

Prader-Willi Syndrome: Causes and Possible Solutions

Prader-Willi Syndrome is a rare and fascinating disorder in both its causes and its potential solutions. It differs from most genetic diseases in that it is caused by the absence of a parental set of genes, rather than the absence or deletion of a particular gene. This causes the syndrome to produce a wide, yet highly specific variety of physiological, behavioral and physical effects as well as distinct problems for detection and possible genetic therapy.

Causes

Prader-Willi syndrome is caused by a small interstitial deletion of chromosome material, specifically on chromosome 15. The syndrome is an example of genetic imprinting, a process in which genes are expressed differently depending on the parent of origin. In a normal individual, the paternally inherited genes on chromosome 15 are expressed normally, while the maternal genes are present but silent, or not expressed. Prader-Willi results when the active copy of the relevant gene, the paternal copy, is absent. Either the deletion of the paternal copy or the presence of two copies of the maternal gene copies, which is termed uniparental disomy, is the cause. For Prader-Willi syndrome and a related disease, Angelman's syndrome, an imprinting center has been identified as determining whether the relevant gene or genes causing these disorders are expressed. This process occurs in the parental gonad; the genes

for Prader-Willi syndrome are activated after passing through the paternal gonad but are silenced through the maternal gonad.

Clinical Effects

The unusual causes of Prader-Willi syndrome produces a great variety of clinical effects that are found in almost all cases. These effects include altered behavioral phenotype, appearance and bodily development. The most widespread effect of Prader-Willi is short stature, which is almost always present by the second half of the second decade. Abnormal pubertal development is also present, evidenced by. Hyperphagia, or excessive eating is also another effect—food-seeking behavior is common, as well as obesity as a result. Facial features include distinctive facial diameter, nasal bridge and mouth. Visual acuity deficit is also present, as well as high pain threshold, skin picking and high threshold for vomiting. As can be seen, these are a set of very specific effects that, yet, still appear in all individuals diagnosed with Prader-Willi syndrome. These effects stress the unusual effects of paternal deletion, causing changes that are mostly behavioral and physiological in nature. Despite having been identified with a deficiency in gene splicing mechanism, as a result of lack of genetic information in forming small nuclear ribonucleoproteins, or snRNP's, there is no direct lethality associated with the seemingly drastic deletion caused by genetic imprinting. Study of the causes of Prader-Willi syndrome can not only

directly aid those affected by its effects, but also increase the knowledge of genetic influences on human behavior and physical development.

Detection

Prader-Willi syndrome is also important in that it is was the first microdeletion syndrome identified by high-resolution chromosome analysis. In fact, high-resolution chromosome analysis remains the first choice for initial tests in detecting deletions in 15q11-q13. However, clinical detection has become much more accurate with the use of fluorescence in situ hybridization (FISH). Current test that search for genetic deletion causal for Prader-Willi syndrome now combines both high-resolution chromosome analysis and FISH. In the cases of uniparental disomy, which occur in approximately %2-%5 of cases, the simplest way to diagnose UPD is with chromosome-specific microsatellite markers. However, these tests are universally expensive and require specialist equipment. The most common test for Prader-Willi syndrome, therefore, consists of testing for extreme low levels in proteins such as growth hormone that are the results of the genetic deletions of Prader-Willi syndrome.

Solutions

The current solution, or “cure,” to Prader-Willi syndrome is to address its most serious symptom, obesity. Obesity can reach extreme levels and is the

only serious cause of death as a direct result of Prader-Willi syndrome. As a result, patients diagnosed with Prader-Willi syndrome are given regular injections of growth hormone, now produced by genetically altered *E. ~~Coli~~coli*, to combat this side effect. In regards to genetic therapy, Prader-Willi syndrome presents a variety of problems. Genetic therapy is just being considered today, in light of new and hopefully upcoming advances in genetic detection, and targeting, as well as the completion of the Human Genome Project. However, even if genetic therapy becomes a possibility, there are several prerequisites in order for a genetically caused disease or syndrome to be treated with such methods. It is necessary to define what product is to be produced from the patient's cells. Next is to define the genetic sequence that codes for said product. It can be seen then, that the disease or syndrome must have an easily alterable genetic sequence that produces a particular protein. Prader-Willi syndrome, however, is the result of not the deletion of an entire set of genes, but the absence of an entire set of genes from one parent. Thus, inserting a new genetic sequence will be extremely difficult, as obtaining another copy of such a genetic set can be both physically (parent may be incapable of donating genetic information) and genetically impossible. However, some solutions can be created from the possibilities presented by gene therapy. Although the behavioral effects of Prader-Willi syndrome are difficult to address through direct genetic alteration, the protein-production elements that are deficient can be addressed. In other words, genes that code for production of growth hormone, or, on a more basic level, code for proper mRNA splicing or correct snRPN formation, can be

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introduced into a patient with Prader-Willi. Such a procedure, however, rests on the identification of the genes responsible for such complex procedures, most probably via the completion of the Human Genome Project, as well as fully developed genetic therapy procedures. However, the great leaps that medical technology maintains gives hope to those affected by the unusual effects of Prader-Willi syndrome.