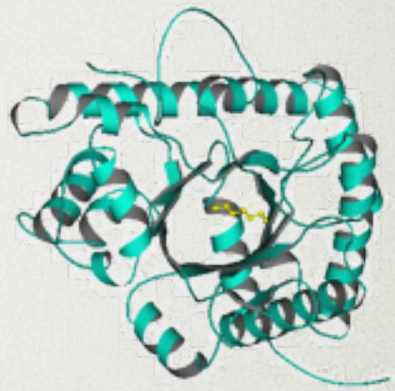
- How do two alleles in a genotype act to define a phenotype?
- They could have independent effects (additive model), or one allele could dominate the other, so that the phenotype of heterozygote is the same as the phenotype of a homozygote for this ‘dominant’ allele
- Dominant allele leads to specific phenotype when presented in homo- or heterozygous state, and the other (recessive) leads to alternative phenotype only in a homozygous state

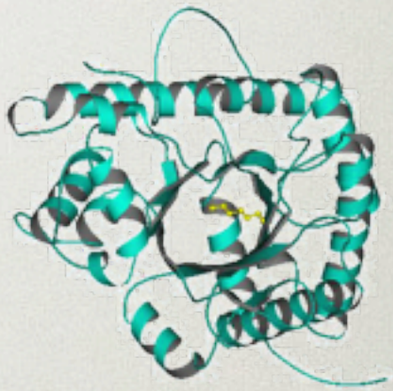


