“Simple Mendelian inheritance” in humans

The beginnings of complications

Well, you may think the world's black and white

And you're dirty or you're clean

You better watch out you don't slip

Through them spaces in between

Bruce Springsteen
“Cross My Heart”

Important distinction

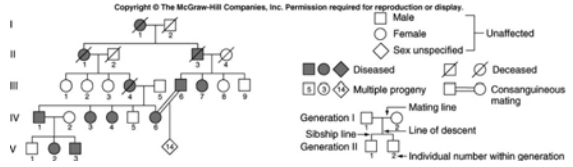
1. “Monogenic disorders” – human diseases whose etiology can in some more or less linear fashion be traced to a single locus genetic lesion.
2. Diseases with a “genetic component” or a “genetic predisposition” – disorders that mankind is known to be genetically polymorphic for (in terms of susceptibility) at multiple loci.
3. All other disease (that may or may not be transcription based).

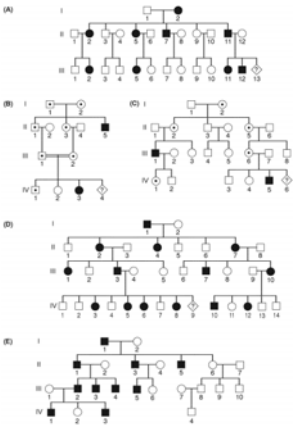
A further distinction

1. Phenomena affecting ploidy (e.g., aneuploidies such as Down, Edwards, Turner, Klinefelter).
2. Phenomena affecting chromosome structure (e.g., translocations in leukemia).
3. Phenomena affecting single loci (genes or relatively small chromosomal segments).

Human “monogenic” disorders

1. Help the patients (diagnose, cure, alleviate symptoms) and prospective parents (genetic counseling).
2. Learn more about disease to learn about how the human genome works, and how genomes in general work.





(A) Autosomal dominant;
(B) autosomal recessive
(C) X-linked recessive
(D) X-linked dominant
(E) Y-linked.

The Incidence of Alkaptonuria: A Study in Chemical Individuality 9

the opposite character. When a recessive gamete meets one of the dominant type the resulting organism (the zygote) will usually exhibit the dominant character, whereas when two recessive gametes meet the recessive character will necessarily be manifested in the zygote. In the case of a rare recessive characteristic we may easily imagine that many generations may pass before the union of two recessive gametes takes place. The application of this to the case in question is further pointed out by Bateson, who, commenting upon the above observations on the incidence of alkaptonuria, writes as follows:[17] "Now there may be other accounts possible, but we note that the mating of first cousins gives exactly the conditions most likely to enable a rare, and usually recessive, character to show itself. If the bearers of such a gamete mate with individuals not bearing it the character will hardly ever be seen; but first cousins will frequently be the bearers of similar gametes, which may in such unions meet each other and thus lead to the manifestation of the peculiar recessive characters in the zygote." Such an explanation removes the question altogether out of the range of prejudice, for, if it be the true account of the matter, it is not the mating of first cousins in general but of those

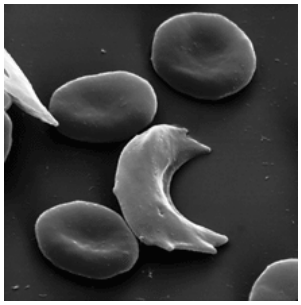
Garrod (1902) *Lancet* **2:** 116.

Sickle-cell anemia – a brief history

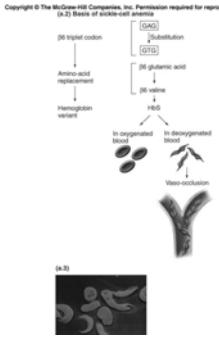
"In the western literature, the first description of sickle cell disease was by a Chicago physician, James B. Herrick, who noted in **1910** that a patient of his from the West Indies had an anemia characterized by unusual red cells that were sickle shaped."

By 1923, it was realized the condition is hereditary.

In 1949, Neel realized that patients with SCA are homozygous, and heterozygous carriers have a much milder condition (sickle cell trait).



