Obesity is a common finding in our general population, the proportion of obese individuals having increased at an alarming rate all over the world in the past 20 years. Compared to growth failure, obesity is rare in a population of individuals with a genetic syndrome. One database for genetic syndromes, Online Mendelian Inheritance in Man, contains 169 matches for obesity and 421 matches for growth failure.

Obesity is a medical problem that increases the risk for heart disease, diabetes (type II), high blood pressure, stroke, orthopedic problems, sleep apnea, and mortality from cancer. Besides medical issues, there are also psychological issues associated with obesity. Our society stigmatizes obese individuals, and poor self-esteem is a common finding. When a child is evaluated for obesity, the list of possible diagnoses that the doctor considers should include genetic syndromes, especially when unusual physical features, mental retardation, or other health problems are present.

Obesity is a multifactorial (interaction of many causes) condition with both genetic and environmental components. One way to quantify obesity is by calculating an individual’s Body Mass Index (BMI). BMI can be calculated by dividing weight in kg, by height squared in (m2) or if converting in the English system, BMI = [Weight in pounds ÷ Height in inches ÷ Height in inches] x 703.

Obesity in adults can be divided into three groups, overweight (BMI of 25.0-29.9); obese (BMI 30.0-39.9); and extremely obese (BMI greater than 40).

For children, the minimum BMI for obesity may vary from approximately 18 for 5-year-old boys and girls to 29-30 for 18-year-olds.

Recent studies have shown that 54 percent of the adult population in the U.S. is overweight and 22 percent are obese. The youth of this country are also showing an increase in BMI: 25 percent of U.S. children can be classified as overweight or obese.

While there is a definite genetic component to obesity, a large part of the current epidemic is due to environmental factors that promote overeating and reduced physical activity. Humans have developed mechanisms to protect against weight loss in times of scarcity, but protection against weight gain in times of abundance is not as prevalent in the population.

Most cases of obesity can be explained by a multifactorial mode of inheritance involving genes, food consumption and energy expenditure. However, rare exceptions to the accepted multifactorial mode of inheritance do exist in monogenic (single gene) syndromes with obesity as a main phenotypic component.

There are many other possibilities that need to be considered in an obesity evaluation. Some are common genetic syndromes that are easily tested for, while others are more obscure.

Genetic syndromes with obesity and delayed/altered intellectual development as a major part of the phenotype include Prader-Willi syndrome, Albright hereditary osteodystrophy, Alstrom syndrome, Bardet-Biedl syndrome, Borjeson-Forssman-Lehmann syndrome, Cohen syndrome and fragile X syndrome. Chromosomal conditions, including Down, Klinefelter and Turner syndromes, also have an increased prevalence of obesity.

In recent years, several single gene mutations have been linked to extreme obesity. Certain forms of brain damage can also be a cause of extreme obesity.

Albright hereditary osteodystrophy (AHO) is characterized by variable mental retardation, short stature, round face, short neck, short bones of the fingers and toes, calcifications or ossifications in subcutaneous tissues often near joints, delayed development of the adult teeth, enamel hypoplasia and obesity.

Individuals with AHO can have obesity of prenatal onset or develop it within the first year of life. AHO is also known as pseudohypoparathyroidism type 1a. AHO can be diagnosed by testing the amount of calcium and phosphorus in the blood and the level of cyclic AMP in urine.
**PWS and Obesity, and PWS look-alikes**

The gene for AHO has been mapped to chromosome 20, and it is inherited as a dominant condition.

**Alstrom syndrome (AS)** produces symptoms in children that include progressive loss of vision and hearing, an unusual rash (acanthosis nigricans) that is seen in people with some types of diabetes, short stature, renal (kidney) failure, dilated or enlarged heart and obesity.

Visual impairment typically begins with photophobia (abnormal sensitivity to light) in the first 6 months and advances to blindness by 30 years. Obesity is typically present before 5 years and increases with age. Deafness usually presents late in the first decade, and renal failure often occurs by the third decade. AS is inherited in an autosomal recessive pattern, and one gene locus has been found on chromosome 2. Testing for AS is available on a research basis.

**Bardet-Biedl syndrome (BBS)** is characterized by more toes or fingers than normal at birth, progressive vision loss, renal (kidney) abnormalities, developmental delay, hypogonadism (lack of sexual development), short to low normal stature and kidney abnormalities, developmental delay, hypogonadism or fingers than normal at birth, progressive vision loss, renal (kidney) abnormalities, developmental delay, hypogonadism

In BBS, the onset of obesity is usually in early childhood. Visual impairment usually presents with color and/or night blindness which progresses to blindness by 20 years. Renal abnormalities are varied, with 60 percent of patients having hypertension with renal failure occurring infrequently. BBS is inherited in an autosomal recessive pattern, and at least 6 gene loci have been found in different families.

Other families have not been linked to any of these loci, leading researchers to continue to look for other loci responsible.

**Cohen syndrome** is characterized by mental retardation with a sociable/cheerful personality, small head size, hypotonia, abnormal curvature or rounding of the spine, short stature, narrow hands, progressive heart disease, near-sightedness, vision problems, prominent incisors, blood white cell problems, and obesity.

In Cohen syndrome, obesity tends to develop by the school-age years, and the mental handicap is non-progressive. Cohen syndrome is inherited in an autosomal recessive pattern. The Cohen syndrome gene is designated COH1 and is located on chromosome 8.

**Fragile X syndrome** is characterized by mental retardation, increased growth in childhood, large head, large ears, dental crowding, and large testicles. In some cases, obesity is also seen in individuals with fragile X syndrome.

