National Cancer Institute

Clinical Genetics Branch (CGB)
Division of Cancer Epidemiology and Genetics (DCEG)

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Family Research Matters

Inherited Bone Marrow Failure Syndromes (IBMFS) Study Newsletter

Thank You for Taking Part in the Inherited Bone Marrow Failure Syndromes Study

Our research team is truly grateful to you and your family members for taking part in this study. We appreciate the time and energy you spent completing the questionnaires, giving us access to your medical records, and providing tissue samples for our research. In this issue, we would like to share some of the early results of the study and update you on current research and future plans.

A lot of work has been done since the study opened more than six years ago, and we are continuing to enroll new families at a steady pace. So far, nearly 400 families have begun the enrollment process, which involves an initial telephone interview, followed by a series of questionnaires which provide us with family and individual medical information. More than 200 families have completed this process, and we have seen almost 80 families and more than 250 individuals at the National Institutes of Health Clinical Center (the "CC Cohort"). The other families are in the Field Cohort ("FC").

Those who traveled to the Clinical Research Center at the NIH received a detailed evaluation of clinical, genetic and laboratory features that might be associated with a specific IBMFS. Those in the Field Cohort supplied similar information from their home communities.

Both groups have made vital contributions to this research. Our research simply could not be done without your willingness to take part in this study.

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Update on IBMFS

The IBMFS are a group of rare genetic blood disorders. The major disorders are:

- Fanconi Anemia (FA)
- Dyskeratosis Congenita (DC)
- Diamond-Blackfan Anemia (DBA)
- Shwachman-Diamond Syndrome (SDS)
- Severe Congenital Neutropenia (SCN)
- Amegakaryocytic Thrombocytopenia (Amega)
- Thrombocytopenia Absent Radii (TAR)

People with an IBMFS usually have some form of bone marrow failure (also called aplastic anemia). The symptoms and signs depend on which IBMFS is involved. An IBMFS family is often identified because at least one family member has a specific blood problem and/or physical finding that leads to the diagnosis.

The blood problems include:

- Anemia (low hemoglobin, hematocrit, or red blood cell count)
- Leukopenia (low white blood cell count, sometimes referred to as "neutropenia," which is one type of white blood cell)
- Thrombocytopenia (low platelet count)

More severe problems include fatigue and pale color, bruises, bleeding or infections. Examining the patient's bone marrow usually shows that it is not making enough blood cells; this is called "bone marrow failure," or "aplastic anemia."

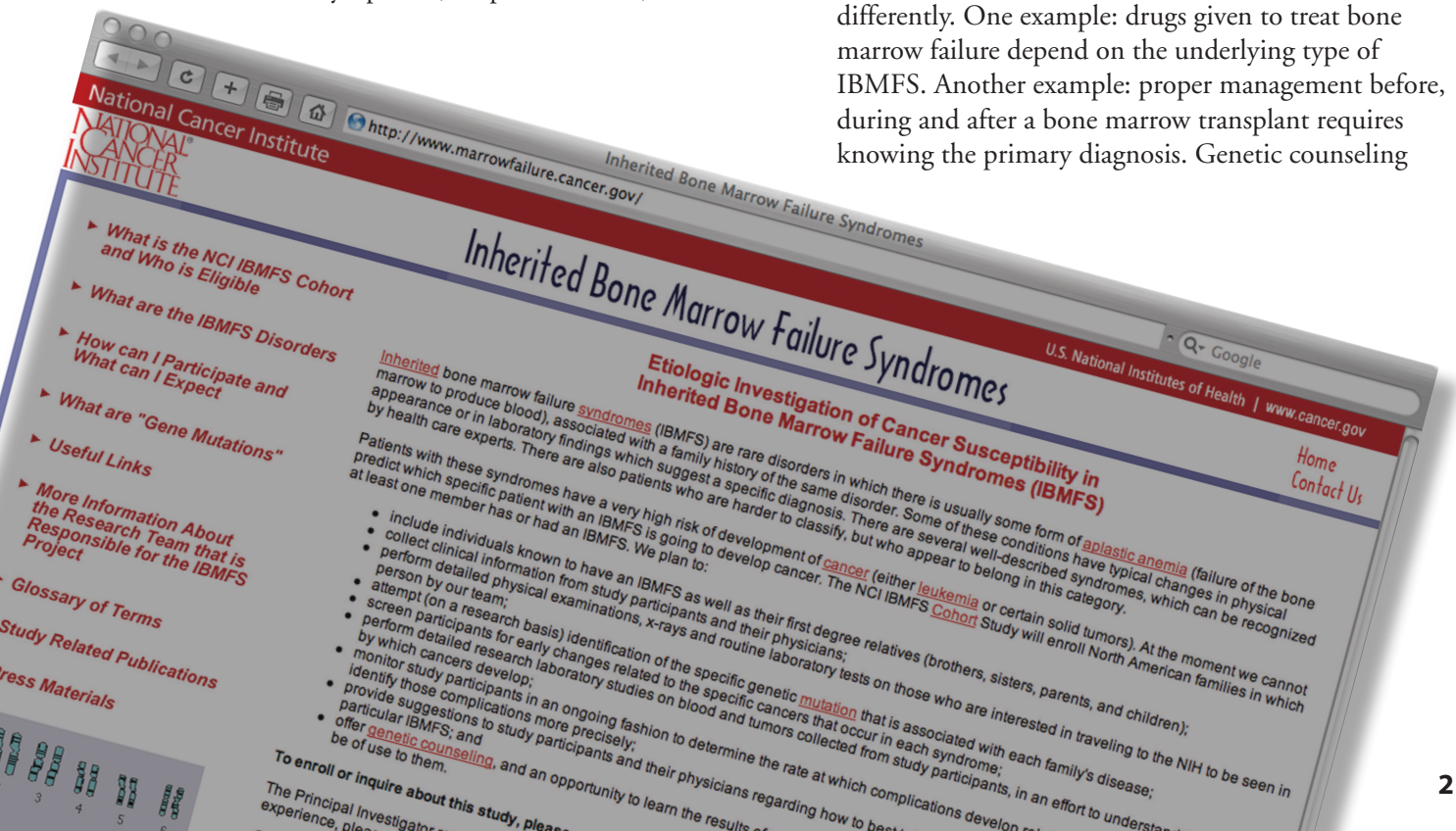
People with an IBMFS also have a very high risk of developing a preleukemic condition called myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), or solid tumors.