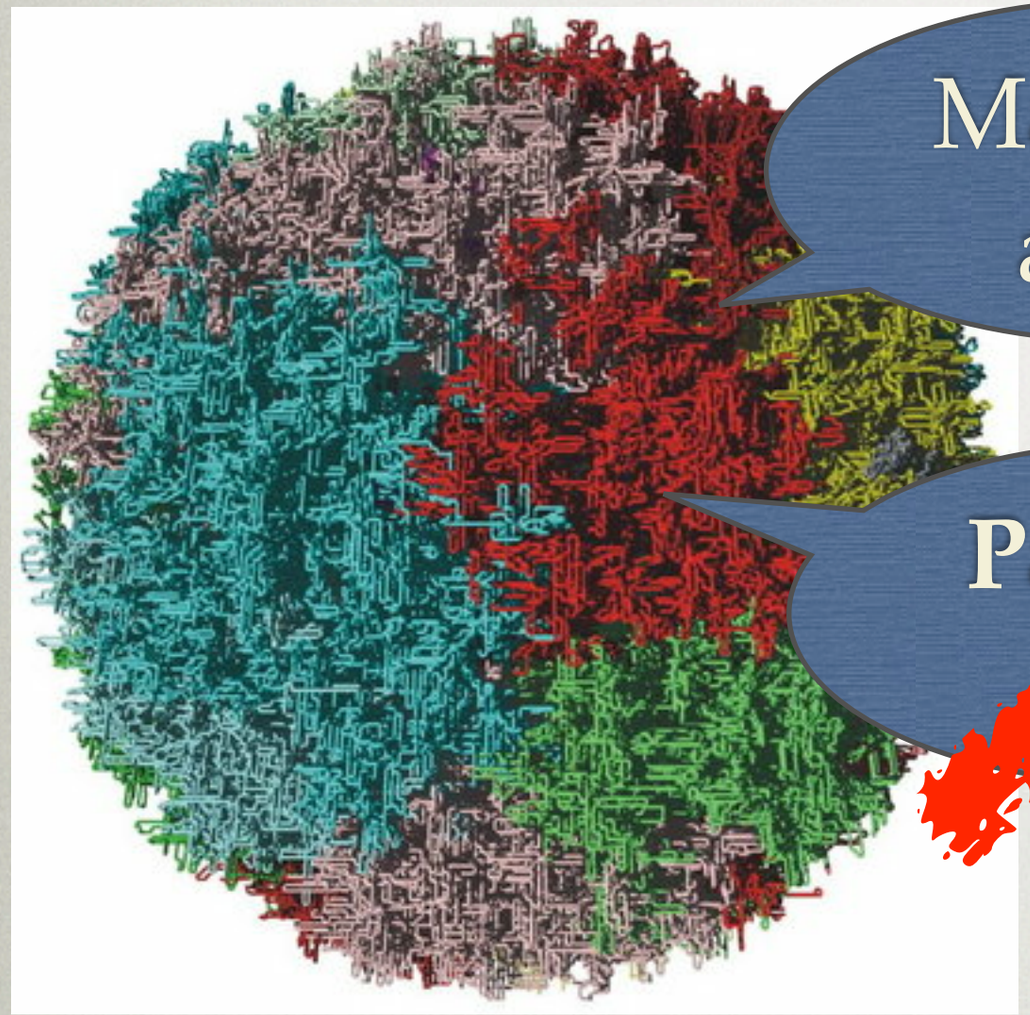


Maternal allele

Paternal allele

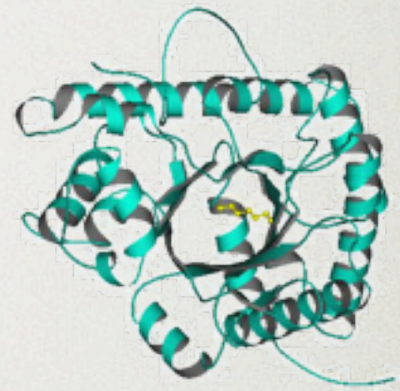




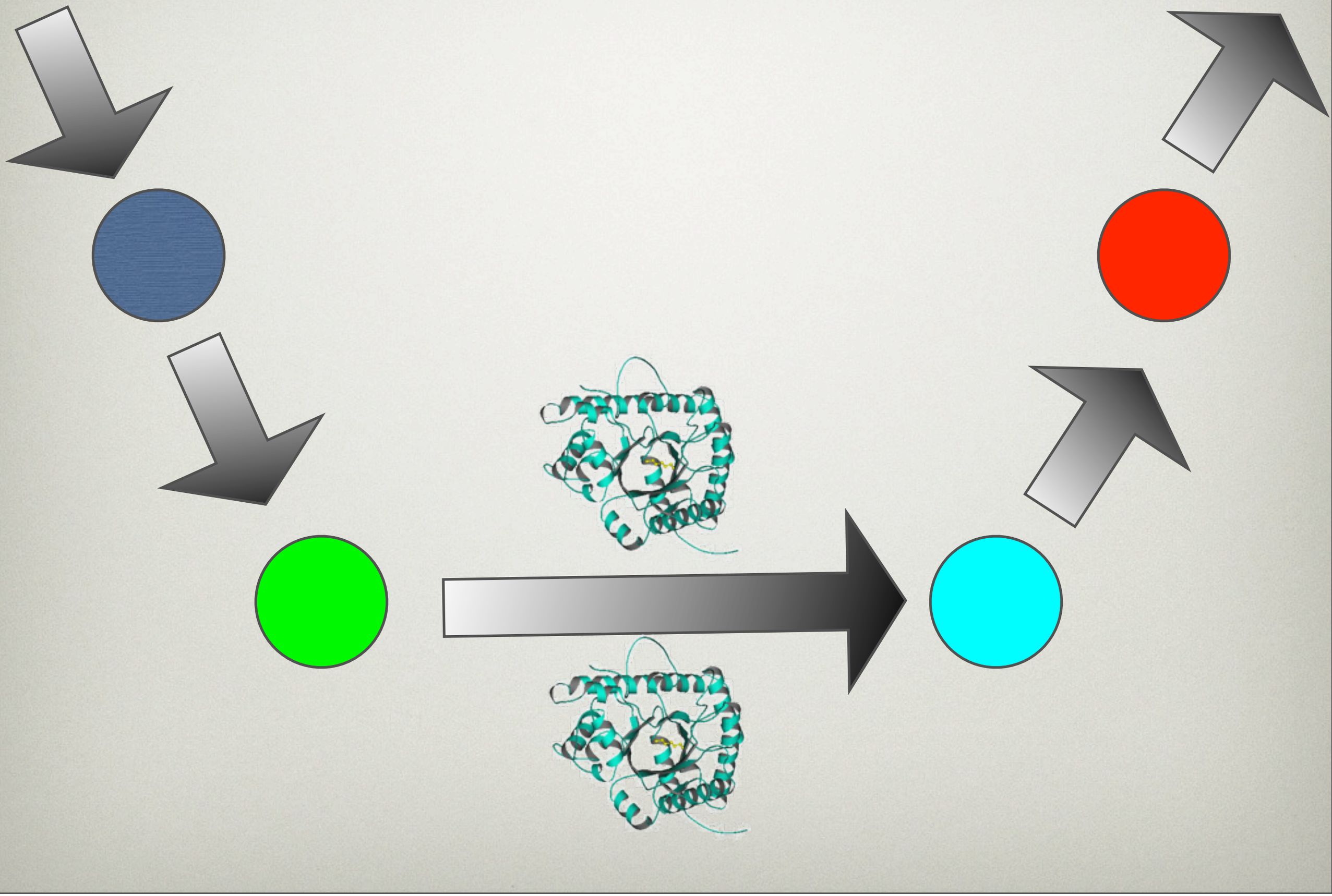


Maternal allele

Paternal allele



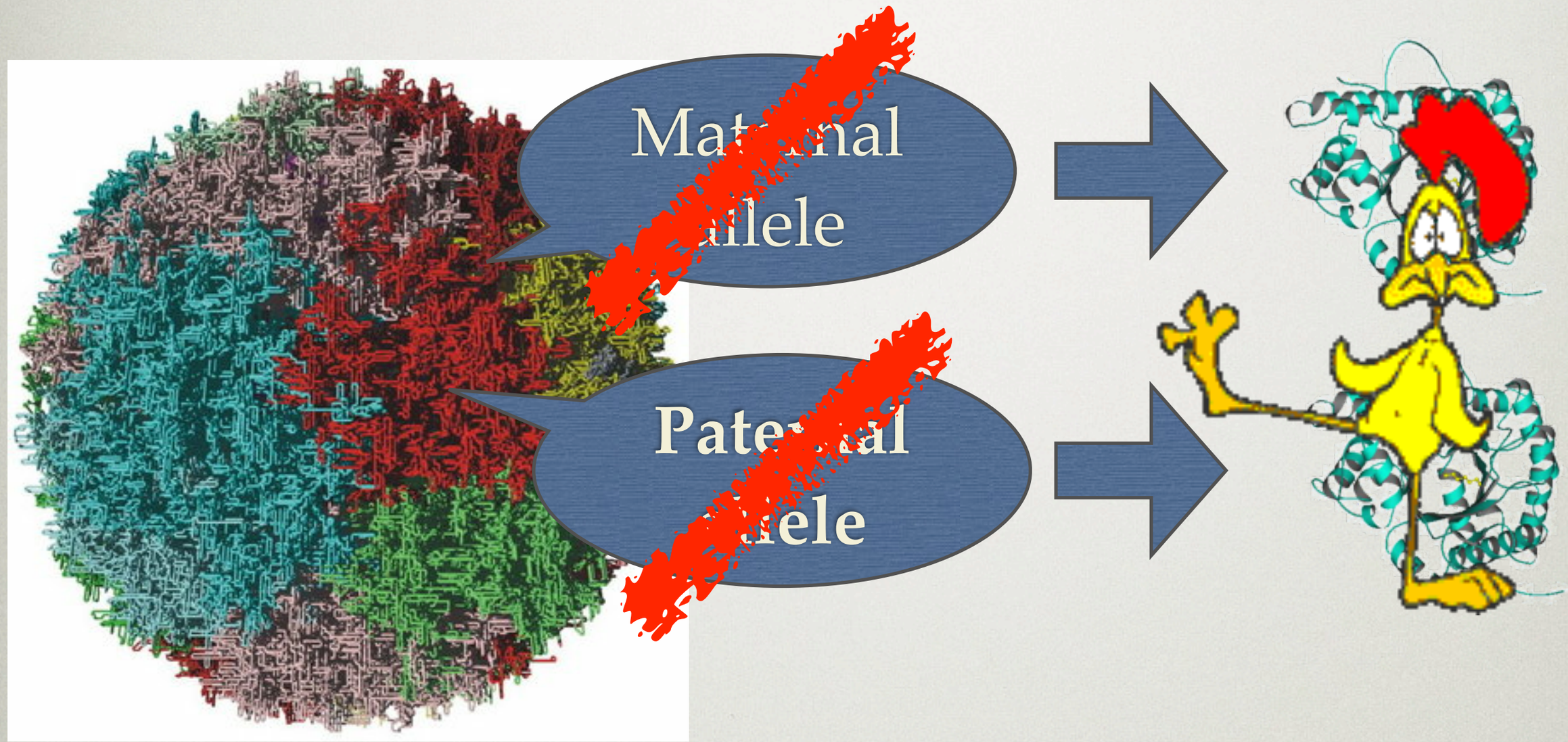
Loss of Function (LOF)



