WHAT IS INCONTINENTIA PIGMENTI?
Incontinentia Pigmenti (IP) is a genetic disease of the skin, hair, teeth and central nervous system. The condition was named because of the way the skin looks under the microscope. "Bloch-Sulzberger Syndrome" is another name commonly used for IP. Other names are: Bloch-Siemens Incontinentia Pigmenti, Melanoblastosis Cutis Linearis, and Pigmented Dermatosis, Siemens-Bloch Type.

Incontinentia Pigmenti (IP) is a rare genetic disorder. The cause has been traced to a defective gene on the X-chromosome called NEMO. The disease varies from very severe to mild and clinically inconsequential. The signs described in this brochure vary in severity from person to person, and there is variability even among affected individuals in the same family. The prevalence of IP is unknown. As is often the case with rare disorders, it is likely that IP often goes undiagnosed or misdiagnosed. A woman with IP has a 50% chance of passing on this gene to each of her daughters. For male fetuses, of the 50% who inherit the IP gene, the great majority will result in a spontaneous abortion (or miscarriage) as IP is nearly always lethal in a male fetus. But for extremely rare exceptions, any live born male will be unaffected. There is no known ethnic or racial predisposition and cases have been reported throughout the world. Treatment is symptomatic and supportive. There is currently no cure for IP. Genetic counseling for affected women, parents of affected children, and relatives at risk is recommended. However, with the discovery of the gene, NEMO, and the relationship of mutations and alterations within NEMO to IP, prenatal diagnosis is now possible.

MALES
As stated above, males have only one X chromosome. If the IP gene on a male's only X chromosome is severely damaged, males cannot survive. A healthy version of the NEMO gene is apparently so critical to life that a nonfunctional version in males causes death before or shortly after birth. There are, however, several cases of males diagnosed with IP. These individuals typically manifest IP due to carrying an extra X chromosome (XXY) or to being mosaic for both XY and XX cells. These cases can be confirmed through testing for NEMO mutations. Some mutations in NEMO manifest in disorders in males that are different from IP. These males are often characterized as having ectodermal dysplasia and/or immune deficiencies. There is disagreement among researchers and clinicians as to whether these boys really have IP, or, do they have a similar disorder that closely resembles IP. One of the benefits of identifying the gene, is that these males can now be definitively diagnosed and it can be determined if they do indeed have IP. Early findings with the NEMO gene suggest that males with features of IP may have more subtle mutations that cause their symptoms. Several articles have been written and are available through the Foundation about males with IP. Further Studies are currently being conducted.

DIAGNOSIS
Now that the gene responsible for IP has been characterized, diagnosis can be supplemented with molecular testing. However, diagnosis of new patients is normally carried out using clinical criteria. If the classic rash is present in a newborn, the diagnosis is fairly straightforward, but it can be more difficult when the rash is mild, when not all the stages are present, or when an adult is seen and the lesions have faded. A skin biopsy that shows the presence of "loose" melanin (the brown-black skin pigment) in the dermis of the skin confirms the diagnosis, in the appropriate clinical setting. When there is little or no skin involvement, IP may be assumed to be the diagnosis in individuals "at risk" for the disease if they have other features such as tooth abnormalities, missing patches of hair, or overgrowth and scarring of the retinal blood vessels. Such an "at risk" individual would be a woman with two (or more) affected daughters, the daughter of an affected woman, or the sister of an affected woman who herself has had the miscarriage of more than one male fetus.
SKIN
The earliest and most striking diagnostic features in IP occur in the skin as progressive rashes. It has four stages which may overlap. The first phase is the erythematous (red) and vesicular (blister-like) stage which appears in infancy and is often present in the newborn. This consists of redness, blisters, and boils. It is the initial manifestation in 90% of patients. It may last from a few weeks to a few months. The extremities and the scalp are most often affected, but the rash can be present on any body part. This rash may recur at times in the first few months of life, and rarely ever later. The rash may be confused with the skin rash seen in other infectious diseases including chicken pox, herpes, impetigo, or scabies. However, virus is never found in the blisters each of these diseases is more common than IP and can be fatal in infants, so an infant may be treated for an infection before the diagnosis of IP is made. Knowledge of a family history of IP will aid in efficient diagnosis. As serious as it looks, the rash does not seem to be painful, although clothing may irritate the blisters. Secondary infection from common skin bacteria should be treated if it occurs. The second phase, which may overlap with the first, are blisters which develop a raised verrucous (wart-like) surface. The lesions look like pustules. There can be thick crusts or scabs with healing and areas of increased pigmentation (darkened skin). It may be present at birth (implying that the vesicular stage took place in the womb), but it usually evolves after the first stage in 70% of patients. The extremities are involved almost exclusively. This stage typically lasts months, but rarely as long as a year. The third phase is the hyperpigmented stage in which the skin is darkened in a swirled pattern often described as a “marble cake” appearance. In some patients, the adjacent areas ultimately thin and widen leaving streaky hypopigmentation. It may be present at birth in 5-10% of patients but usually appears between 6 and 12 months of life. This may or may not correspond to the areas that were involved in stages I and II. The heavy pigmentation tends to fade with age in most affected individuals. The fourth stage is the atrophic (scarred) stage. These scars often are present before the hyperpigmentation has faded and are seen in adolescents and adults as pale, hairless patches or streaks, also referred to as hypopigmentation. These are most easily seen when they are on the calf in or in the scalp. Once most patients reach adulthood (late teen and beyond), the skin changes may have faded and may not be visible to the casual observer.