Sickle cell anemia



NIH:

"Sickle cell anemia is the most common inherited blood disorder in the United States, affecting about 72,000 Americans or 1 in 500 African Americans. SCA is characterized by episodes of pain, chronic hemolytic anemia and severe infections, usually beginning in early childhood."

Pleiotropy

TABLE 1. CLINICAL FEATURES OF SICKLE CELL DISEASE.

TYPE OF COMPLICATION	FEATURES
Vaso-occlusive complications	
Painful episodes	In more than 70 percent of patients; very frequent in some, rare in others
Stroke	In about 10 percent of patients in childhood; "silent" central nervous system damage with cognitive impairment in 5 to 9 times as many patients
Acute chest syndrome	In 40 percent of all patients; more common in children; more severe in adults
Priapism	In 10 to 40 percent of men; severe cases cause erectile dysfunction
Liver disease	In <2 percent of patients; many causes (e.g., iron overload, hepatitis B or C)
Splenic sequestration	In children <6 yr old; often preceded by infection
Spontaneous abortion	In about 6 percent of pregnant women with sickle cell anemia; much less frequent in sickle cell–hemoglobin C disease
Leg ulcers	In about 20 percent of adults with sickle cell anemia; rare in sickle cell–hemoglobin C disease
Osteonecrosis	In 10 to 50 percent of adults with sickle cell anemia and sickle cell–hemoglobin C disease
Proliferative retinopathy	Rare in sickle cell anemia; in 50 percent of adults with sickle cell–hemoglobin C disease
Renal insufficiency	In 5 to 20 percent of adults; severe anemia often present
Complications of hemolysis	
Anemia	Hematocrit values of 15 to 30 percent in sickle cell anemia; higher values in sickle cell–hemoglobin C disease
Cholelithiasis	Present in most adults; often asymptomatic
Acute aplastic episodes	Due to parvovirus B19 infection; appears with rapidly occurring, severe anemia
Infectious complications	
Streptococcus pneumoniae sepsis	In 10 percent of children <5 yr old with sickle cell anemia
Osteomyelitis	Due to salmonella and *Staphylococcus aureus*
Escherichia coli sepsis	In adults, initiated by urinary tract infection

Steinberg M. N Engl J Med 1999;340:1021-1030

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Linus Pauling, 1949: HbS has different charge!!

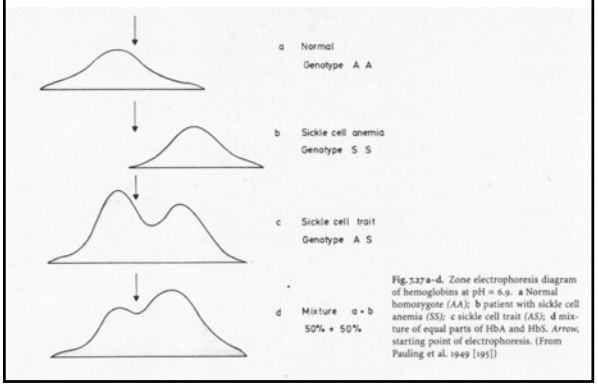

Fig. 7.17 a–d. Zone electrophoresis diagram of hemoglobins at pH = 6.9. a Normal homozygote (*AA*); b patient with sickle cell anemia (*SS*); c sickle cell trait (*AS*); d mixture of equal parts of HbA and HbS. Arrow, starting point of electrophoresis. (From Pauling et al. 1949 [195])

V. Ingram, *Nature* 1956

"On [the existing] evidence alone, it is not possible to decide whether the difference between the proteins, which is in any event small, lies in the amino-acid sequences of the polypeptide chains, or whether it lies in the folding of these chains leading to the masking of some amino-acid side chains."

V. Ingram (1956) *Nature* **178:** 792.

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The third most-famous experiment in the history of molecular biology

- Digest Hb A and Hb S with trypsin (protease – cuts hemoglobin into ~30 peptides).
- Separate resulting fragments by electrophoresis, and then by chromatography.
- Trace the peptide map.

