Counselling

Most genetic disorders have variable expressivity, and some have reduced penetrance. This makes it challenging to predict how any one individual might be affected in the future. Genetic counselling can help to explain these concepts and discuss what is known about a specific disorder.

In order to assess the expressivity and penetrance of a genetic disorder, medical professionals rely on detailed information published in medical journals and specific databases. This is one of the reasons why it is important to publish detailed information about children and adults with diagnosed genetic changes and for details to be made available (anonymously) on databases used by medical professionals. Sharing information with *Unique*, and other support groups, will also help to define and follow the difficulties that children and adults with rare chromosome and gene disorders face.

It is important to remember that often the most severely affected children and adults are offered genetic testing more readily than those with milder symptoms, so there can be an underrepresentation of those who are less severely affected. This is known as ascertainment bias and can affect how the severity of a genetic disorder is described. As more people are offered genetic testing, and more information is made available to the medical community, the spectrum of features and symptoms and range of severity for each disorder may become more clear.

An additional complication is that many individuals are given a genetic test result that includes a variant of uncertain significance (VUS). VUS are chromosomal or gene changes of uncertain significance with regards to health and development. If a parent (assumed to be unaffected) is found to pass on a VUS to a child, who is showing signs of being affected by a genetic disorder, it means further research is needed to understand if the genetic change could be causing any symptoms and if variable expressivity (and/or reduced penetrance) is involved.

For some situations, it may be difficult to distinguish between reduced penetrance and variable expressivity until more information is available.

Complete Penetrance

Everyone is affected

Reduced Penetrance

Some people are not affected

Complete Penetrance & Variable Expressivity

Everyone is affected but in different ways

Reduced Penetrance & Variable Expressivity

Some people are not affected, others are but in different ways

Inform Network Support

Rare Chromosome Disorder Support Group,
The Stables, Station Road West,
Oxted, Surrey. RH8 9EE. UK.
Tel +44(0)1883 723356
info@rarechromo.org
www.rarechromo.org

Join Unique for family links, information and support.
Unique is a charity without government funding, existing entirely on donations and grants. If you can, please make a donation via our website at www.rarechromo.org/donate Please help us to help you!

This information guide is not a substitute for personal medical advice. Families should consult a medically qualified clinician in all matters relating to genetic diagnosis, management and health. Information on genetic changes is a very fast-moving field and while the information in this guide is believed to be the best available at the time of publication, some facts may later change. Unique does its best to keep abreast of changing information and to review its published guides as needed. This booklet was written and compiled by Unique (AP) and reviewed by Dr Gregory Costain, Division of Clinical and Metabolic Genetics, The Hospital for Sick Children, Toronto, Canada.
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Unique
Understanding Chromosome & Gene Disorders

Variable Expressivity & Reduced Penetrance

Learning disability & developmental delay

rarechromo.org

What does expressivity mean?

In genetics, the word expressivity is used to describe the range and severity of features and symptoms that occur in different individuals with the same or similar genetic change.

What is variable expressivity?

For some genetic changes, it is thought that everybody with the same or similar change will have a specific clinical feature or symptom.

However, it is often the case that a spectrum of features and symptoms are identified in individuals with the same or similar genetic change. Also, while some individuals may be identified as mildly affected, others are moderately, severely or profoundly affected.

If the majority of individuals are identified as having similar features, in terms of type and severity, then expressivity may be described as low. In contrast, if there is a broad spectrum of features observed in different individuals, and there is a broad range of severity, then expressivity may be described as high.

How common is variable expressivity?

It's difficult to estimate how common variable expressivity is since there are so many different genetic disorders for which there is little information, but it is thought to be common for genetic changes, such as deletions and duplications, that are associated with learning disabilities and developmental delay. Variable expressivity in the more recently identified single gene disorders is currently more difficult to measure since so few families have been described but it is known to exist.

How does variable expressivity affect me or my child?

Variable expressivity means that individuals, including different family members with the same or similar genetic change, may be affected differently and to a varying degree. It is not possible to determine exactly how an individual will be affected based on their genetic diagnosis.

What does penetrance mean?

In genetics, the word penetrance is used to describe the proportion of individuals with a particular genetic change e.g. a duplication, deletion or gene variant, who exhibit any sign or symptom of that genetic disorder.

What is reduced penetrance?

For some genetic disorders, it is thought that everybody with the same or similar genetic change will be affected (have clinical symptoms). This is known as complete penetrance.

However, it is sometimes the case that, while some individuals are obviously affected by a specific genetic change, others with the same or similar genetic change do not display any obvious features or symptoms, this means the penetrance of that genetic change is reduced (or incomplete).

The penetrance of a genetic disorder is measured as a percentage. For example, if 90 individuals out of 100, with the same genetic change, show clinical symptoms and 10 individuals appear to be unaffected, the genetic change would be described as having 90% penetrance.

A high percentage penetrance means that features and symptoms will be observed in a large proportion of individuals with a specific genetic change. A low percentage penetrance means that symptoms are only observed in a few individuals with that specific genetic change so it's difficult to be sure that the genetic change is causing (or contributing to) the symptoms.

How common is reduced penetrance?

It's difficult to estimate how common reduced penetrance is since there are so many different genetic disorders for which there is little information, but it has been observed for some genetic changes, such as deletions and duplications, that are associated with learning disabilities and developmental delay. Penetrance in more recently identified single gene disorders is more difficult to measure since so few families have been described and the tests used to identify such genetic changes are not yet commonly offered to unaffected individuals (unless they are parents of an affected child).

How does reduced penetrance affect me or my child?

While complete penetrance is easier to understand, reduced penetrance can be confusing for any given diagnosis because, while some people may be obviously affected, others with the same genetic change may show no apparent features or symptoms. This can occur in families where an unaffected parent passes on a genetic change to a child who is affected.

For genetic conditions with reduced penetrance, it is not possible to reliably determine if a child will be affected or not based on their genetic diagnosis.

Factors that can affect expressivity and penetrance

Overall, very little is currently known about factors that shape expressivity and penetrance. The expressivity and/or penetrance of a genetic disorder can be very difficult to determine.

For many genetic conditions, the onset of symptoms can be related to different factors such as age, sex, genetic background, additional genetic changes, variations in gene activity levels and other environmental factors.

Expressivity and penetrance are likely to be affected by the unique genetic background of each individual. We all have numerous genetic changes that we are unaware of that, on their own, may not have any effect on our health and development but, in combination with other genetic changes, may contribute to symptoms. Individuals can also have different levels of gene expression for any given gene.

Expressivity and penetrance may also be affected by whether the individual is male or female. This is not only true for genetic variants on the X chromosome (usually, females have two X chromosomes and males have one), but because we have many genes that are imprinted, meaning their activity depends on the biological sex of the person (e.g. some genes are 'switched off' in males, others are 'switched off' in females).

Penetrance is sometimes given a different value at different ages (especially for late onset symptoms).