

How to Conquer a Chromosome Abnormality—

How does a chromosome abnormality cause disease?



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The “Big Picture”

Special points of interest:

- * Genes → Proteins → You
- * Copy number variations
- * Finding key genes
- * Genotype/Phenotype

How does a chromosome abnormality cause disease? Not all genes cause a problem when they are present in too few or too many copies. In fact most genes do not cause a problem when there is a gene copy number abnormality. This is important because as more is learned about the role of the various genes, some of the infor-

mation about the chromosome 18 genes will impact us and other information will not. Here we present a framework for understanding these differences.

From a strictly “big picture” perspective of what is happening in someone with a chromosome abnormality, this

explanation will include just the central dogma of genetics. That is to say, genes are the instructions for proteins. Proteins have critical functions in biology that when working correctly result in a happy and healthy you. Therefore that path is from genes to proteins to you.

Gene Function

This diagram represents the normal genetic condition. There are two copies of a gene, shown in the first column. The two copies produce a certain amount of protein represented by the blue blobs in the center. This normal amount of protein results in a happy and healthy you!



For this discussion we assume that all the genes work normally to produce a normal protein. This means we are

ignoring a huge category of genetic conditions. We are concentrating on the consequences of copy number variations.

Inside this issue:

Gene Function continued	2
Human Chromosome 18	2
Genotype/Phenotype	2
What is a Phenotype?	3
Genotype/Phenotype Mapping	4
Rare Phenotypes	4

Here are three scenarios for possible consequences of three copies of a particular gene.

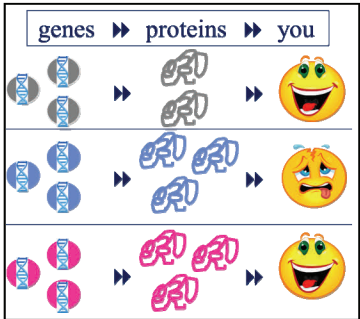
At the top, is the gray gene. When in 3 copies, this gene has some sort of dosage compensation mechanism, so that even though there are three copies the normal amount of protein is produced.

The blue gene has no dosage compensation mechanism so three

genes produce three proteins. This is 1.5 times the normal amount which has a bad affect on you.

The third possibility is the pink gene. Here three copies produce 1.5 the normal amount of protein, yet for whatever biological process that protein is involved in, it just does not matter. So you are happy and healthy.

Just because there are three copies of a gene does not automatically mean



there is a bad outcome. Some genes will have bad outcomes with there are three copies and some will not.

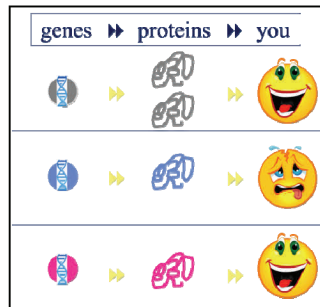
Gene Function continued

A similar set of scenarios can happen when there is one copy of a gene instead of the normal two copies.

The gray gene can be upregulated so that it produces the normal amount of protein, and you are happy and healthy.

The blue gene produced its normal protein but because there is only one gene, the total protein produced is 1/2

the normal amount needed for normal function, thereby causing disease.



The pink gene makes its normal protein, but because there is one copy of the gene instead of two, the overall amount of protein is 1/2 of normal.

For the processes that this protein is involved in to happen normally, 1/2 the

normal amount is sufficient and you are happy and healthy.

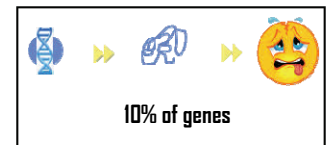
Here again we have three scenarios, some with normal outcomes and some with bad outcomes. We cannot assume that because there is one copy of a gene that disease will be the outcome.

Our central challenge is to discover which genes adversely affect you when there is an abnormal copy number.

“Our challenge is to discover which genes have adverse affects when existing in abnormal copy numbers.”

