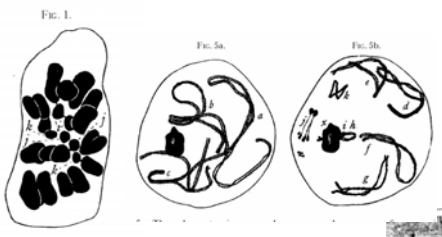
Walter Sutton, 1902-03



What was clear about meiosis

1. That it involves two consecutive cell divisions, not one.
2. That the number of chromosomes appears to be reduced as a result of that fact.

Sutton's conclusions

1. Chromosomes have individuality.
2. Chromosomes occur in pairs, with members of each pair contributed by each parent.
3. The paired chromosomes separate from each other during meiosis, and the distribution of the paternal and maternal chromosomes in each homologous pair is independent of each other.

I may finally call attention to the probability that the association of paternal and maternal chromosomes in pairs and their subsequent separation during the reducing division as indicated above may constitute the physical basis of the Mendelian law of heredity. To this subject I hope soon to return in another place.

The most important fact in classical genetics

(both Mendel's first and second law are explained by the behavior of chromosomes during meiosis)

On chromosomes, chromatids, sisters, nonsisters, and homologs

Fact 1

The human genome contains ~35,000 genes.

Each gene is – from a physical perspective – a stretch of DNA. The sequence of base pairs in that DNA encodes the amino acid sequence of a protein (note: this simplified narrative disregards noncoding DNA elements of a gene, such as regulatory DNA stretches, untranslated 5' and 3' UTRs, introns, and polyadenylation signals; furthermore, most of the RNA produced by the human genome is noncoding, but you will learn that in graduate school, if you go there).

Furthermore

In principle, it is imaginable that each gene could be on a separate piece of DNA, so the nucleus of a human cell would contain 35,000 separate pieces of DNA.

In actual fact, in a human being, the genome is distributed onto 23 pieces of DNA (well, 23 pieces plus one additional somewhat important gene on a separate small piece of DNA, but more on that later).

What you call those pieces depends on who you are.

1 genome = 35,000 genes = 23 pieces of DNA

For now, let us call EACH of those pieces a chromosome. More later on that "for now" bit.

We can now ask: those 35,000 genes mentioned earlier – how are they distributed between those 23 chromosomes? In alphabetical order, perhaps? Or, which would be cool – by pathway (in order of appearance in Stryer)? For example, chr. 1 would all the genes for glycolysis, chr. 2 – for the Krebs cycle, and chr. 3 – for oxidative phosphorylation.

Or – why not? – maybe different people have a different distribution of genes on their chromosomes? In other words, maybe my chr. 1 has different genes than your chr. 1?

Genetic unity of a species

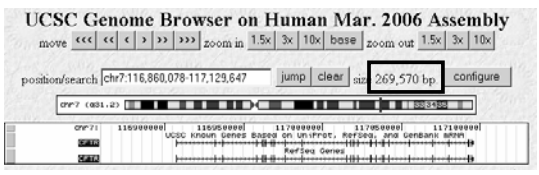
This issue has been studied experimentally, and it was found that in a given species, the distribution of genes between chromosomes, and – within each chromosome – their order are both invariant.

In other words, if we examine chr. 1 (by the way, they are numbered according to size, eXcept for the X), then in every human being, that chromosome will contain the exact same genes (note – I did not say the exact same allelic form of the genes – simply the same genes).

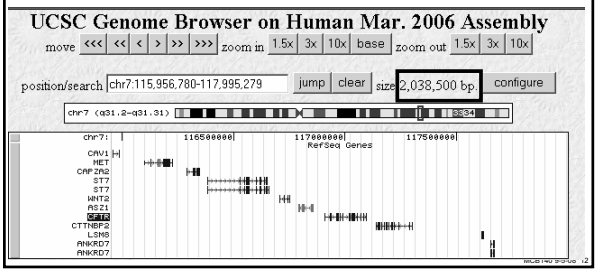
With a few interesting exceptions, no meaningful relationship has been found between the function of a gene product and its placement within the genome. For example, the X chromosome contains the second most important male gene (the receptor for testosterone, known as the androgen receptor), the genes for two factors involved in blood clotting (factor VIII and factor IX), and the genes for receptors required for color vision.