At the National Cancer Institute (NCI) we are studying the types, patterns, and causes of development of cancer in families with an IBMFS. Our overall goal is to better describe these disorders and their genetic causes, and to understand the relationship between clinical, genetic and laboratory findings, and the development of leukemia and solid tumors. These advances will improve health care for patients with these conditions. You can view more detailed information about this clinical research project at our study Web site:

www.marrowfailure.cancer.gov

Clarifying the Diagnosis

It is critical to make the correct diagnosis in each family, because the risks and types of bone marrow failure, leukemia, or cancer are different for each disorder. Each condition is followed and managed differently. One example: drugs given to treat bone marrow failure depend on the underlying type of IBMFS. Another example: proper management before, during and after a bone marrow transplant requires knowing the primary diagnosis. Genetic counseling



depends entirely on correctly classifying the syndrome, and on knowing the inheritance pattern in the family.

While many people with these disorders have physical signs and/or laboratory findings that are specific to each syndrome, there is a subset who are harder to classify, even though they may have some features of an IBMFS. By studying all of those who might have an IBMFS and their immediate relatives in a uniform manner, we have developed a systematic approach to help clinicians diagnose each disorder (see right box).

Whenever possible we analyze the genes associated with each syndrome to confirm the diagnoses. So far, we have found that about one in ten families who entered the study did not actually have the diagnosis they thought they had. For some of those families, we could not confirm the original diagnosis but were able to reclassify them. A few families remain currently unclassified (but we have not given up!). In several families, we also identified additional family members who did not know that they had the disorder. Some had no signs or symptoms, while others were very mildly affected.

MAKING THE CORRECT DIAGNOSIS

- **Fanconi Anemia (FA)**: There is an increase in chromosome breakage when a chemical that damages DNA is added to blood or skin cells in the laboratory
- **Dyskeratosis Congenita (DC)**: Telomeres, long repeats of DNA that protect the ends of chromosomes, are abnormally short in white blood (and other) cells
- **Diamond-Blackfan Anemia (DBA)**: There is an increase in a red blood cell enzyme (protein) called adenosine deaminase (ADA)
- **Shwachman-Diamond Syndrome (SDS)**: There are very low serum levels of specific enzymes made in the pancreas (trypsinogen and isoamylase), plus a low white blood cell count
- **Thrombocytopenia Absent Radii (TAR)**: The bone between the elbow and the thumb is missing, plus there is a low platelet count
- **Amegakaryocytic Thrombocytopenia (Amega)**: There are no physical abnormalities, but there are low platelet counts in infancy
- **Severe Congenital Neutropenia (SCN)**: There are very low neutrophils (a type of white blood cell) in infancy and a specific, related finding in the bone marrow

Genetic Education and Counseling

We look for the genetic changes (mutations) within each family. Genetic education and counseling are essential parts of this process. Patients can make informed choices about their own and their family's health care by receiving information and answers to their questions.

GENETIC TESTING MAY:

- Confirm a clinically-suspected diagnosis
- Identify a person as having the abnormal IBMFS gene which is present in their family, even if there are no obvious symptoms or clinical findings
- Identify carriers of the family mutation
- Confirm that an individual did not inherit the family mutation
- Not be able to find a mutation at this time

For genetic results to be given to a person in the IBMFS study, that person should have received genetic counseling either as part of his or her NIH visit or with a genetics provider in their local community.

Additionally, the laboratory testing must be performed in a CLIA-certified laboratory (Clinical Laboratory Improvement Amendments), to ensure quality.

Those of you who visited the NIH have personally met with one of our genetic counselors, while others may have spoken with them on the telephone or had counseling at home.

Defining the Clinical Spectrum of Each IBMFS

We collaborate with many experts in order to define the clinical features of each of the IBMFS and find out which are present or absent in each person in our study.

Your medical data and thorough medical evaluations are helping us to more precisely distinguish one IBMFS from another. This is the first study to look at both the physical and laboratory findings for each of the major IBMFS in all individuals, no matter which type of syndrome is in their family, and independent of whether they have the disorder or are a relative of someone with an IBMFS. ❖

FA is primarily an autosomal recessive (AR) disorder. This means that patients with FA received an abnormal (or mutated) FA gene from each parent, while carriers (parents and some siblings) have one abnormal and one normal FA gene. Siblings who are unaffected and do not carry the gene receive only a normal gene from each parent. One rare type of FA, called FA-B, is seen only in boys, who inherit the abnormal gene from their mother.

More than 90% of patients with FA fall into one of thirteen subgroups, each defined by mutations in a different FA-related gene (see the chart below). Five to 10% of patients cannot yet be assigned to one of the known groups; more genes await discovery.

We will try to identify more genes in order to expand beyond the 13 genes we already know about. We will determine the specific genetic mutation in each person in our study, in order to confirm a person's diagnosis as either affected, carrier or non-carrier. Knowing this level of detail will help us to rule out other syndromes that may be similar to FA.

We will look at the link between genes, environment, physical signs and symptoms, aplastic anemia, leukemia, and solid tumors. We will offer genetic counseling, including before marriage, during a pregnancy, and through pre-implantation genetic diagnosis (called PGD).

Fanconi Anemia Genes

Gene	Chromosome Location	% of Patients	Genetics
FANCA	16q24.3	~65%	AR*
FANCB	Xp22.31	rare	XLR**
FANCC	9q22.3	~10%	AR
FANCD1 (BRCA2)	13q12.3	rare	AR
FANCD2	3p25.3	rare	AR
FANCE	6p21.3	~10%	AR
FANCF	11p15	rare	AR
FANCG (XRCC9)	9p13	~10%	AR
FANCI(KIAA1794)	15q25-26	rare	AR
FANCJ (BACH1/BRIP1)	17q22.3	rare	AR
FANCL (PHF9/ POG)	2p16.1	rare	AR
FANCM (Hef)	14q21.3	rare	AR
FANCN (PALB2)	16p12.1	rare	AR
To be identified		~5-10%	

*AR, autosomal recessive. **XLR, X-linked recessive.
See Glossary for explanations.