HAIR
About 50% of women with IP have minor abnormalities of their hair, usually a loss or lack of hair (alopecia) on the crown of the head. The alopecia is probably caused by scarring from the rash, but this is not proven. As with other children, sparseness of hair as a child does not correlate with the quantity of hair as an adult. Hair color is normal, but the hair strands themselves may be coarse, wiry, and "lusterless". For the most part, individuals do not have substantial problems with their hair.

TEETH
More than 80% of IP patients have abnormalities of their teeth, and these can be useful in making the diagnosis of IP. The primary (baby) teeth may be delayed. Both the baby and adult teeth may be affected. Some teeth may be missing altogether or when they do erupt, the teeth may be unusually shaped, typically peg-like or cone-shaped. The quality of the teeth and the enamel covering them is normal. Few individuals have serious dental problems, and most can be helped with cosmetic dentistry (orthodontics or prosthodontics) as necessary. Adult teeth can be affected even when baby teeth have been fairly normal. Unfortunately, issues with baby teeth do not predict the course of adult tooth development.

NAILS
The nails of the hands and feet may be involved. That involvement is usually mild and transient but can recur. The nails may be ridged, pitted, thickened, or completely disrupted. If these signs are present, they typically involve most or all the finger and toenails, not just one or two nails. Benign tumors have been described to grow under the nail bed and correspond with the blistering skin lesions seen in stage II. In extreme cases, these growths can be painful and may be associated with deformities of the finger bones.
EYES
The majority of IP patients have normal vision. Some problems, like near- and far-sightedness, are common in IP individuals, but these are probably no more frequent than in the general population without IP. The classical eye finding in IP is an abnormality in the growth of blood vessels in the inside of the eye (the retina). Growth of abnormal blood vessels, and the associated scarring can cause loss of vision but may be treated if recognized early enough. For this reason, babies diagnosed with IP should have an eye examination immediately after birth and be followed by an ophthalmologist closely during the first few years of life. Careful examination by a pediatric ophthalmologist or retinal disease specialist should be done 3-4 times in the first year, then every 6 months until age 4 years, then annually. Rare eye abnormalities have included small eye (microphthalmos), cataract, and degeneration of the optic nerve (optic atrophy). Permanent visual deficiency or total blindness may occur.

NERVOUS SYSTEM
Although most individuals are neurologically normal, severe neurologic complications can occur as a consequence of IP. Abnormalities of the nervous system can include Seizures (epilepsy*) occurring in infancy are an indication that the nervous system has not been spared. Paralysis, developmental and mental retardation, and small head size in infancy are an indication that the nervous system has not been spared. Careful studies of the frequencies of these symptoms in individuals with confirmed IP are underway. Currently, it is unknown how common neurological problems are in IP. The discovery of NEMO mutations in IP has allowed more patients to be identified, leading to the appreciation that IP is more common than previously recognized. While this is not enough information upon which to base strong conclusions, it does suggest that the vast majority of individuals with IP will be neurologically normal. There is increasing evidence that, if problems are going to arise, they will within the first year of life. Seizures or other complications should be treated as in any other infant, but these problems do not need special or unusual management. The most current study released (2014) and available is Learning Disabilities Are a Fundamental Hallmark of the Disease

BREAST
Developmental abnormalities of the breast range from a missing breast, extra nipples, small or asymmetric size of breast development after puberty or abnormalities in nipple pigmentation. No consistent pattern has been observed.