V. Ingram (1956)
Nature **178:** 792.

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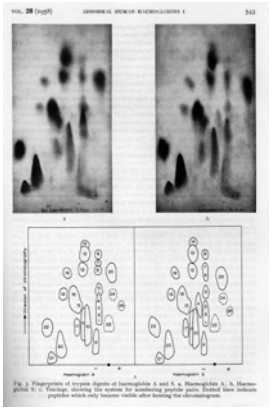

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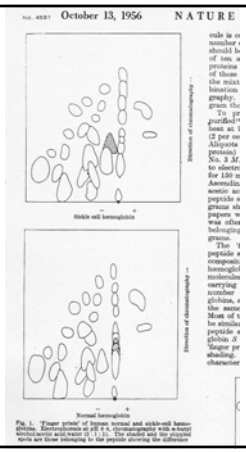

V. Ingram (1956)
Nature **178:** 792.

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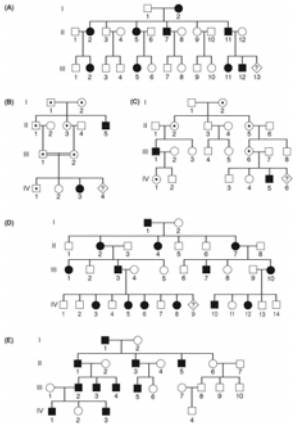
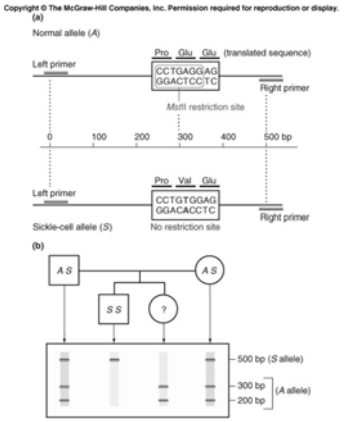
Correct

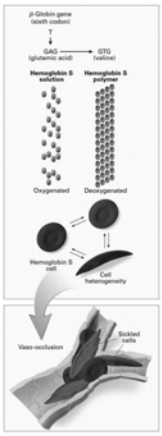
"One can now answer at least partly the question put earlier, and say there there is a difference in the amino-acid sequence in one small part of one of the polypeptide chains. This is particularly interesting in view of the genetic evidence that the formation of hemoglobin S is due to a mutation in a single gene."

V. Ingram (1956) *Nature* **178:** 792.

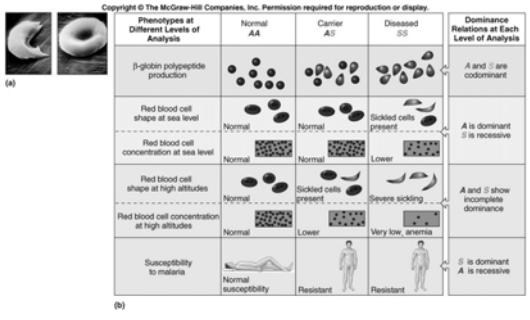




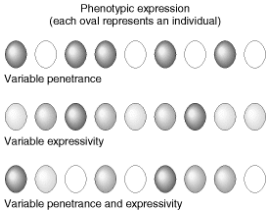
RFLP!!!



Incomplete dominance



Penetrance and expressivity



"The terms *penetrance* and *expressivity* quantify the modification of the influence on phenotype of a particular genotype by varying environment and genetic background; they measure respectively the percentage of cases in which a particular phenotype is observed when the specific allele of a gene of interest is present and the extent of that phenotype."

Variable expressivity

The importance of genetic background

"**Treatment Directed at the Relief of Symptoms** – Painful Episodes"

"In a given year, about 60 percent of patients with sickle cell anemia will have an episode of severe pain. A small minority of patients have severe pain almost constantly. These differences are one manifestation of the heterogeneity of this disease, which complicates the choice of treatment. Episodes of pain are sometimes triggered by infection, extreme temperatures, or physical or emotional stress, but more often they are unprovoked and begin with little warning."