Cancer in FA

Dr. Blanche Alter, the Principal Investigator, has been studying FA for many years, and a lot of our current knowledge on cancer comes from her studies:

- Eighty to 90% of patients with FA develop bone marrow failure, with a peak at around 10 years old.
- In teenagers and young adults, the risks of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) are very high for patients who have not already received a bone marrow transplant, as are the risks of solid tumors, particularly head and neck, esophageal, and gynecological cancers.
- Patients with several abnormal physical findings at birth were more likely to develop early bone marrow failure, while those with less severe or no physical abnormalities were more likely to first develop AML or solid tumors as young adults.
- Bone marrow transplant appeared to increase the risk of head and neck cancer to an even higher level than that observed in patients who did not have a transplant.
- One-third of FA patients with leukemia or a solid tumor had cancer as the first FA-related finding and only later were diagnosed with FA. Some of those patients had normal blood counts, and were called "hematopoietic somatic mosaics" (meaning their blood stem cells had undergone gene correction, while all other cells in the body continue to have the FA defect). We have seen this pattern in a few of the adult patients in our study.
- A mutation which is common in Ashkenazi Jews, called *FANCC* IVS4+4A>T, is also seen in some Japanese, but the birth defects and early-onset bone marrow failure tend to be more severe in the Jewish than in the Japanese individuals. This may be due to differences in other (non-FA) genes, or environmental factors, or both.
- Patients with mutations in *FANCD1/BRCA2 or FANCN/PALB2* tend to have severe birth defects and develop brain tumors, leukemia, and kidney cancers very early in childhood.
- Family members who are carriers (have one mutated and one normal gene) of *FANCD1/BRCA2, FANCN/PALB2, or FANCJ/BACH1* may be at increased risk of breast or ovarian cancer.

What Have We Found in Our FA Research So Far?

There is more than meets the eye: More than 80% of the patients in our study had various FA-related abnormalities on physical or laboratory examination more often than were previously reported:

- **Hearing Loss:** About 70% of the patients with FA had deformities of bones of the middle ear. This leads to hearing loss, which can be treated with hearing aids and/or surgery. Several patients were not aware that their hearing was abnormal until these research examinations were done.
- **Hormones:** More than 70% of the patients had low levels of thyroid hormone, growth hormone, or male and female sex hormones; high cholesterol levels; elevated glucose or frank diabetes; and some adults had fertility problems. Most adults also had loss of bone calcium. Treating many of these problems will improve the quality of life.
- **Brain:** Magnetic resonance imaging (MRI) of the brain led to our discovery of small pituitary glands, particularly in those FA patients with short stature who also had hormone problems. MRI does not use radiation, and thus can be recommended for patients with FA.
- **Eyes:** More than 80% of the patients with FA had small eyes and/or corneas.
- **Ear, Nose and Throat:** A large number of young adults had white or red patches in the mouth, which require close monitoring because they may be pre-cancerous. Several biopsies were done. Some of the young adults in our study already had or developed cancer of the head and neck region, mainly on the tongue or elsewhere in the mouth or throat.
- **Females:** Precancerous changes or even gynecologic cancers were found in some young women.

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Recent Discoveries in Fanconi Anemia (FA)

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- **Psychosocial:** Dr. Sadie Hutson from our group recently published a report in which she identified four major psychosocial themes in the siblings of patients with FA: containment, invisibility, worry and despair. This highlights the need for physicians to be involved in the management of all members of FA families, not just those individuals who actually have FA.

What Are We Currently Studying in FA?

We are continuing to enroll new families since larger numbers of participants will allow us to:

- Accurately analyze FA-related cancer risks
- Identify clinical and laboratory factors which help us to predict which FA complications may develop
- Better define management strategies

Other Questions We Hope to Answer

- How are patients with FA who develop cancer different from those who do not develop cancer?
- How do FA gene mutations relate to cancer development in the general population?
- Do viruses (such as hepatitis or human papillomavirus) play a role in cancer in FA?
- Are extended family members at increased risk of cancer?
- How can we help families manage FA? ❖

Recent Discoveries in Dyskeratosis Congenita (DC)

DC is a rare bone marrow failure disorder, and is traditionally characterized by abnormal nails, lacey pigmentation of the skin, and white spots in the mouth ("the diagnostic triad"). DC is a disease of abnormal telomere maintenance (telomeres are complex structures that protect the ends of chromosomes). Telomeres shorten with age in normal individuals, and shorten more rapidly in DC.

There has been an explosion of research regarding the mechanisms of this disease, including the recent discovery of new DC-related genes. All types of inheritance patterns have been seen in families with DC. Many patients with DC have mutations in genes that are important in the biology of telomeres. So far, mutations in five genes have been identified in more than half of the reported patients; this includes the

Dyskeratosis Congenita Genes

Gene	Chromosome Location	% of Patients	Genetics
DKC1	Xq28	60% of males	XLR*
TERC	3q26	20%	AD**
TERT	5p15.53	6%	AD, AR†
NOP10 (NOLA3)	15q14-q15	<1%	AR
TINF2	14q11.2	30%	AD
To be identified		~30%	?

*XLR, X-linked recessive. **AD, autosomal dominant.
†AR, autosomal recessive.

recent discovery by Dr. Sharon Savage from our group of a new DC gene called *TINF2*. A significant number of DC patients still do not have a mutation in any of the known genes, including about one-third of the families in our study; further gene discovery remains a priority for us.

What Have We Found in Our DC Research So Far?

- Patients with DC have extremely short telomeres in their white blood cells. Working with Canadian collaborators, we recently developed a diagnostic test that measures the length of telomeres in each type of white blood cell. With this test, we found several individuals with very short telomeres, even though the patients did not have the physical signs of DC and in families where a mutation was unknown. For these families, a diagnosis of DC was or would have been missed without the telomere length test.

- DC is an under-diagnosed (or under-recognized) disorder. Bone marrow failure sometimes occurs before the physical changes of DC appear. Some patients who were diagnosed in the past as "acquired aplastic anemia" were found to have mutations in DC-related genes. A few patients with a different disorder, called "familial idiopathic pulmonary fibrosis" also have mutations in DC genes. Patients with DC have a wide range of findings, from none, to mild, to severe.

- Some patients with low blood counts who were thought to have acquired (i.e., non-genetic) aplastic anemia but who failed to respond to the usual immunosuppressive treatment for aplastic anemia, turned out to have DC.

- Clinical features of DC may become apparent as patients get older. In our IBMFS group, most of the patients did not have the typical abnormal nails, lacey pigmentation and pre-cancerous white or red patches in the mouth. Many children had a severe form with aplastic anemia, delayed development, and speech, learning and balance problems which were associated with a small cerebellum (the lower part of the brain which is responsible for maintaining balance). Some of the adults with DC in our study had normal blood counts.

- Rupture of the spleen. Two patients who were being treated with the combination of androgens (male hormones) and Neupogen® (G-CSF, the bone marrow white blood cell growth factor) had ruptured spleens. This rare complication had not been described before in DC and suggests a DC-related sensitivity to this combination of drugs.