What are the chances of any of these possible outcomes even occurring? Much less is known about the consequences of three copies of a gene than about a single copy of a gene.

But data from multiple sources leads us to expect that only about 10% of the genes will have a bad outcome when they exist in one copy instead of two.



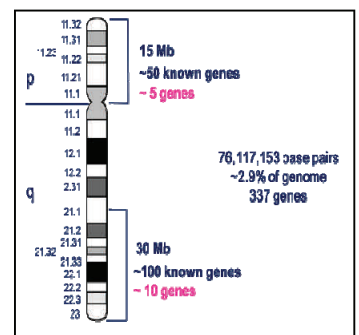
Human Chromosome 18

What this means is, for someone with a deletion of the entire short arm (18p-) a region with only about 50 genes, there will probably be only about five genes that have major consequences.

For someone with the largest possible distal 18q deletion, a region including

about 100 genes, there are probably only about 10 key genes having deleterious consequences.

Wow! This may not be such a big problem to solve after all! First we need to determine which genes are those key genes.



Definitions—Genotype and Phenotype

To understand how we determine key genes, you need some new terminology.

The genotype is a person's genetic makeup—the actual size and location of a region of chromosome 18 that is either in one, three, or four copies instead of the normal two copies.

The phenotype are the manifestations of

the genotype; such as, short, a heart malformation, hearing loss, ??

In most chromosome 18 conditions, we don't know which genes cause which phenotypes. The linking of these two is one of the goals of our research. This process is called genotype phenotype correlations.

Genotype

—Genetic Makeup

Phenotype

—A physical characteristic of an individual (has been expanded to include biochemical, radiological or other characteristic which lends itself to some form of objective measurement, e.g. height, eye color, bone deformity of a growth plate)

What is a phenotype?

It is important to understand what a phenotype is. Technically, a phenotype is any expression or outward manifestation of the genotype. This might be a physical finding like blue eyes or a chemical finding like low blood sugar. The more precise a phenotype is, the more likely it is to be helpful in understanding the relationship between a specific gene and its manifestation. For example, short is clearly a phenotype. However, it is not a very precise phenotype since there are many different ways that one can end up being short. A short person may have growth hormone deficiency, a bone growth disorder, a nutritional deficiency or even growth hormone resistance. In other words, there are many different ways to get to "short." The genes involved in growth hormone deficiency are likely to be quite different from the genes involved in bone growth and those genes are likely to be quite different from those involved in malnutrition secondary to gut

abnormalities that interfere with nutrient uptake.

Growth hormone deficiency is a more precise phenotype since we now have honed in on a single system. However, there are many components of the system that make growth hormone and release growth hormone and a defect in any component can lead to growth hormone deficiency. For example, there can be a tumor that destroys the growth hormone producing cells. There can be a congenital defect that causes the pituitary to not form properly. Also, there can be a defective gene that makes it impossible for the growth hormone producing cells to produce a normal growth hormone molecule.

One of the common ways we test for growth hormone deficiency is to use a medication called clonidine. The

mechanism by which clonidine works is clearly understood. Thus if the child provides a normal response to clonidine, we are quite confident that the mechanisms that respond to clonidine are intact. In much the same way when you press the start button on your computer and it starts, you are quite confident that the electrical systems in the computer are intact. Of course, if the computer does not start one still has to check all of the components of this more limited system.

We are constantly trying to get the most precise phenotype possible, because the more precise that it can be, the more likely that the phenotype will relate to a very limited set of genes.

"The more precise the phenotype, the more likely it will relate to a very limited set of genes."

Samples of Phenotypes

- **Short**
 - there are lots of ways to get to "short"
 - *hormonal, bone disorder, nutritional status, general health, growth hormone resistance
- **GH deficient**
 - there are many ways to get to GH deficiency
 - *brain structural abnormality, hypothalamic dysregulation, brain tumor
- **Response to clonidine stimulation**

Genotype/Phenotype Mapping

Let's explore how we correlate genotype with phenotype to determine the location of key genes on chromosome 18. The diagram shows 18q deletions but the approach is the same for any chromosome 18 abnormality.