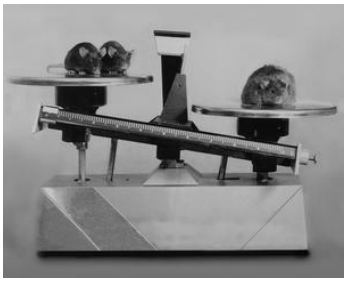
Steinberg M. N Engl J Med 1999;340:1021-1030

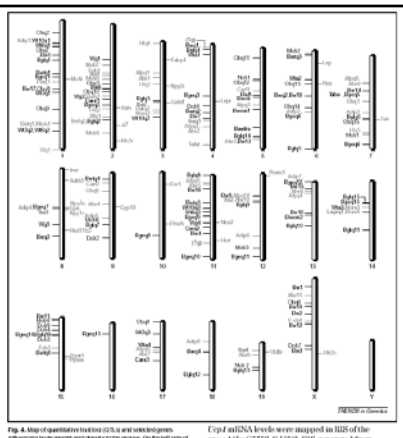
Calling Michael Crichton "Gene for …"?!

"Patients who are homozygous for the sickle hemoglobin mutation can present with remarkably different clinical courses, varying from death in childhood, to recurrent painful vasoocclusive crises and multiple organ damage in adults, to being relatively well even until old age. Increasing numbers of genetic loci have now been identified that can modulate sickle cell disease phenotype, from nucleotide motifs within the beta-globin gene cluster, to genes located on different chromosomes. With recent success of the human genome project, it is anticipated that many more genetic modifiers of sickle cell disease will be discovered that can lead to the development of more effective therapeutic approaches. The multigenic origin of the variable phenotype in sickle cell disease will serve as a paradigm for the study of variation in phenotypes of all single gene disorders in man."

Curr Opin Pediatr. 2001 Feb;13(1):22-7.

The *ob* mouse

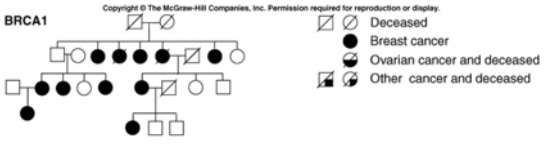




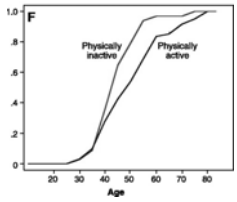
Variable penetrance

The importance of the environment and genetic background

Hereditary breast cancer caused by mutations in BRCA1 is incompletely penetrant



Risk of breast cancer and physical exercise in BRCA1/2 mutation carriers: an example of how the norm of reaction illuminates the modification of a "genetic tendency" by environment



"Physical exercise and lack of obesity in adolescence were associated with significantly delayed breast cancer onset."

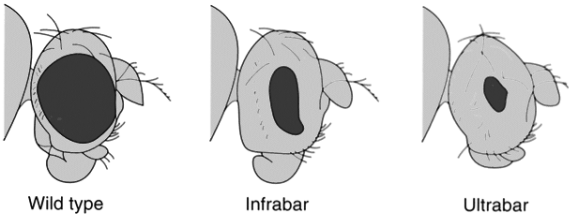
M.-C. King et al. *Science* 2003

Norm of reaction

A plot of carefully measured phenotype in large pool of genetically identical individuals grown under a range of environments.

D. Rio (UCB)

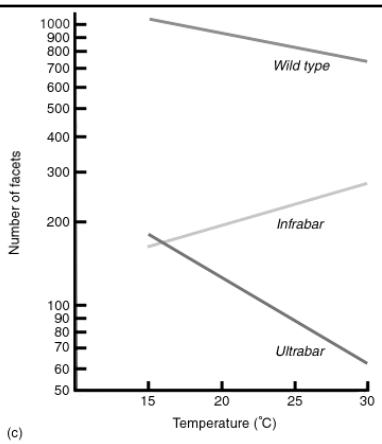
Three mutants that affect facet



(b)

Norm of reaction of different genotypes of the *bar* locus to temperature.Note, in general, that wild-type flies have a "tendency" to have more facets than the two mutants. WT flies, however, have less facets as the temperature increases, so one cannot claim that the WT genotype predisposes to more facets! Further, ultrabar "tends" to have less facets than infrabar, except at 15°, where it has slightly more facets.