A famous example

The long arm of chr. 7 – in all humans – contains a gene called CFTR (cystic fibrosis transmembrane conductance receptor) – it encodes a transmembrane channel required for cation transport. Note that the location of this gene on this specific position of this specific chromosome, and the distribution of its coding sequence between exons and introns are invarant between humans.



With rare exceptions, the nature, relative orientation, and distance from each other of genes on a given stretch of a given chromosome is the same between different human beings. For example, in the overwhelming majority of humans, some 700,000 bp (700 kb; 0.7 Mb) upstream of the CFTR gene lies a gene called MET (this is an important fact in the history of genetics, and will be dealt with shortly).



"What are you doing tonight?"

Humans happen to be obligate sexual outcrossers – propagation of our species can only occur through the fusion of two gametes, each with its own genome.

That has an important consequence for the relationship between the life cycle of a human and the chromosomal composition of its genome.

Ploidy

A conventional adult cell of a human contains two complete sets of instructions for the construction of a human being.

One set of instructions was received from Mom, and the other – from Dad.

This means that a typical cell in a living human being contains not 23, but 46 pieces of DNA – two chromosomes #1 (one from Mom, one from Dad), two chromosomes #2 (you get the point).

Humans are diploid – their adult cells contain two complete copies of the human genome.

Homolog

By tradition, the two copies of chromosome 1 that you inherited from your two parents are known as:

a homologous pair (or a pair of homologs)

For example, your chromosome #7 (which is a piece of DNA with the MET and CFTR genes on it) that you received from Mom has – inside your nucleus – a homolog = a piece of DNA that you inherited from Dad, that is approximately the same size, and has the MET and CFTR genes on it, and a large number of other genes that humans tend to have on chr. 7.

Alleles

I mentioned that the position of CFTR on that specific spot of chr. 7 is invariant between humans. It is the case, however, that – when one compares the genomes of two different human beings – one sees a difference, on average once every 1,000 bp (typically, a single base pair change, known as a SNP – "snip" – a single nucleotide polymorphism). There are two very famous such polymophisms in the human genome, and you are **required** to know both. One is on chr. 7 of the CFTR gene – it is a deletion of a triplet, "TTT," that encodes phenylalanine #508 in the primary amino acid sequence of that protein. This mutation, known as "Δ508," causes cystic fibrosis in homozygous form. The other is on chr. 15, in the β-globin gene – it is a point mutation (A->T) that changes a glutamate to a valine – in homozygous form, this mutation causes sickle cell anemia.

The outbred human (especially the outbred American)

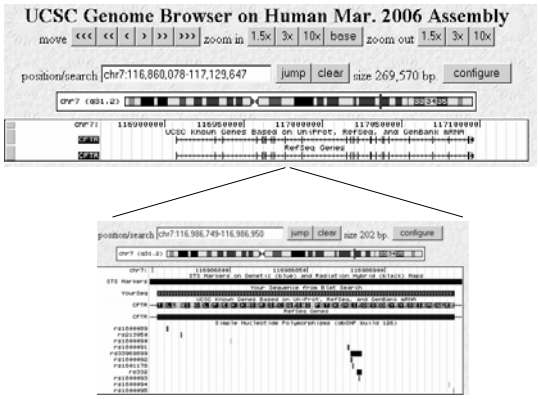
As you will learn later in the class, humanity – especially in the US – exhibits a very high degree of admixture – the union of genomes with different ancestral histories.

From a genomic perspective, this means that if we take an average American, and compare the two alleles of any given gene that this person has, it is quite likely that this person will be heterozygous for a number of point mutations (in other words, the allelic form of a given gene this person inherited from Mom, and from Dad, are different).

Important consequence of that

Two homologous chromosomes – let's say, chr. 7 from Mom and from Dad – do NOT have the same DNA sequence.