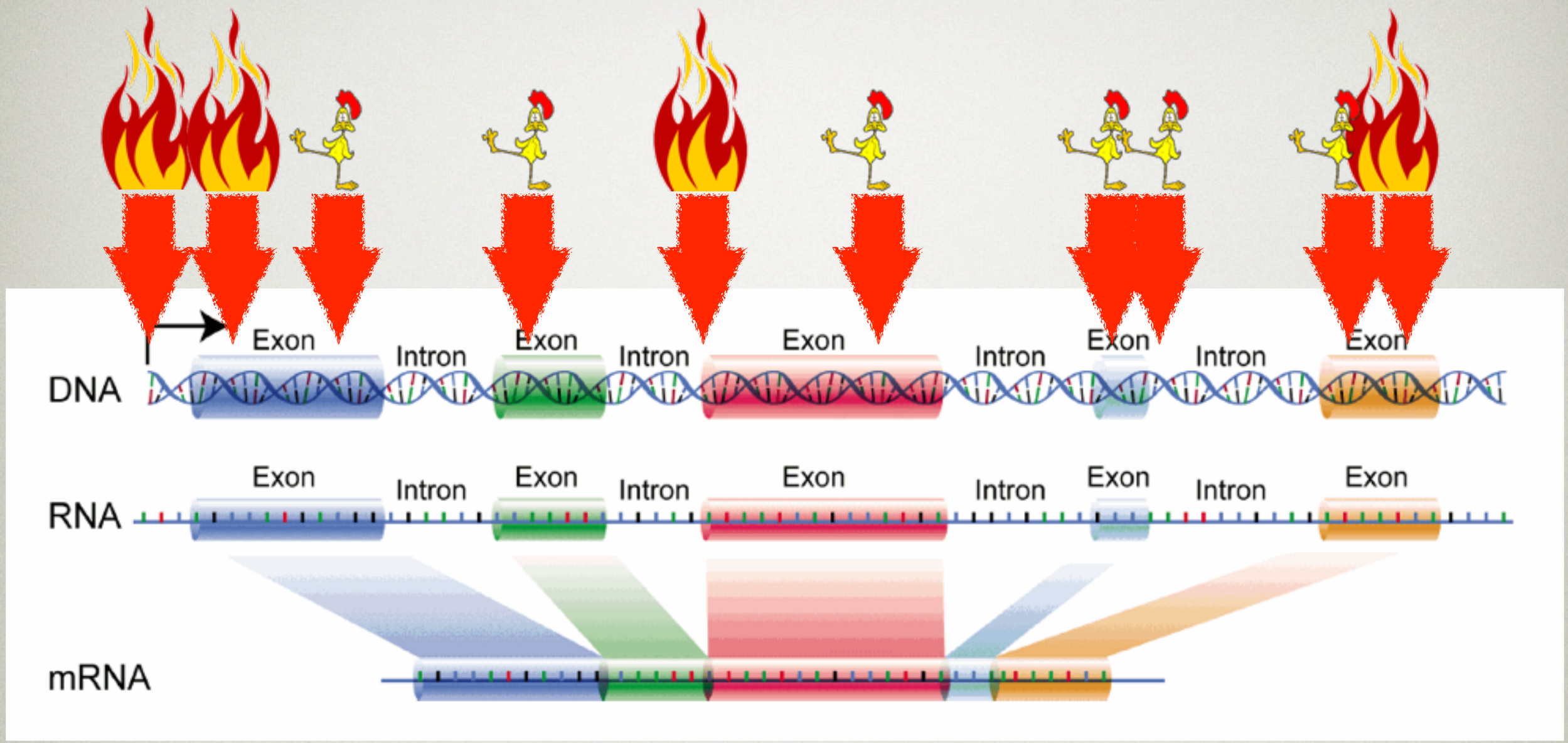
Complex biological systems

When a single piece is 'broken', complex biological systems still have the ability to compensate/buffer the defect via

- Adjusting the physiological parameters
- Taking alternative routes

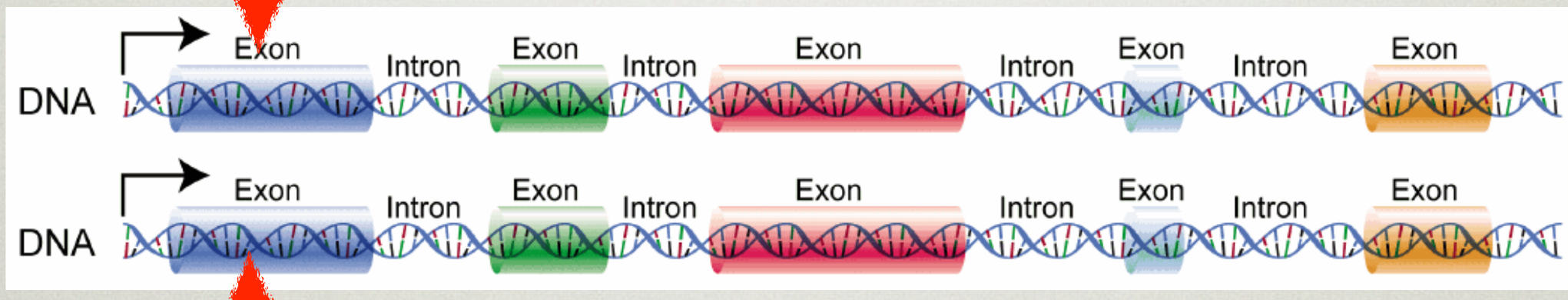

Maternal
allele
Paternal
allele

May have
(strong)
phenotypic
effect


Exon
Intron
Exon
Intron
Exon
Intron
Exon
Intron
Exon
DNA
Exon
Intron
Exon
Intron
Exon
Intron
Exon
Intron
Exon
RNA
mRNA