This means that the genetic "predisposition" of ultrabar cannot be stated in one sentence.

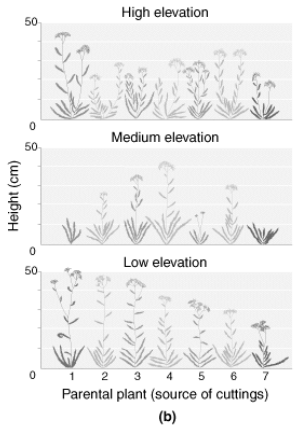


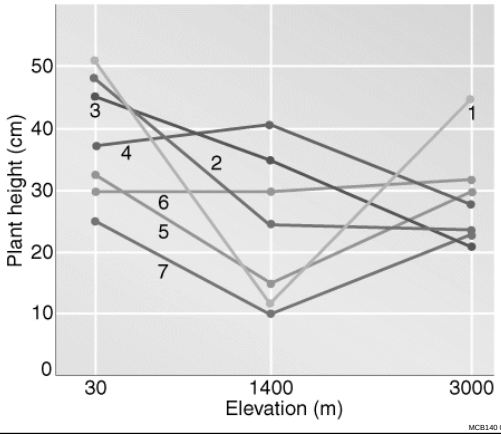
(c)

Achillea millefollium (yarrow)

Take 7 yarrow plants, grow cuttings from each one at different elevations.

Measure each "child" at each elevation.





Multiple allelism

The meaning of the term multiple allelomorphs may be illustrated by the following example:

1. If a white-eyed male of Drosophila is mated to a red-eyed female, the F_2 ratio of 3 reds to 1 white is explained by Mendel's law, on the basis that the factor for red is the allelomorph of the factor for white.

2. If an eosin-eyed male is mated to a red-eyed female, the F_2 ratio of 3 reds to 1 eosin is also explained if eosin and red are allelomorphs.

3. If the same white-eyed male is bred to an eosin-eyed female, the F_2 ratio of 3 eosins to 1 white is again explained by making eosin and white allelomorphs.

There are here three factors, any two of which may meet, and whenever they do, they behave as allelomorphs. They form a system of triple allelomorphs.

On the chromosome hypothesis the explanation of this relation is apparent. A mutant factor is located at a definite point in a particular chromosome; its *normal allelomorph is supposed to occupy* a corresponding position (locus) in the homologous chromosome. If another mutation occurs at the same place,

155

156 MULTIPLE ALLELOMORPHS

the new factor must act as an allelomorph to the first mutant; as well as to the "parent" normal allelomorph.

FIG. 50.—Himalayan, black and white rabbits. The factor that stands for each is allelomorphic to the others.

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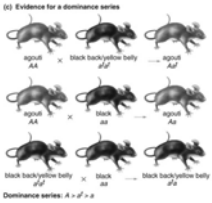
(a) *Mus musculus* (house mouse) coat colors

(b) Alleles of the *agouti* gene

Genotype	Phenotype
$A-$	agouti
$a^{y}a^{y}$	black/yellow
aa	black

(c) Evidence for a dominance series



Dominance series: $A > a^{y} > a$

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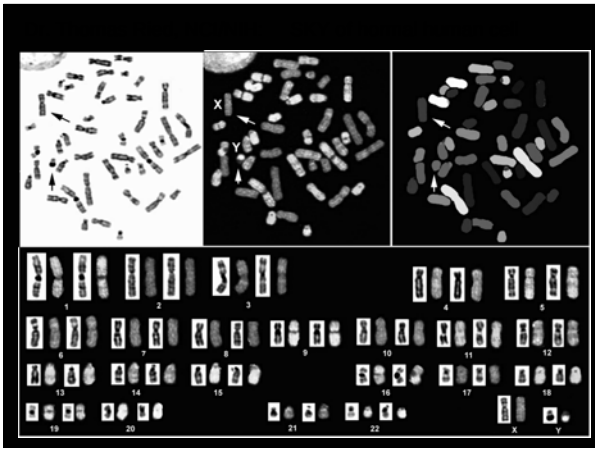