Fragile X syndrome is an X-linked recessive condition involving the expansion of a repeated sequence DNA in the FMR1 gene on the X chromosome. There are three levels of repeats: normal, premutation, and full mutation.

Individuals with a premutation, especially females, have an increased risk of passing on a full mutation to offspring because of instability in the FMR1 gene.

A subset of patients with fragile X syndrome have a phenotype that is different from the classic presentation. These individuals have a full, round face, small and broad hands/feet, areas of more darkly colored skin (hyperpigmentation), and obesity. The reported phenotype in these patients has been compared to the PWS phenotype, with differences being lack of infantile floppiness and food seeking in childhood. In one study, individuals with these characteristics were found to have full fragile X syndrome mutations and no abnormalities in the PWS region. Fragile X analysis is widely available and should be considered in cases of childhood obesity.

**Obesity linked to Chromosomes**

There are also several well-defined chromosomal abnormalities that are associated with increased risk for obesity. Individuals with Down, Klinefelter, and Turner syndromes have a high risk of becoming overweight and obese.

**Down syndrome** is caused by three copies of chromosome 21 and is a highly recognized genetic syndrome. Individuals with Down syndrome can develop obesity stemming from environmental causes such as overeating and lack of exercise.

However, several features of Down syndrome can also explain a higher prevalence of obesity. Individuals with Down syndrome can have short stature, hypotonia and hypothyroidism, all of which increase the likelihood of becoming obese.

**Klinefelter syndrome** occurs in males and is also known as XXY syndrome. Characteristics of this syndrome include hypogonadism, infertility, long limbs, progressive enlargement of the breast tissue, truncal obesity and increased risk for certain kinds of tumors.

Testosterone therapy has proven useful in patients with XXY to normalize adolescent development and increase muscle mass.

**Turner syndrome** occurs in females and is the usual result of losing one X chromosome during fetal development. Short stature, broad chest, developmental abnormalities of the heart and large blood vessels and neck webbing are common characteristics.

Growth hormone replacement therapy is becoming common treatment for short stature individuals with Turner syndrome.
PWS and Obesity, and PWS look-alikes

Leptin deficiency and MC4R mutations

Several genes have also been linked to severe childhood obesity without being associated with other congenital defects characteristic of traditional childhood obesity syndromes.

The leptin gene, a homolog of the mouse gene ob, has been mapped to chromosome 7. Leptin deficiency leading to morbid obesity has been recently described in two families. Leptin mutations have been associated with morbid obesity, increased appetite and hyperphagia, and poor or slow sexual development. Both of these families illustrated autosomal recessive inheritance.

Leptin replacement therapy has been initiated with success in patients with congenital leptin deficiency. Weight reduction was sustained due to decreased appetite and food consumption. Gonadotropin (brain sex hormones) levels also increased after 12 months of leptin therapy. This treatment may help prevent the lack of sexual development seen in adults with leptin deficiency.

Leptin receptor mutations have also been associated with the characteristics of leptin deficiency plus initial growth retardation and hypothalamic obesity due to changes in the hypothalamus of the brain. Three sisters have been described with high serum leptin levels with mutations in the leptin receptor gene on chromosome 1. These individuals had normal birth weight, early growth deficiency and hyperphagia that led to obesity. Autosomal recessive inheritance was suggested.

Another gene with a possibly greater effect on the presence of obesity in the general population is MC4R, located on chromosome 19. MC4R, melanocortin receptor, is present in high levels in areas of the hypothalamus that are known to be involved in feeding behavior. Mutations in MC4R have been described in several families and have been found by screening populations of obese children and adults. Studies have found that 3-5 percent of individuals with a BMI greater than 40 have a mutation in the MC4R gene. Most individuals have one copy of the changed gene and one copy of the normal gene, implying autosomal dominant inheritance for obesity associated with MC4R mutations. MC4R mutations appear to cause a “pure” obesity syndrome; no other endocrine abnormalities have been associated with mutations.

Head trauma may be a factor in obesity

A thorough evaluation of obesity in children should also include consideration of head trauma affecting the hypothalamus. This condition is termed hypothalamic obesity and is thought to arise from overeating due to poor regulation of satiety and hunger.

Besides obesity, hypothalamic insult can lead to other endocrine abnormalities including growth hormone deficiency and hypothyroidism, both of which exacerbate obesity. However, hormone replacement has not proven to be effective in treating obesity in these patients.

Hypothalamic obesity can be seen in children with brain tumors, those who have undergone surgery, or those who have had radiation. One study of patients with craniopharyngioma showed that these patients have increased serum leptin concentrations and severe obesity. This is contrary to expected effects of increased leptin, based on obese patients with leptin deficiency. A proposed explanation is hypothalamic insensitivity to endogenous leptin due to the underlying brain damage of study patients.

Psychological impacts of obesity

Obesity, regardless of cause, has psychological impacts on affected individuals and families. In children who are mentally retarded, that impact may actually be greater on the parents and caregivers. Our society favors and holds individuals who are not overweight/obese in better esteem. This attitude is overtly expressed in the media, and a great amount of resources are aimed at persuading individuals that weight loss is not only desired, but also required for a successful life.

Many studies have shown that obese children demonstrate increased psychopathology and social problems when compared to non-obese peers. The data have also suggested that weight loss leads to improvement in psychological functioning. Many previous studies have used children seeking psychological or psychiatric treatment as a study population to observe differences between obese and non-obese children. It is very important that a correct diagnosis be made because of the varied treatment options available that are syndrome specific. Quality of life can be improved through treatments, and better psychological adjustment can be achieved through proper family education about a particular diagnosis.