They have the same genes (CFTR, Met, and others), but not the same allelic forms of those genes! For example, ca. 1 in 10,000 individual of Northern European origin is a carrier for the Δ508 CFTR mutation. This means that the two homologous chromosomes #7 in this person differ, in the following way (see next slide).



Chr. 7 ♀

K E N I I F G V S Y D E
AAAGAAAATATCATCTTTGGTGTTTCCTATGATGAA
TTTCTTTTATAGTAGAAACCACAAAGGATACTACTT

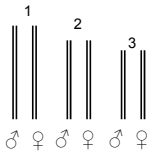
Chr. 7 ♂

K E N I I G V S Y D E
AAAGAAAATATCATCGGTGTTTCCTATGATGAA
TTTCTTTTATAGTAGCCACAAAGGATACTACTT

Inside a cell

And so – when we peek inside the nucleus of a human cell, we see 46 pieces of DNA – 23 pairs of homologous chromosomes.

If we remove all the proteins that coat them, and stretch them out, they will look like this (each object is a double helix of DNA) – note that only 3 pairs are shown here:

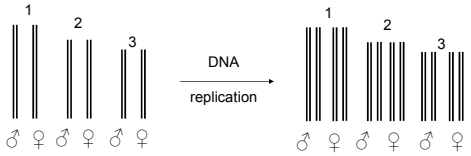


… and so on, 20 times more

Division

At certain times during human ontogeny, certain cells have to divide. This involves the duplication – precise copying – of all the DNA inside a human cell. Each chromosome – piece of DNA – in the cell is replicated, and a fairly accurate copy of it is made.

Hmmmm

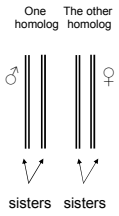


Inside a human cell that is about to divide, there are 92 pieces of DNA. Each is a normal human chromosome. There are four copies of chr. #1 – two identical copies of the one you got from Mom, and two identical copies of its homolog of the one you got from Dad.

Brace yourselves

This is where it gets bad, stops making sense, is illogical and generally bleh. I know, I know, but just live with it.

"Sister"??!!



1

- The two identical copies of chr. 1 are called "sisters."
- In a premitotic human cell, therefore, there are **two** sister chromosomes #1 (the ones from Dad), and **two** sister chromosomes #1 (that are from Mom).
- Yes, four chromosomes #1.

If you think about it …

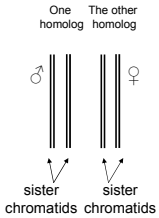
- The word "sister" in this context is, probably, the single worst one that geneticists could have chosen. We think of sisters as siblings – nonidentical but related. It would be overwhelmingly more appropriate to call the two chromosomes **in each homologous pair** "sisters."
- But nooooo. That would have been too easy.
- Once again: when a human chromosome (piece of DNA) is replicated, its **identical** copy is formally known as its "sister."

29 31 38

Bleh, part II

- To make life even worse, at that point, geneticists – both molecular and classical – and cell biologists start using a new word: "chromatid."
- Ahem. What, exactly, is a chromaTID? Is it different from a chromoSOME?
- Well, we know now it isn't. Back in the day, however, they didn't know that.
- In other words, this term is an atavism (like the ear lobe, or the appendix) – it's a relic. It will never go away, so learn it. Explanation shortly.

Sister chromatids



1

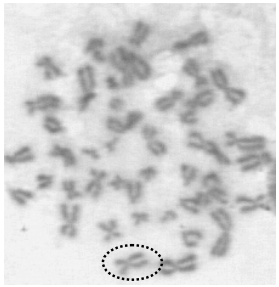
- The two **identical** copies of chr. 1 are actually called "sister chromatids." Each is a perfectly normal piece of DNA, a nice and proper human chromosome #1. But no, at that point, it is called a "chroma**tid**."
- In a premitotic human cell, therefore, there are two sister chromatids #1 (the ones from Dad), and two sister chromatids #1 (that are from Mom).

What is going on?!!

- This ghastly nomenclature is an artefact of the history of development of science.
- The structure of DNA was solved in 1953. The first genes were sequenced in the 1970s, and at that time, genes were directly localized – by physical means – onto chromosomes.
- The first chromosomes, however, were observed almost a century prior to that! Walther Flemming discovered and named mitosis in 1879, and Heinrich Waldeyer stained and named the threads he saw in the nucleus "chromosomes" in 1888.