- Other important findings in DC:
  - Excessive tearing due to blocked tear ducts;
  - Reduced oxygen exchange by the lungs (possible early signs of lung scarring or fibrosis);
  - Small teeth with thin enamel, large pulp chambers, and short roots;
  - Destruction of the hip bone (called avascular necrosis), requiring replacement in persons in their 20s or 30s.

What Are We Currently Studying in DC?

Persons with DC have a high risk of developing bone marrow failure, myelodysplastic syndrome, leukemia, or cancers of the head and neck and anal areas. Our current studies focus on learning more about how telomere genes contribute to cancer development and to aging, and to identify new genes for DC.

Dr. Sharon Savage is leading the effort to look for additional new DC-related genes using state-of-the-art, gene-finding technologies. The DNA samples and the information you have provided are currently being analyzed, and more DNA samples from new families are constantly being added to this set of genetic samples for future linkage analysis. ❖

We are planning the first Dyskeratosis Congenita clinical research conference on September 19, 2008. Parents of patients with DC and adult patients with DC will be invited to attend to learn about recent DC research and to participate in forming a family support group. All DC families will receive an invitation in the next few weeks.

Most people with DBA have severe anemia starting in early childhood, but the cause of the anemia is still unclear. Many laboratories around the world are studying this disease. The cancers found in some patients with DBA include acute myeloid leukemia (AML), osteogenic sarcoma (tumors that originate in bones), and others. Preleukemic myelodysplastic syndrome (MDS) has also been reported.

Three genes have been identified to be abnormal in patients with DBA, accounting for less than one-third of the patients. DBA is inherited as an autosomal dominant; in patients with DBA, one DBA gene is mutated and the other is normal. It can be passed from parent to child, or develop as a new mutation.

Diamond-Blackfan Anemia Genes

Gene	Chromosome Location	% of Patients	Genetics
RPS19	19q13.3	25%	AD*
RPS24	10q22-23	2%	AD
RPS17	15q25	Rare%	AD
To be identified	N/A	75%	?

*AD, autosomal dominant.

What Have We Found in Our DBA Research So Far?

- About 25% of the families with DBA have mutations in *RPS19*, and about 2% have mutations in *RPS24*. The majority of DBA families do not have a detectable mutation in any of the three genes so far known to cause this disorder.
- Elevated levels of the red blood cell enzyme adenosine deaminase (ADA) help to make the diagnosis of DBA. In our families, ADA levels were high in more than 80% of the individuals with DBA. However, a few patients with DBA have normal levels of this enzyme, so this test is very helpful but does not identify all patients with a DBA diagnosis. In addition, a few family members had elevated ADA levels but were not anemic. These individuals need to be followed in case they later develop anemia or cancer.
- Close to half of the persons with DBA in our cohort were shorter than expected for their age, and nearly 60% had physical findings that have been previously described in DBA.
- Many individuals who had iron overload from red blood cell transfusions or had received prednisone treatment developed endocrine abnormalities such as diabetes, hypothyroidism or osteoporosis.

What Are We Currently Studying in DBA?

We provide thorough and systematic examinations and long-term follow-up of study participants, with a major focus on bone marrow function and possible evolution to MDS, AML, or solid tumors. We will seek to identify new genes for DBA. With longer monitoring of a larger number of patients, our thorough studies will lead to understanding the associations between genes, clinical features, and outcome, including better estimates of the risk of leukemia or tumors. ❖

Update on Shwachman-Diamond Syndrome (SDS)

Symptoms of SDS include poor absorption of food due to low production of enzymes by the pancreas, and low white blood cell counts (neutropenia, low neutrophils) due to decreased production by the bone marrow. The function of the pancreas may improve with age, and low white blood cell counts may come and go, which causes difficulty reaching a diagnosis. The diagnosis is made by:

- Low white blood cell counts at least 3 times over 3 months
- Low serum levels of enzymes from the pancreas (trypsinogen and isoamylase). Trypsinogen levels sometimes improve and become normal with age, while isoamylase levels are low after 3 years of age
- Other tests such as ultrasound or CT imaging may show a fatty pancreas

The diagnosis of SDS has been confirmed in more than 90% of the patients who have mutations in the SBDS (Shwachman Bodian Diamond Syndrome) gene. These mutations are inherited in an autosomal recessive manner; each parent has a normal and a mutated *SBDS* gene, and the affected child has only the abnormal genes. However, 5-10% of patients who meet stringent clinical criteria have not been found to have mutations in the *SBDS* gene. There may be at least one more SDS gene that has not yet been found.

What Have We found in Our SDS Research So Far?

SDS is the major disorder for which diagnosis is the most confusing. Using the criteria outlined above, we were able to clarify or change the diagnosis in several cases. We (and others) have introduced a new term, "Shwachman-like," for those who have some SDS features, but do not have enough features to confirm the SDS diagnosis.

Since patients with SDS are at increased risk of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML), we are studying repeat bone marrow tests over time to look for early changes that suggest MDS or AML. Some patients with SDS have abnormal chromosomes in the bone marrow cells, but this does not necessarily predict development of MDS or AML. In particular, some of these abnormalities, such as i(7q) [isochromosome 7q] and del(20q) [deletion of the long arm of 20], may persist for a very long time without the development of MDS or AML.

In order to learn more about how neutrophil abnormalities contribute to the complications of SDS, we are studying neutrophil function in saliva and blood.

Long-term follow-up of our SDS cohort may enable us to quantify the risk of MDS and AML, and to determine whether patients with SDS have an increased risk of solid tumors. ❖

Recent Discoveries in Thrombocytopenia Absent Radii (TAR)

Patients with classical TAR are diagnosed at birth due to missing radial bones (the smaller of the two bones between the elbow and the wrist), with normal thumbs and low platelet counts. This pattern is different from FA, in which the thumbs are missing if the radii are absent. As with other IBMFS, there are individuals who may have TAR but do not fit the classic definition; the diagnosis in these individuals may be difficult to prove.

A deletion in region q21 of chromosome 1 was recently found in TAR patients, but because this deletion was also detected in some clinically normal relatives, the presence of this abnormality alone does not explain the whole picture of TAR. We and others are currently looking for other genetic mechanisms that act along with the chromosome 1 deletion to produce TAR. ❖

Other IBMFS

Several families who enrolled in our IBMFS Study do not fit the criteria for any of the syndromes discussed above. We have enlisted the aid of collaborating scientists throughout the USA and abroad in order to determine whether these families are unusual examples of syndromes we already know about, or whether they might represent new syndromes. Stay tuned for further developments! ❖

Where Do We Go From Here?