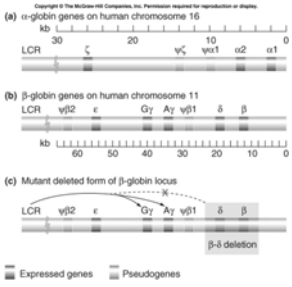

Thalassemia (from the Greek word for "the Mediterranean sea") – a hemoglobinopathy

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(a.1) Major types of structural variants causing hemolytic anemias

Name	Molecular basis of mutation	Change in polypeptide	Pathophysiological effect of mutation	Inheritance
HbS	Single nucleotide substitution	β 6 Glu ↓ Val	Deoxygenated HbS polymerizes → sickle cells → vascular occlusion and hemolysis	Autosomal Recessive
HbC	Single nucleotide substitution	β 6 Glu ↓ Lys	Oxygenated HbC tends to crystallize → less deformable cells → mild hemolysis; the disease in HbS:HbC compounds is like mild sickle-cell anemia	Autosomal Recessive
Hb Hammer-smith	Single nucleotide substitution	β 42 Phe ↓ Ser	An unstable Hb → Hb precipitation → hemolysis; also low O_2 affinity	Autosomal Dominant

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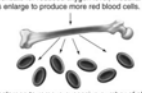
(b.2) A β-thalassemia patient makes only α globin, not β globin.

Four α subunits combine to make abnormal hemoglobin.

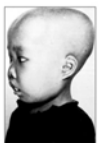
Abnormal hemoglobin molecules clump together, altering shape of red blood cells. Abnormal cells carry reduced amounts of oxygen.

To compensate for reduced oxygen level, medullary cavities of bones enlarge to produce more red blood cells.



Spleen enlarges to remove excessive number of abnormal red blood cells.

Too few red blood cells in circulation result in anemia.



(b.3)

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Table 17.2. The main β-thalassemia mutations in different countries

Population	Mutation	MIM no.*	Frequency (%)	Clinical effect
Sardinia	Codon 39 (C>T)	.0312	95.7	β^0
	Codon 6 (delA)	.0327	2.1	β^0
	Codon 76 (del C)	.0330	0.7	β^0
	Intron 1–110 (G>A)	.0364	0.5	β^+
	Intron 2–745 (C>G)	.0367	0.4	β^+
Greece	Intron 1–110 (G>A)	.0364	43.7	β^+
	Codon 39 (C>T)	.0312	17.4	β^0
	Intron 1-1 (G>A)	.0346	13.6	β^0
	Intron 1–6 (T>C)	.0360	7.4	β^+
	Intron 2–745 (C>G)	.0367	7.1	β^+
China	Codon 41/42 (delTCTT)	.0326	38.6	β^0
	Intron 2–654 (C>T)	.0368	15.7	β^0
	Codon 71/72 (insA)	.0328	12.4	β^0
	-28 (A>G)	.0381	11.6	β^+
	Codon 17 (A>T)	.0311	10.5	β^0
Pakistan	Codon 8/9 (insG)	.0325	28.9	β^0
	Intron 1–5 (G>C)	.0357	26.4	β^+
	619-bp deletion	-	23.3	β^+
	Intron 1-1 (G>T)	.0347	8.2	β^0
	Codon 41/42 (delTCTT)	.0326	7.9	β^0
US black African	-29 (A>G)	.0379	60.3	β^+
	-88 (C>T)	.0372	21.4	β^+
	Codon 24 (T>A)	.0369	-7.9	β^+
	Codon 6 (delA)	.0327	0.8	β^0

Next time

Simple Mendelian inheritance – the exception, not the rule – and what one can learn from that.