The X files

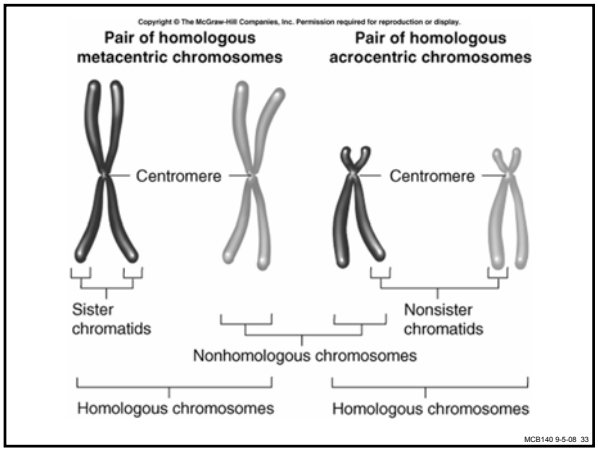
- Cytologists **saw** an X shaped object.
- They called it a “chromosome.”
- Within each chromosome, they say two threads. They called each one a “chromatid.”
- We now know that there are two separate pieces of DNA in each X shaped object. Genetically speaking, each one is a proper, normal chromosome (a piece of DNA).
- This means that each “chromatid” (cytologically), two of which supposedly form a “chromosome” (cytologically), is, in fact, TWO chromosomes (genetically) – two pieces of DNA!

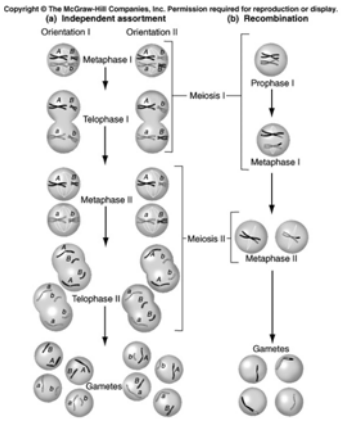


Nonsister homolog

In other words, the 4 copies of chromosome #1 just before mitosis in a human cell have the following frightening nomenclature attached to them:

1. Two identical DNA molecules are called “sister chromatids.” Ew.
2. The ones from Dad have a “homolog” – the ones from Mom.
3. Furthermore, there is this lovely term: “nonsister homolog.” This brings “appalling” to new shades of meaning, but is ubiquitously used. It simply means, the other homologous chromosome.

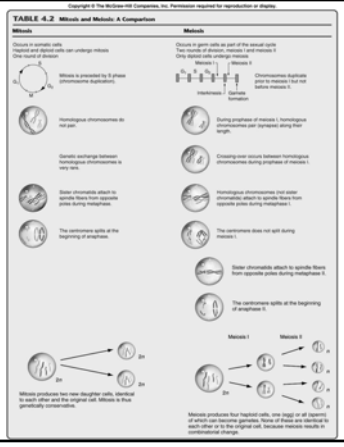


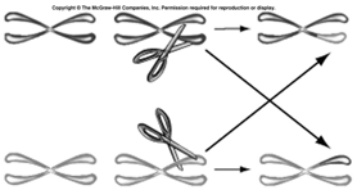


Mitosis vs. meiosis

46 chromosomes (23 pairs of homologs)
↓
DNA replication
↓
92 pieces of DNA (split into groups of 4 – in each group, 2 pairs of sister chromatids)
↓
Division – sister chromatid separate – within each pair, each sister goes to a separate cell.

46 chromosomes (23 pairs of homologs)
↓
DNA replication
↓
92 pieces of DNA (split into groups of 4 – in each group, 2 pairs of sister chromatids)
↓
Division – sister chromatids STAY TOGETHER, and each pair of sisters goes into a separate cell.





"Crossing-over involves cutting, at the same position, one chromatid from each chromatid pair."

What is being omitted for lack of time

1. The rediscovery of Mendel's laws by Correns, Tschermak, and de Vries.
2. The finding – by Cuenot and by Castle – that Mendel's laws also apply to mammals, such as mice and guinea pigs.