Clinical Analysis

One of our main goals is to precisely define the disease-specific clinical features of each IBMFS disorder. We are analyzing all the data from the study's detailed questionnaires, medical records, subspecialty evaluations, X-rays, laboratory tests and other research tests. By combining all this information we hope to identify features that are common to all IBMFS, as well as define those that differ between the syndromes. We continue with ongoing data collection by sending follow-up questionnaires to study participants and by enrolling new families.

Psychosocial Analysis

We are looking at the effect of an IBMFS diagnosis on the function of individuals within families by studying factors associated with stress, depression, and anxiety. We also are studying factors which influence decision-making regarding treatment choices for affected individuals (such as transfusion, medication, or bone marrow transplantation). This will help us to identify specific issues in order to help families as they cope with these challenging illnesses.

Genetic Analysis

We are studying how well our study participants understand basic genetic concepts and the genetic details related to their specific IBMFS. If gaps in knowledge are found, we will change our educational efforts as needed.

We continue to study the genes in each of the IBMFS, looking for specific mutations underlying the risk of cancer in each family, and other genes and markers which may interact to produce clinical and genetic differences between individuals. We are also trying to identify factors that are related to differences in disease severity among persons with identical mutations (a genetic phenomenon known as "penetrance").

Cancer Analysis

Since the IBMFS are considered to be disorders with an increased risk of cancer in affected individuals, we are documenting the types of cancers and the ages at diagnosis in each IBMFS. We want to identify early markers (predictors) of cancer.

We have been specifically looking for early markers of preleukemia (MDS) in bone marrow samples. We are monitoring any abnormal findings over time to determine whether they predict an abnormal outcome. We need to find MDS, AML, or solid tumors as early as possible, so that treatment can be started at a stage when cure may be more readily achieved. If we succeed in understanding the changes that lead to cancer, it may be possible to prevent its occurrence.

We are looking at the role played by the human papillomavirus (HPV) in the development of oral and gynecological cancers in patients with an IBMFS. Dr Lauren Wood, our collaborator in the NCI Vaccine Branch, is planning an HPV vaccine study for persons with FA and DC, to find out whether they will develop enough immunity to protect against HPV infection, and prevent future cancers.

Other Laboratory-based Studies

Some individuals with an IBMFS may have abnormal immune system functions, which could contribute to the risk of infection or cancer. We are planning a detailed study to define immune functions in patients in our study, in order to determine whether there is a relationship between immune status, bone marrow failure and cancer risk.

Cancer in Grandparents and Other Relatives

Some studies currently suggest there may be an increased rate of certain cancers among the carriers of FA while other studies refute this claim. We are systematically studying all the family members in all the IBMFS to determine whether cancer is increased in these relatives. ❖

Recommendations for Screening and Management

We do not completely understand the role of environment and lifestyle factors in causing cancer, either in the general population or in persons with an IBMFS, but we do know that a generally healthy lifestyle is associated with overall health, and may reduce the risk of cancer.

General Recommendations

- **Do not smoke.** If you are currently smoking, find a way to stop.
- **Do not drink excessively.** One or two drinks a day is generally considered acceptable, although avoiding alcohol altogether is the safest course.
- **Protect your skin** from too much sun exposure to reduce the risk of skin cancer. Avoid getting a sunburn.
- **Eat a well-balanced diet** with multiple portions of fruits and vegetables.
- **Exercise regularly.** Thirty minutes of exercise 4-5 times a week is associated with reduced risks of many cancers, and is also good for your heart.
- **Maintain ideal body weight,** since being overweight is associated with increased risks of many cancers and an increased risk of heart disease, high blood pressure and diabetes.
- **Wear your seatbelt** whenever traveling in your car.
- **Follow general population cancer screening recommendations,** appropriate to your age and gender. Don't let your concerns about the specific issues related to your family's IBMFS cause you to overlook routine general health maintenance activities.

Specific Recommendations

We recommend that all individuals with an IBMFS undergo regular evaluations by their physicians, because disease-specific or other complications may develop over time. Early detection and treatment of cancer can improve the quality of life and life expectancy. In general, all ***affected*** individuals should have the following annual evaluations:

- **Hearing Tests (Audiology)** – Patients should have an annual hearing test, especially those with FA, since hearing problems are common. Early treatment of hearing loss leads to improved speech and long-term learning.
- **Cardiology** – People with an IBMFS should be checked by a cardiologist (a doctor specializing in heart function). Follow-up may be needed if heart problems are found.
- **Dental** – See a dentist twice a year. This is critical for FA and DC patients so that they may be checked for pre-cancer or cancer. Patients with FA, DC and SDS may have more gum infections and cavities. Persons with DC and FA have early receding of gums, and those with DC have abnormalities of tooth enamel and pulp. White or red patches should be looked for in the mouth, monitored, and biopsied if they persist for more than 2-3 weeks.
- **Dermatology** – People with an IBMFS need to have regular skin exams and cancer screening. This means having a total skin exam and evaluation of suspicious skin lesions by a dermatologist (a doctor specializing in disorders of the skin). He or she will look for changes in skin pigment, or color patches, along with abnormal nails. Use of skin protection and moisturizers decreases breaks and cuts to thin, dry and scaly skin and nail beds in DC patients. Both FA and DC patients have very high risks of skin cancer, due to the underlying defect in DNA in each condition. Skin lesions that are suspicious for cancer should be biopsied.
- **Ear, Nose and Throat Exams** – People with FA and DC should see head and neck surgeons to screen for early signs of mouth, throat or laryngeal (voice box) cancers. This should begin by age 10 years, or within one year after bone marrow transplant, whichever comes first. Regular oral screening for head and neck cancers should be done at least twice a year (or more often if needed) by dentists and ENT surgeons. This is especially important for individuals with FA and DC. Any suspicious lesions should be biopsied.

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- **Eye Exams** – Patients should be seen regularly by an ophthalmologist (eye doctor) to find and correct vision problems, blocked tear ducts (common in DC), retinal changes, bleeding, cataracts, and glaucoma.

- **Endocrine/Hormone Evaluations** – Regular check-ups are required to find hormone deficiencies, abnormal glucose, cholesterol, and bone loss (osteopenia and osteoporosis). Endocrine problems are seen frequently in some people with an IBMFS, along with early signs of diabetes. Patients with an IBMFS who are taking androgens (male hormones, used in FA and DC to treat bone marrow failure) may have abnormally high levels of cholesterol.