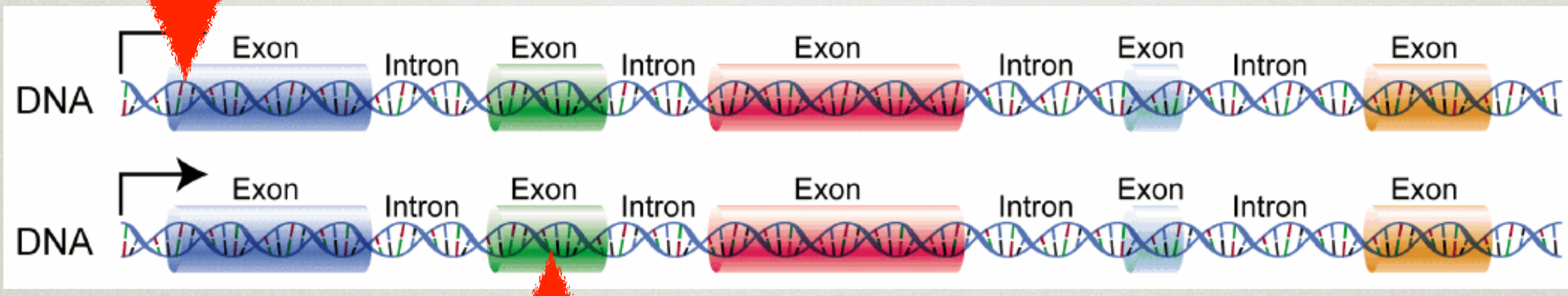
Homozygosity

- The same mutation is present on both maternal and paternal chromosome



Compound heterozygosity (CH)

- Different mutations, but similarly disrupting the function of the same gene



Outline

- Recessive model
- **Examples of Compound Heterozygosity**
- Compound Double Heterozygosity (CDH) test

Cystic fibrosis

- Lungs are affected; abnormal transport of chloride and sodium across an epithelium, leading to thick, viscous secretions.
- Recessive mutations in the CFTR gene
  - More than 1500 are known
  - 50% patients homozygous for F508del (50%)
  - ~40% are **compound het** F508del/other

Red hair

- MC1R gene LOF => red hair / fair skin pigmentation (inability to tan)
- Prevalent mutations: R151C (0.14), R160W (0.11)
- Of carriers of 2 LOF mutations ~50% are CH

More examples...

- Look up in Liu et al., PLoS ONE, 2011

variants in a gene collectively influence a phenotype. Some examples are HFE and hemochromatosis [7], PLA2G7 and coronary heart diseases [8], SLC22A12/SLC2A9 and renal hypouricemia [9,10], KCNQ1 and Jervell and Lange-Nielsen syndrome [11], NCCT and Gitelmańs syndrome [12], ABCC6/GGCX and pseudoxanthoma elasticum [13,14,15], TG and congenital goiter [16], SCN5A and Brugada syndrome [17], P2RX7 and inflammatory response [18], ABCA12 and congenital ichthyoses [19], TRIM32 and nephrogenic diabetes insipidus [20], WFS1 and Wolfram syndrome [21], and CLDN16 and hypomagnesaemia [22]. Through this study we use LOF variants in

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- **Compound Double Heterozygosity (CDH) test**