RESEARCH
IPIF was responsible for creating the International IP Research Consortium which identified NEMO as the gene which causes IP. The Consortium consisted of 5 laboratories in 5 countries. Mapping and cloning the gene required clinical data-gathering, analysis of patients, review of symptoms, signs of IP, analysis of features, diagnostic investigations, and then summarizing the findings. Most importantly, however, none of this progress could have occurred if families and individuals with IP had not volunteered blood and other tissue samples to the dedicated research scientists committed to these programs. The results will lead to a better understanding of this disorder and eventually treatment. There are two significant ways to assist research. One is to provide funding, which the IPIF cannot do alone. Second, and equally important, is to identify individuals and families, both multi-generational families and new mutations, for participation in molecular studies. Many ask why a woman with IP, who has no visible symptoms, should participate in research or a data-gathering program. The answer is quite simple: To provide more accurate counseling about the spectrum of clinical severity, She is at risk for transmitting the gene to her offspring and may want to have the option of prenatal diagnosis. Finding the gene is only the first step in understanding the disease process and in developing directed therapy for those who need it.
IPIF MISSION

Research
IPIF was responsible for creating the International IP Research Consortium which consisted of 5 laboratories in 5 countries that collaborated in the effort to isolate the IP gene. IPIF paid the salaries of some of the researchers, and provided funds for members of the consortium to attend meetings. Equally important was identifying individuals and families for participation in molecular studies of this disorder, both multigenerational families and those with unknown mutations.

➢ Devise an accurate and safe prenatal diagnostic test.
➢ Develop a database to assess more accurately clinical variation, natural history, and prognostic indicators.
➢ Identify additional mutations which cause IP
➢ Study treatment modalities.
➢ Understand related anomalies, particularly in males.
➢ Animal models of IP already exist, transgenic mice are fomenting studies of the gene’s lethality and the expressivity of the disease. The researchers are now better able to study treatment modalities.

Family Support
It can be a devastating experience for parents to be told that their baby has IP. When a child has a rare disease, close personal contact among families and friends can provide emotional support and lessen the feeling of isolation.

IPIF supports individuals and families through:
➢ Multi-lingual Web site to keep patients and their families informed of new developments.
➢ National database of health professionals, with expertise in IP, to help direct individuals to appropriate medical resources and consultants
➢ Emotional support and the sharing of resources.
➢ Access to other families and patients via the web site.
➢ Keeping Families updated with Current News via Social Media.

Education
➢ Provide the medical care community with relevant medical information to enable accurate diagnoses and appropriate treatment.
➢ Create awareness of IP on a worldwide basis.
➢ Maintain a bibliography of articles written about IP for medical journals. A list of the articles is available on the web site. Articles are available, at no charge, to members of IPIF and their medical providers.
➢ Provide the medical care community with relevant medical information to enable accurate diagnoses and appropriate treatment.

For additional information please visit the IPIF website www.ipif.org
The web site contains detailed information on a wide variety of subjects ranging from genetics and genetic testing to an explanation of the gene NEMO, as well as many other subjects of interest to those with IP.
Incontinentia Pigmenti International Foundation

IPIF is a voluntary nonprofit organization founded in 1995 by Susanne Bross Emmerich. IPIF is guided by a Scientific Advisory Council, whose members are acknowledged experts in their fields. IPIF consists of patients, physicians, educators, parents, relatives, and volunteers who are striving to take leadership in supporting research, education, and funding. IPIF is a source of reliable information and support for patients and families in the United States and worldwide. Its mission is to encourage and support research on IP, and to provide family support and education.

Become a Member and Join IPIF’s Mission

The Incontinentia Pigmenti International Foundation, Inc. (IPIF) relies upon contributions from Individuals and Private and Corporate Foundations and Companies. All funds go directly to research projects, support programs, awareness, education, and office maintenance. It will require much hard and inspired work and a great deal of financial support to realize our goals. Please join us by making a contribution, or requesting a matching gift from your employer.

Yes, I wish to make a tax-deductible contribution and become a Member to Join IPIF’s Mission

___$25  ___$50  ___$100  ___$250  ___$500  ___Other

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I am interested in Incontinentia Pigmenti as a:

__ Individual with IP  __ Parent  __ Relative  __ Friend
__ Physician  __ Research  __ Genetic Counselor  __ Other

___ Please send me additional information  __ I would like to be in touch with other families

Payment Methods

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Please make checks payable to: IPIF
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