- **Gastroenterology** – Children with SDS, FA, DC and others with failure to gain weight should be seen by a gastroenterologist, a doctor specializing in digestive system disorders. Esophageal narrowing, webs or strictures may be seen in DC; patients with FA may also have abnormal structures.

- **Genitourinary** – Kidney and other urinary tract abnormalities may be seen in those with an IBMFS, especially those with FA and DC.

- **Gynecological Exams** – Females, particularly those with FA and DC, should have an annual exam with cervical cancer screening by age 16, or earlier if they begin to have their periods. All females should receive the HPV vaccination at age 9 years or later. Regular gynecological exams and biopsies should be done as needed for suspicious or early changes of cancer in the vulvar, vaginal and cervical areas.

- **Hematology** – Blood counts should be obtained every 3-4 months, even if they have been normal, because bone marrow failure may develop at any age. All IMBFS patients should have annual bone marrow exams to screen for early changes of MDS or AML.

- **Neurology** – An individualized education plan (IEP) is needed for children with neurological abnormalities. We recommend an initial MRI of the brain for all patients with FA and DC, since abnormalities have been identified in these conditions. These abnormalities may explain problems with growth, mental development, and physical balance.

- **Pulmonary** – Lung function tests are particularly important for DC, due to the increased risk of lung fibrosis (scarring). The best test is carbon monoxide diffusion capacity.

- **Radiology** – A skeletal survey should be done at least once to characterize disease-specific deformities. An annual bone density is recommended in those older than 20 years to look for bone loss, since osteoporosis may develop early in those with IBMFS. Patients with FA or DC should have a yearly ultrasound of the liver to look for tumors or abnormal structure, especially but not limited to those who are receiving androgens. ❖

Please inform us at least 2 weeks ahead of any planned bone marrow tests scheduled in your home community so that we can coordinate research on your samples.

Please continue to update us on changes in your medical history and medications. We are always happy to assist you and your physician(s) in providing the best care possible and appreciate the opportunity to participate in the decision making process, whether it is adjusting medication doses or considering bone marrow transplantation.

How Do We Protect Your Rights and Confidentiality?

We have pioneered research methods of collecting and storing personal data and samples (blood, DNA, serum, plasma and tumor tissue) from people who take part in our studies. In fact, the research program which we are a part of (NCI's Division of Cancer Epidemiology and Genetics), has been using this design for more than 30 years. We keep the samples stored for many years, so that as tests, tools and knowledge improve, we can continue our research using these samples, rather than collecting new ones.

Protecting your privacy is our utmost concern, so we want to share with you more details of how the Clinical Genetics Branch (CGB) handles your samples:

- When we first design a study (called a protocol), we make every effort to list the specific uses we intend for the samples and to give scientific reasons why laboratory studies are necessary. Having NCI's Institutional Review Board (IRB) review our study plans gives you another layer of protection. The IRB has the right to deny research if it believes the risk is too high or the scientific reasons are not sound.
- At the beginning of a study, each participant signs an informed consent form. This form describes the study and outlines possible uses of samples in the future. Those who take part in the study can allow or decline use of their samples for these purposes. In general, you can refuse to give samples and still take part in the study. The consent form also makes it clear that you have the right, at any time, to request that your samples be taken out of storage and destroyed.
- We collect samples and store them in a special laboratory that keeps them in a stable condition. These are closely-guarded, highly-secure facilities. Special safeguards are in place to protect your samples. We use a custom-designed computer system to track the location of samples, whether they are in our facility or are in the laboratories of other researchers with whom we are working. **All samples are given a code number and do not carry your name or other identifying information**.
- We use samples only for the purposes outlined in the IRB-approved protocol and informed consent form. If we find new uses for your samples beyond those listed in the study design or consent form, then we must bring new proposals to the IRB for review and approval. The IRB has the right to approve the plan, refuse the plan, or require that we come back to you and ask for your consent to use your samples in the manner we propose.
- Investigators who are either part of NCI or the National Institutes of Health, or are in laboratories anywhere in the U.S. or overseas who have formal agreements with us can study your samples. If we send samples to them, the samples are coded so that it is impossible for the researcher to identify you personally.
- The data we obtain from laboratory studies can help us learn more about the disease we are studying. Often, these data give us clues for more research, but usually they are not useful to individual patients as they make decisions about their ongoing health care. If we unexpectedly learn something new that we believe is important for you to know, we will contact you and your health care providers.
- All samples are labeled with coded specimen numbers. Your name or other personal data are not on the label. Personal data is not shared with collaborators. The only people who can make the connection between the code and your personal data are those CGB staff who are directly involved in this specific study. The number of CGB staff with access to this sensitive information is kept to a minimum.
- All information is kept in password-protected computer files, or in secure, locked file cabinets. Access to this is strictly limited and controlled.
- A Certificate of Confidentiality given to CGB by the U.S. Department of Health and Human Services also protects your research data. This certificate strictly limits outside parties from gaining access to your information.
- Our research staff has formal training on protection of your data, with yearly update trainings. We take the duty of protecting your information very seriously. ❖

Our goal is to learn as much as we can about the IBMFS as quickly as possible, without placing you or your privacy at risk. We hope you will be reassured that the system we have in place will safely allow us to do both. Your samples are an incredibly valuable gift to science and the community at large. They are, without a doubt, the gift that keeps on giving! Thank you again for your remarkable generosity.

Resources

Disease-specific Web sites

- Diamond-Blackfan Anemia Foundation: *www.dbafoundation.org*
- Diamond-Blackfan Anemia Registry: *www.dbar.org*
- Daniella Maria Arturi Foundation: *www.dmaf.org*
- Dyskeratosis Congenita Outreach Network: *www.dcoutreach.com*
- Fanconi Anemia: *www.fanconi.org*
  www.fanconicanada.org
- Shwachman-Diamond Syndrome Foundation: *www.shwachman-diamond.org*
- The Severe Chronic Neutropenia International Registry: *http://depts.washington.edu/registry*

General Sites for Information about Bone Marrow Failure, Aplastic Anemia, Cancer or Genetics