Risk

	aa	Aa	AA
bb	b	b	bR
Bb	b	bR	bR
BB	bR	bR	bR

Risk

	aa	Aa	AA
bb	b	b	bR
Bb	b	b & bR	bR
BB	bR	bR	bR

Test for collapsed double heterozygosity

Cases

	aa	Aa	AA
bb	b	b	bR
Bb	b	bR	bR
BB	bR	bR	bR

Controls

	aa	Aa	AA
bb	b	b	bR
Bb	b	bR	bR
BB	bR	bR	bR

CDH test

	Cases	Controls
<2 LOF		
2 LOF		

Tagging scenario

C - rare allele at locus 1

D - rare allele at locus 2

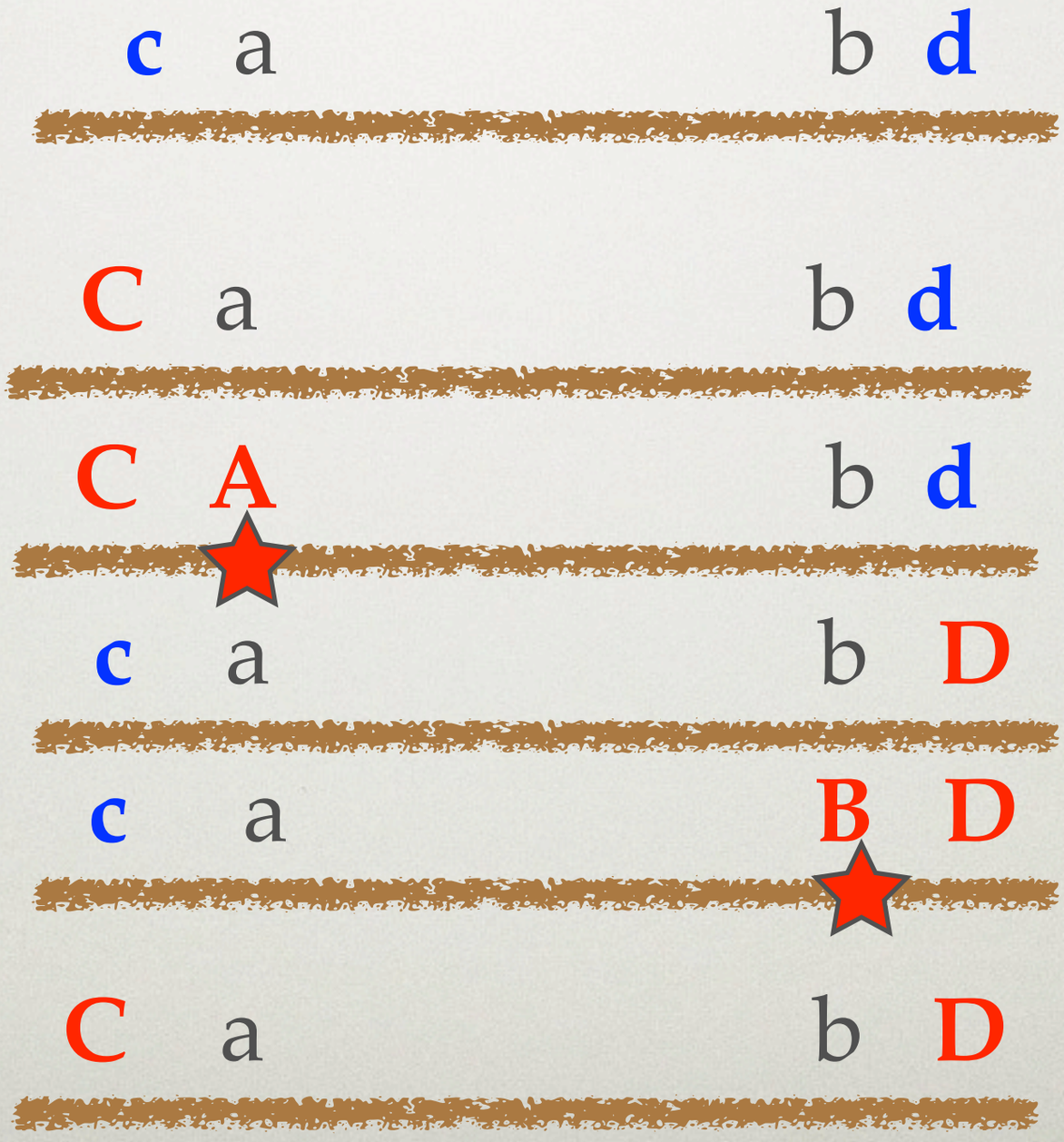
c a b **d**	Common
C a b **d**	Rare
c a b **D**	Rare
C a b **D**	Very rare

Tagging scenario

Mutations can occur here, but C/D can not be tags!