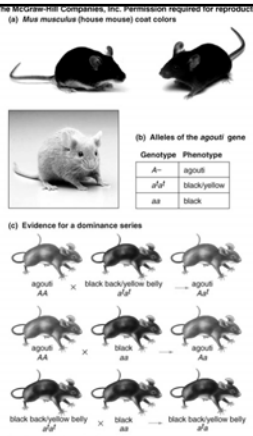


Fig. 3.7

William Bateson

"… he privately subsidized his small book, *Mendel's Principles of Heredity: A Defence* and he sent copies to all of the leading students of heredity to make sure that Mendel would not suffer another 35 years of neglect." Carlson *Mendel's Legacy*

results into Mendelian terms. Such an exercise would show that the change which must now come over the conceptions of biology can only be compared with that which in the study of physical science followed the revelations of modern chemistry.

The outcome of such a revision of current conceptions it is impossible to foresee, but we propose in the present paper to consider some of the more important questions which are immediately raised.

To denote the new conceptions some new terms are needed. Several have already been suggested by Correns, but in practice we have not found his terminology altogether convenient, or that it meets the new requirements. Correns proposes the terms "heterodynamous" and "homodynamous" to express that an organism is dominant or not dominant in respect of a given character. There are unfortunately objections to the use of these terms, though in some respects they are very suitable. First, they are in use by Weismann and his followers in quite different senses, as Correns states. Secondly, it is not clear whether they are to be applied to the variety, the individual, or the character. Besides these objections, it is fairly clear that dominance is a phenomenon presenting various degrees of intensity; and while the single phenomenon of dominance is well expressed by that word itself, other conditions probably consist of various phenomena which are not conveniently denoted by one word.

Correns' terms "homoögonous" and "schizogonous" cannot as yet be used with precision to mean more than breeding "true" and not breeding "true," and, for reasons given later, the metaphor of splitting may be incorrect.

Bateson 1902

In the introduction (R. p.12)[1] we attempted to distinguish precisely the essential fact discovered by Mendel, and to separate it from other subordinate appearances. We may now briefly recall and amplify that reasoning, showing how we propose to denote the several phenomena.

By crossing two forms exhibiting antagonistic characters, cross-breds were produced. The generative cells of these cross-breds were shown to be of two kinds, each being pure in respect of *one* of the parental characters. This purity of the germ cells, and their inability to transmit both of the antagonistic characters, is the central fact proved by Mendel's work. We thus reach the conception of unitcharacters existing in antagonistic pairs. Such characters we propose to call *allelomorphs*,[2] and the zygote formed by the union of a pair of opposite allelomorphic gametes we shall call a *heterozygote*. Similarly, the zygote formed by the union of gametes having similar allelomorphs, may be spoken of as a *homozygote*. Upon a wide survey, we now recognise that this first principle has an extensive application in nature. We cannot as yet determine the limits of its applicability, and it is possible that many characters may really be allelomorphic, which we now suppose to be "transmissible" in any degree or intensity. On the other hand, it is equally possible that characters found to be allelomorphic in some cases may prove to be non-allelomorphic in others.

αλληλος = "each other"

Bateson 1902

MCB140 9-5-08 43

Archibald Garrod (1902)

Higher frequency of children with alkaptonuria (urine turns dark on standing and alkalinization) from consanguineous marriages.

Why?

"There is no reason to suppose that mere consanguinity of parents can originate such a condition as alkaptonuria in their offspring, and we must rather seek an explanation in some peculiarity of the parents, which may remain latent for generations…"

http://www.esp.org/foundations/genetics/classical/ag-02.pdf

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Ah!

"It has recently been pointed out by Bateson that the law of heredity discovered by Mendel offers a reasonable account of such phenomena. …"

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

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.

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Two facts

1. The motions of chromosomes during meiosis explain both Mendel's first and second laws.
2. Mice and humans follow both of Mendel's laws.

How does one **formally** prove that chromosomes contain Mendel's "factors" – ie, the genes?

MCB140 9-5-08 47

Enter the fruit fly

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