- American Cancer Society: *www.cancer.org*
- Aplastic Anemia & MDS International Foundation, Inc: *www.aplastic.org*
- Hematology 101: *http://dceg.cancer.gov/files/FA-HEME101-2003.pdf*
- IBMFS Protocol: *http://clinicalstudies.info.nih.gov/detail/A_2002-C-0052.html*
- National Cancer Institute: *www.cancer.gov*
- National Cancer Institute, Clinical Genetics Branch: *http://dceg.cancer.gov/cgb*
- National Cancer Institute, Division of Cancer Epidemiology and Genetics: *http://dceg.cancer.gov*
- National Cancer Institute, Understanding Cancer Series: *http://newscenter.cancer.gov/sciencebehind*
- National Human Genome Research Institute, Glossary of Genetic Terms: *www.genome.gov/glossary.cfm*
- National Organization for Rare Disorders, Inc: *www.rarediseases.org*
- Online Mendelian Inheritance in Man: *www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM*

Related Medical Articles

Background Articles by the NCI IBMFS Team

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The IBMFS Team

The physicians involved in the IBMFS study include:

Blanche P. Alter, MD, MPH is the Principal Investigator responsible for developing and spearheading the study. She is a pediatric hematologist/oncologist. She is regarded as an expert in the IBMFS, both in the U.S. and abroad, and she has been caring for and studying patients with FA and other IBMFS for the past 30 years.

Sharon A. Savage, MD is the Principal Investigator on the dyskeratosis congenita study. She is a pediatric hematologist/oncologist with a special interest and expertise in telomere biology. She is studying how genes associated with telomeres contribute to cancer development and is responsible for identifying new susceptibility genes for DC.

Neelam Giri, MD is a Staff Clinician on the IBMFS study. She is a pediatric hematologist/oncologist with special training in stem cell transplantation. She is responsible for the clinical aspects of the study.

Christine M. Mueller, DO is a medical geneticist who is a Staff Clinician. Her major research interests are familial/hereditary cancers, cancer screening and chemoprevention in genetically at-risk populations. She is responsible for studying the dysmorphology (physical features) of all the IBMFS participants and also provides internal medicine expertise for adult family members.

The support staff of the IBMFS team includes research nurses, genetic counselors, research assistants, study managers, and interviewers. These are the people you speak with first when you join the study.

Lisa Leathwood, RN, BSN research nurse, is the study coordinator. She is the primary contact person for the IBMFS team. She can answer your questions and provide information or direct your queries to the appropriate team members.

Ann Carr, MS, CGC is the genetic counselor who provides genetic education and counseling for the IBMFS study. She is certified by the American Board of Genetic Counseling and the American Board of Medical Genetics.

Several other support staff members who are an essential and integral part (indeed, the backbone) of the study team and with whom you may have spoken at various points are Luda Brenner, Lauren Edukat, and Jennifer Emel, research assistants, and Stephanie Steinbart, research associate. ❖

Abbreviations

AD	Autosomal dominant
ADA	Adenosine deaminase
Amega	Amegakaryocytic thrombocytopenia
AML	Acute myeloid leukemia
AR	Autosomal recessive
CC	Clinical Center
CT	Computerized Tomography
CLIA	Clinical Laboratory Improvement Amendments
DBA	Diamond-Blackfan Anemia
DC	Dyskeratosis Congenita
ENT	Ear Nose and Throat
FA	Fanconi Anemia
FC	Field Cohort
HPV	Human papillomavirus
IBMFS	Inherited bone marrow failure syndrome
IVS	Intervening syndrome
MDS	Myelodysplastic syndrome
NCI	National Cancer Institute
NIH	National Institutes of Health
SCN	Severe congenital neutropenia
SDS	Shwachman-Diamond Syndrome
TAR	Thrombocytopenia Absent Radii
XLR	X-linked recessive

Glossary of Terms

We have provided a list of definitions of some of the genetic and technical terms that will make this information easier to understand.

For definitions of terms that do not appear on this list, please refer to the online glossary of terms provided in the IBMFS website:

www.marrowfailure.cancer.gov

as well as the glossaries provided for patients by the NCI:

www.cancer.gov/cancertopics/genetics-terms-alphalist

and by the National Human Genome Research Institute:

www.genome.gov/glossary.cfm

Acute myeloid leukemia (AML) - A cancer of white blood cells, characterized by the rapid proliferation of abnormal cells which accumulate in the bone marrow and interfere with the production of normal blood cells.

Affected - An individual in a pedigree or family who has the condition that is being studied.

Allele - One of the variant forms of a gene at a particular locus, or location, on a chromosome. Different alleles produce variation in inherited characteristics such as hair color or blood type. In an individual, one form of the allele (the dominant one) may be expressed more than another form (the recessive one).

Amegakaryocytic - Absence of megakaryocytes. Megakaryocytes are bone marrow cells responsible for the production of platelets necessary for normal blood clotting.

Anemia - A low red blood cell count. Red cells are the cells which carry oxygen from the lungs through the bloodstream to other organs throughout the body.

Aplastic Anemia - A disease in which the bone marrow fails to make all three types of cells which it normally produces. These include red cells, white blood cells and platelets. Aplastic anemia has many causes including exposure to toxic chemicals, certain unusual infections (acquired) and rare genetic abnormalities (inherited).

Autosomal - Refers to any of the chromosomes numbered 1-22 or the genes on chromosomes 1-22. This term excludes the sex-determining chromosomes, X and Y.

Autosomal Dominant - A pattern of Mendelian inheritance whereby an affected individual possesses one copy of a mutant allele and one normal allele. (In contrast, recessive diseases require that the individual have two copies of the mutant allele.) Individuals with autosomal dominant diseases have a 50-50 chance of passing the mutant allele and hence the disorder onto their children.

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Avascular necrosis - A disease that results from the temporary or permanent loss of blood supply to a bone, often the hip or shoulder.

Cancer - Diseases in which abnormal cells divide and grow unchecked. Cancer can spread from its original site to other parts of the body and can also be fatal if not treated adequately.

Carcinoma - Any of the various types of cancerous tumors that form in the epithelial tissues, the tissue forming the outer layer of the body surface and lining the digestive tract and other hollow structures. Examples of this kind of cancer include, breast, lung, and prostate cancer.

Carrier - An individual who possesses one copy of a mutant allele that causes disease only when two copies are present. Although carriers not affected by the disease, two carriers can produce a child who has the disease.

Chromosome - One of the threadlike "packages" of genes and other DNA in the nucleus of a cell. Different kinds of organisms have different numbers of chromosomes. Humans have 23 pairs of chromosomes, 46 in all: 44 autosomes and two sex chromosomes. Each parent contributes one chromosome to each pair, so children get half of their chromosomes from their mothers and half from their fathers.