Tags + likely

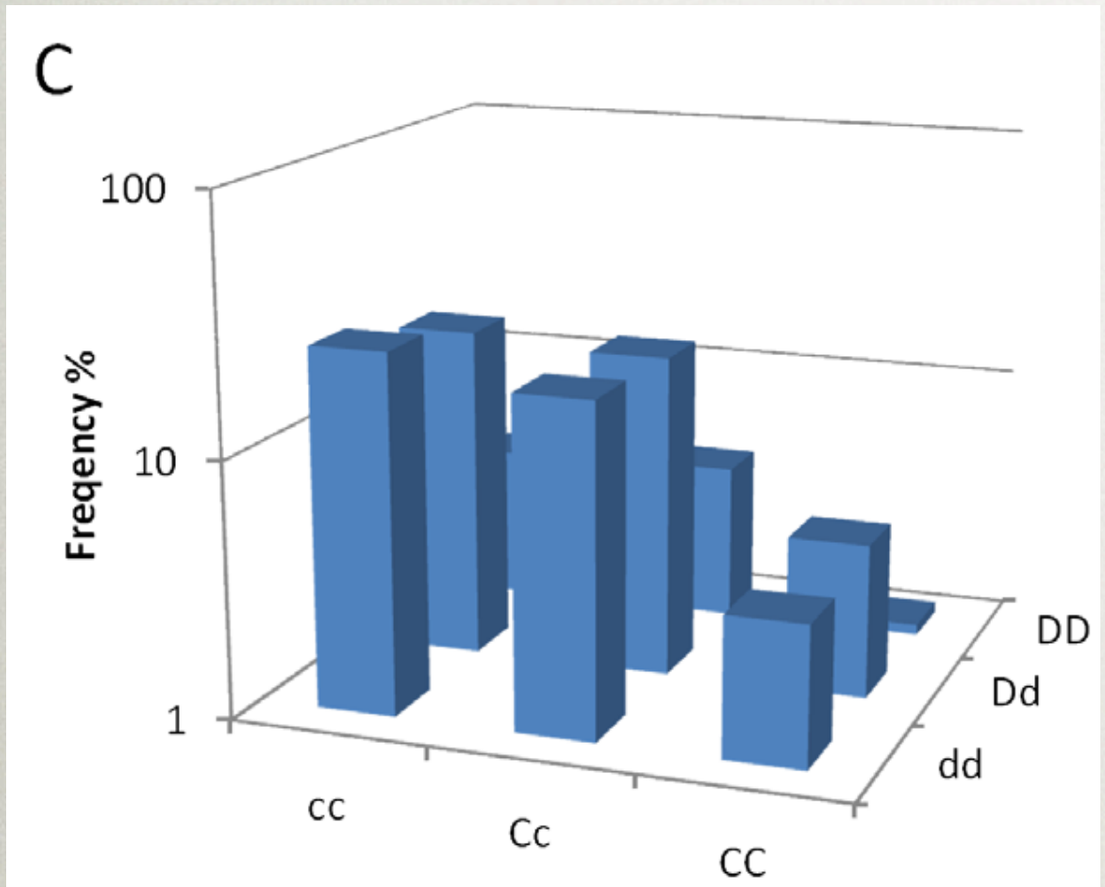
Not likely

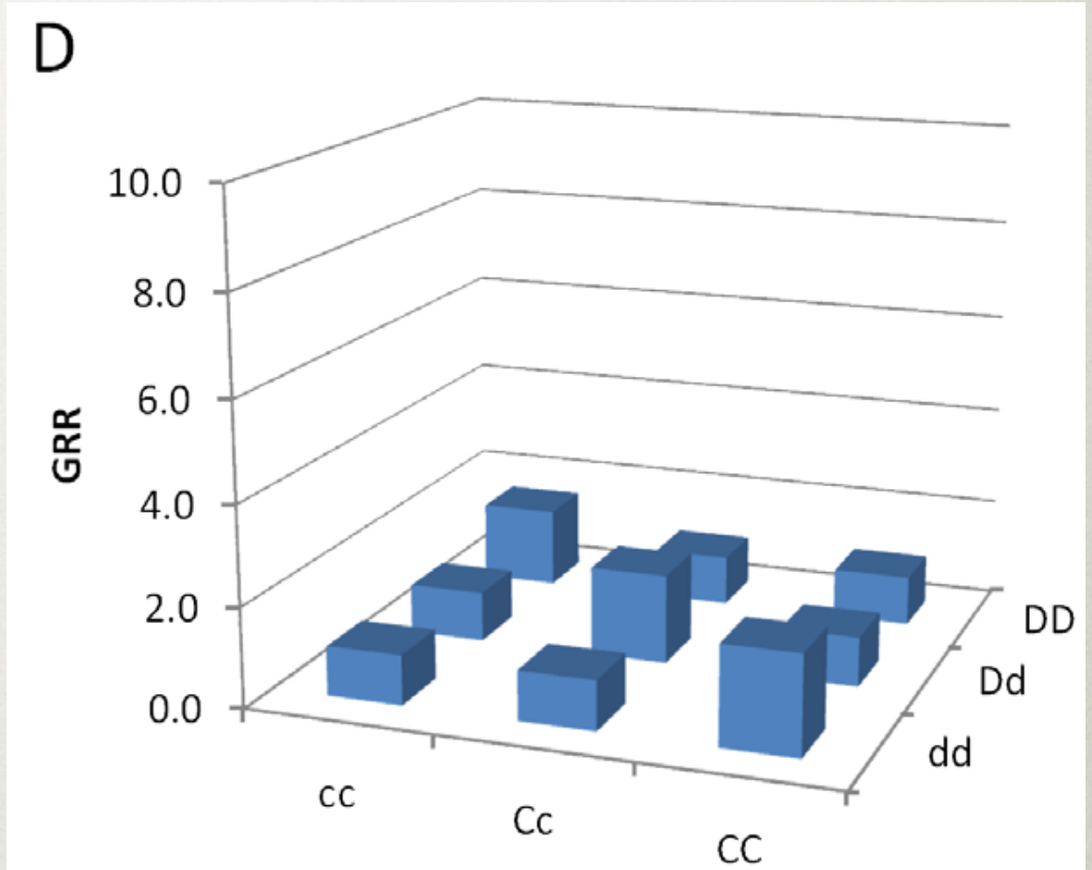


Summary

- The mutations are present on haplotypes combining common and rare tag allele
- A haplotype containing two rare tag alleles is NOT likely to carry a mutation

Empirical proof





Liu et al., PLoS ONE, 2011

Red hair example

Table 2. Frequency of red hair phenotype as a function of genotype of two non-causal SNPs tagging the causal variants at the *MC1R* gene locus.

		rs2011877		
		GG	**GT**	**TT**
rs2302898	AA	0.00	0.02	0.14
	AG	0.02	0.06	0.01
	GG	0.22	0.01	0.00

Liu et al., PLoS ONE, 2011

This would not work for tags!