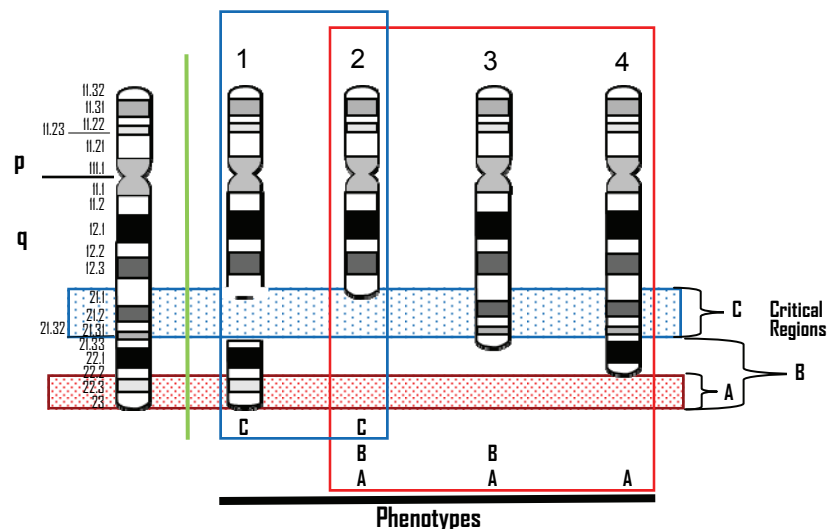
To the left of the green line is a diagram of chromosome 18. To the right are the pictorial genotypes of 4 individuals, each with a different 18q deletion. Under each is a list of their phenotypes—A, B and C.

To determine the location of the gene for phenotype A, we look at only those individuals with phenotype A, in the red box. Their common region of deletion is at the end of chromosome 18, in red dotted box. We call that region the critical region for phenotype A.

To locate the critical region for phenotype C, we use the same approach. We look at only those individuals with phenotype C, in the blue box. We

locate their common region of deletion on chromosome 18 and call this the critical region for phenotype C, in blue dotted box.

In order to identify small critical regions with a small number of genes, we need lots of study participants with 18q deletions and extensive medical records and research data to determine precise phenotypes.



“Chromosome 18 only contains about 3% of all genes, so many genetic issues are unrelated to chromosome 18 copy number changes.”

Rare Phenotypes

Genotype/phenotype mapping may help identify the common phenotypes, but what about those phenotypes that only one or two people share? Can these be related to their chromosome 18 abnormality?

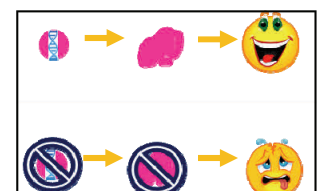
Yes, these rare phenotypes can also be the result of a chromosome abnormality. This is how we think it can happen for those individuals with chromosome deletions.

As explained earlier, many genes on chromosome 18 are expected to have no ill effect when there is one copy instead of

two. However, this means that the single remaining gene must be working perfectly. If the single remaining gene has a mutation so that it does not function then there is no functional gene and disease is like to result.

The chance that someone with a chromosome 18 deletion has a mutation within one of the remaining genes is very small. We estimate that the occurrence of rare phenotypes in only one or two percent of the individuals could be the result of this type of chromosome 18 related problem.

Remember that chromosome 18 is only one chromosome and contains only about 3% of all genes, so there can be genetic issues completely unrelated to a chromosome 18 copy number change.





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Our Motto

To provide individuals and families affected by chromosome 18 abnormalities with comprehensive medical and educational information with a focus on treatment options.

We are on the web!

<http://pediatrics.uthscsa.edu/centers/chromosome18/>

Information provided by The Chromosome 18 Clinical Research Center to:



<http://www.chromosome18.org/>

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