Clone - To make copies in the laboratory of a specific piece of DNA, usually a gene. When geneticists speak of cloning, they do not mean the process of making genetically identical copies of an entire organism.

Cohort - A cohort is a group of people who participate in a research study in which participants' health is monitored over time.

Cancer screening - Clinical testing designed to identify the presence of a specific cancer in an individual who is thought to be at risk of developing that specific cancer, and who has no symptoms to suggest the presence of cancer. The intent is to find cancers at the earliest possible stage in their development, in order to improve the chances for disease cure.

Complementation group – The subgroup of mutant genes to which a patient with Fanconi Anemia belongs.

Cytogenetics - The study of the structure, function, and abnormalities of human chromosomes.

Deletion - A particular kind of mutation: loss of a piece of DNA from a chromosome. Deletion of a gene or part of a gene can lead to a disease or abnormality.

DNA – Deoxyribonucleic acid, the chemical inside the nucleus of a cell that carries the genetic instructions for making living organisms.

Disease-causing mutation - A gene change or alteration that causes or predisposes an individual to developing a specific disease.

Encoding - The process of transforming information from one format into another.

Enzyme - A protein that encourages a biochemical reaction, usually speeding it up. Organisms could not function if they had no enzymes.

Epidemiology - Study of factors affecting the health and illness of populations.

Familial - A characteristic or trait that occurs with greater frequency in a given family than in the general population. These may have either a genetic or a non-genetic cause.

Family history - The genetic relationships within a family combined with the medical history of individual family members. When represented in diagram form using standardized symbols and terminology, it is usually referred to as a "pedigree" or a "family tree."

Gene - The functional and physical unit of heredity passed from parent to offspring. Genes are pieces of DNA, and most genes contain the information for making a specific protein.

Genetic disorder - Disease that is caused by an abnormality in an individual's DNA.

Genetic counseling - A short-term educational process for individuals and families who have a genetic disease or who are at risk of such a disease. Genetic counseling provides patients with information about their condition and helps them make informed decisions about their medical care.

Gene expression - A process in which the inheritable information in a gene, such as the DNA sequence, is made into a functional gene product, such as RNA or protein.

Genetic marker - An identifiable segment of DNA with enough variation between individuals that its inheritance and co-inheritance with alleles of a given gene can be traced; used in linkage analysis.

Gene penetrance - A term used in genetics describing the proportion of individuals carrying a particular variation of a gene (an allele or genotype) that also express a particular trait (the phenotype). If an allele is highly penetrant, the trait it produces will always or almost always be apparent in an individual carrying the allele. Penetrance is said to be reduced or incomplete when some individuals fail to express the trait, even though they carry the allele.

Genetic predisposition - Increased likelihood or chance of developing a particular disease due to the presence of one or more gene mutations and/or a family history that indicates an increased risk of the disease. Also called genetic susceptibility.

Genetic screening – Laboratory testing of a specific gene for disease-related changes or mutations; it is designed to identify specific individuals in a given population who are at higher risk of having or developing a particular disorder, as a result of carrying an altered gene for that disorder.

Genetic susceptibility - Increased likelihood or chance of developing a particular disease due to the presence of one or more gene mutations and/or a family history that indicates an increased risk of the disease. Also called genetic predisposition.

Inherited - Transmitted through genes from parents to offspring (children).

Leukemia - Cancer of the developing blood cells in the bone marrow. Leukemia leads to overproduction of white blood cells (leukocytes); symptoms usually include anemia, fever, enlarged liver, spleen, and/or lymph nodes.

Leukoplakia (white patches) or erythroplakia (red patches) - Precancerous lesions that develop on the tongue or the inside of the cheek.

Linkage - The tendency for genes or segments of DNA that are located very close to one another along a chromosome to be inherited together.

Linkage analysis - A gene hunting technique that traces patterns of disease in high-risk families, by identifying genetic markers of known chromosomal location that are inherited along with the trait or disease of interest.

Mutation - A permanent change in the usual DNA sequence within a particular gene. Mutations can be harmful (that is, they may increase the risk of disease), beneficial (they may protect against developing disease), or neutral (they have no effect one way or the other on disease risk).

Myelodysplastic syndrome (MDS) – A disorder of the bone marrow characterized by ineffective production of blood cells and varying risks of transformation to acute myeloid leukemia.

Neutropenia - Neutrophils are a particular kind of white blood cell. They are a very important part of the body's defense against bacterial infection. If the neutrophil count in the blood is lower than normal, the patient is said to have "Neutropenia."

Pedigree - A simplified diagram of a family's genealogy that shows family members' relationships to each other and how a particular trait or disease has been inherited.

Phenotype - The observable physical or laboratory characteristics in an individual that result from the expression of a gene or set of genes; the clinical presentation of an individual with a particular genetic background.

Platelets - Platelets are the cells which help the blood to clot. They are made in the bone marrow, and circulate through the body in the bloodstream, where they are carried to sites of injury.

Preimplantation genetic diagnosis (PGD) - A technique used to identify genetic defects in embryos created through in vitro fertilization (IVF) before transferring them into the uterus. Because only unaffected embryos are transferred to the uterus for implantation, PGD provides an alternative to

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current postconception diagnostic procedures, i.e., amniocentesis or chorionic villus sampling, which are frequently followed by pregnancy termination if results are unfavorable. PGD is performed in conjunction with IVF.

Recessive - A genetic disorder that appears only in patients who have received two copies of a mutant gene, one from each parent.

Ribosomes - Complexes of RNA and protein that are found in all cells.

RNA – Ribonucleic acid, the chemical that carries information from DNA to protein.

Susceptibility gene - A germline mutation that increases an individual's susceptibility or predisposition to a certain disease or disorder. When such a mutation is inherited, development of the illness is more likely, but not certain. Also called a predisposing mutation.

Syndrome - The group or recognizable pattern of symptoms or abnormalities that indicate a particular trait or disease.

Telomere - A region of repetitive DNA at the ends of chromosomes, which protect the ends of the chromosomes from destruction.

Thrombocytopenia -The technical term for a low platelet count.

Unaffected - An individual who does not have the condition or disease occurring in his or her family.

White blood cells - White blood cells are part of the body's immune system. They play an important role in fighting off infection and cancer. There are several different varieties of white cells, including neutrophils, lymphocytes, eosinophils and basophils.

X-Linked (or sex linked) - Located on the X chromosome. X-linked (or sex-linked) diseases are generally seen only in males. ❖

We would once again like to express our profound gratitude and deepest appreciation to all of you. Without your participation, this study would not be possible.

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