Cases

	aa	Aa	AA
bb	b	b	bR
Bb	b	bR	bR
BB	bR	bR	bR

Controls

	aa	Aa	AA
bb	b	b	bR
Bb	b	bR	bR
BB	bR	bR	bR

CDH test

	Cases	Controls
<2 LOF		
2 LOF		

CHD test for tagging SNPs

Cases

	aa	Aa	AA
bb	b	b	bR
Bb	b	bR	bR
BB	bR	bR	bR

Controls

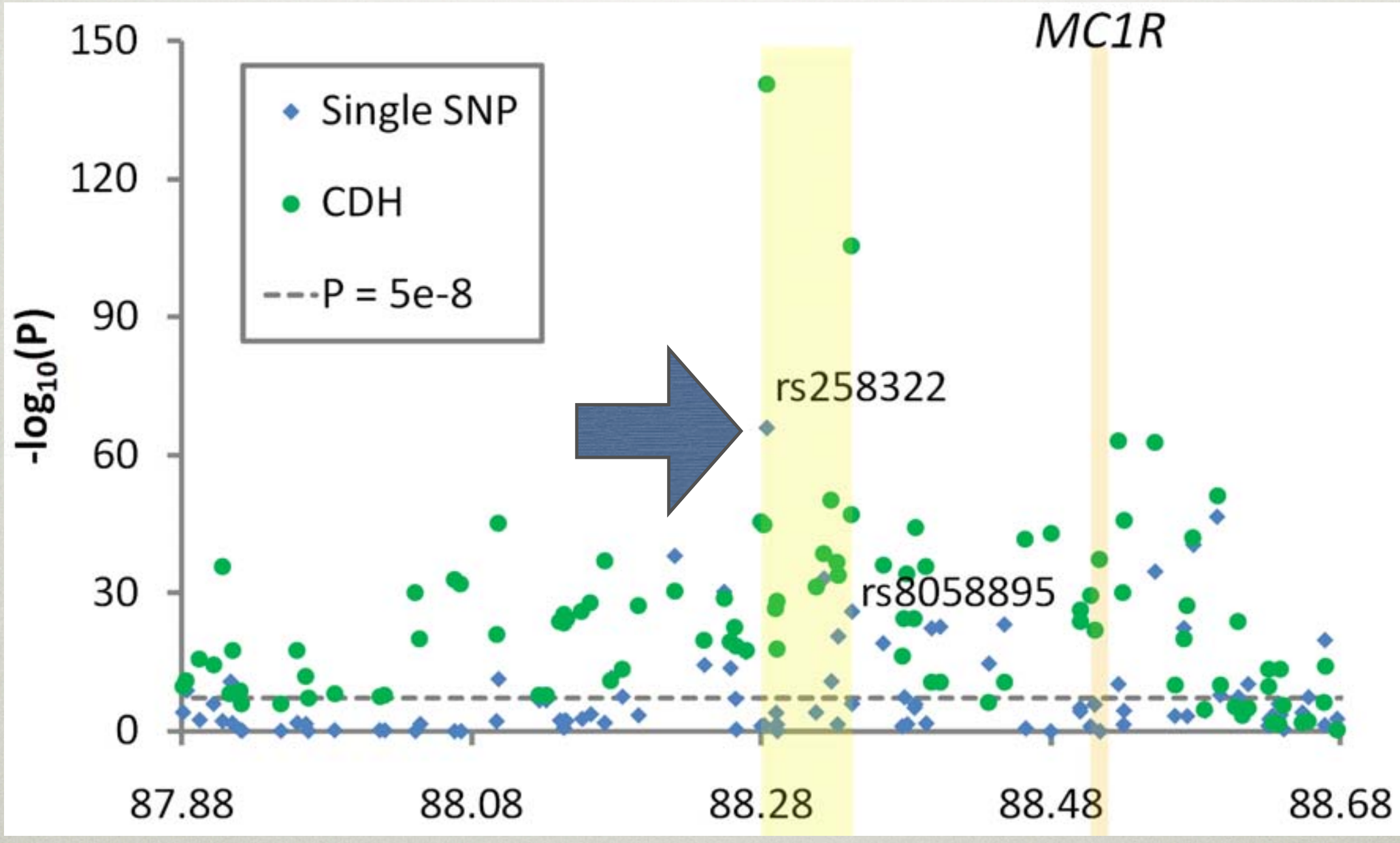
	aa	Aa	AA
bb	b	b	bR
Bb	b	bR	bR
BB	bR	bR	bR

	Cases	Controls
<2 LOF		
2 LOF		

Genome-wide CDH

1. Choose size of sliding window (e.g. 200 SNPs or 100 kb)
2. Start with SNP 1 on chromosome 1
3. Within the window, test all pairs of SNPs using the CDH test
4. If not last SNP on last chromosome, move sliding window one SNP forward and repeat the step (3)

Finding CH mutations in Red Hair



Liu et al., PLoS ONE, 2011

Conclusions

- Compound heterozygosity (CH) may be an important player in recessive traits
- The role of CH is likely to be under-estimated because until recent we did not have tools (sequencing, exome chip) and data (large cohorts) to systematically evaluate its effects