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PEARLS OF LABORATORY MEDICINE

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TITLE: Chromosome Instability Syndromes

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Slide 1:

My name is Jude Abadie, and I am the Chief and Medical Director of the core laboratory and Chief of Molecular Diagnostics at Brook Army Medical Center in San Antonio, TX. This Pearl of Laboratory Medicine will focus on salient characteristics of seven chromosome instability syndromes.

Slide 2:

Chromosome instability syndromes (CINs) can be generally characterized as a group of autosomal recessive, inherited conditions that are associated with failures in molecular repair mechanisms that normally correct chromosomal damage. Phenotypic characteristics are generally associated with small stature but very little if any intellectual disability. Because of the unrepaired damage to chromosomes, CINs eventually present with a variety of malignancies.

Slide 3:

The CINs reviewed in this Pearl include Fanconi anemia (FA), Bloom syndrome (BLS), Ataxia telangiectasia (A-T), Nijmegen breakage syndrome (NBS), Immunodeficiency, Centromere instability, & Facial anomalies syndrome (ICFS), Werner syndrome (WS), Rothmund-Thompson syndrome (RTS).

Slide 4:

FA can present with a diverse group of phenotypic conditions that include non-specific Café au lait spots, small stature with microcephaly, and more commonly urogenital abnormalities that is associated with renal agenesis. Skeletal malformations such as absent radii and hypoplastic thumbs are two

characteristic features of FA. Malignancies associated with FA include gastrointestinal, gynecologic, and skin carcinomas. Pituitary and thyroid endocrine changes are usually present in FA. Androgen therapy that is used to prevent bone marrow failure in FA patient often leads to hepatocellular carcinoma. In addition to thrombocytopenia and myelodysplasia that can lead to failure of bone marrow, acute myelocytic leukemia is another hematological malignancy common in FA patients.

Slide 5:

The figure illustrated in this slide shows the FA complex of proteins involved in mechanisms that repair breaks in double-stranded DNA. FA can result in mutations in any of the genes that code for any one of these proteins within the complex. All of these are autosomal recessive with the exception of FANCB, which is X-linked. About 70% of FA cases are associated with one of more than 85 pathogenic variants currently identified in the FANCA gene. As presented in the previous slide, patients with FA have > 95% risk for a hematologic abnormality by 40 years old that accompanies an 80% mortality rate at this time.

Slide 6:

This slide illustrates chromosome and limb characteristics in patients with FA. In the cytogenetic study, chromosome breakage is apparent. This results in triradials and quadriradials are indicted by the arrows. Absent radii and hypoplastic thumbs are evident in the photos and x-ray images.

Slide 7:

Phenotypic manifestations of Bloom syndrome (BLS) include a small but proportionate body with microcephaly. Young children can present with telangiectasias on sun-exposed skin, especially the face. BLS patients typically have a high-pitched voice, low to average intellectual ability, and generalized immunodeficiency. Because of chromosome instability and damage, patients with BLS are predisposed to an early onset of multiple cancers that include leukemia, lymphoma, gastrointestinal adenocarcinoma, genital-urinary tumors, breast and respiratory cancers, sarcomas, and rarely Wilms tumor. Hematologic surveillance in children with BLS is not recommended, and half of the standard chemotherapy does are used. Characteristic damage to chromosomes is evident cytogenetically as high rates of sister chromatid exchange rates. Chromosomal damage usually limits chemotherapy doses for malignancies.

Slide 8:

BLS is an autosomal recessive condition. One founder mutation in the Ashkenazi Jewish population a 6-base pair deletion and a 7-base pair nucleotide insertion in the BLM gene on chromosome 15 at at 15q26.1. Numerous premature truncating mutations with nonsense mediated decay have also been implicated and support a loss-of-function genetic model. The image on the left is normal, while the image on the right shows the fragmented appearance due to the high rate of sister chromatid exchanges. Alternate staining patterns can show many quadriradial configurations in cytogenetic studies.

Slide 9:

Phenotypic features of ataxia telangiectasia (A-T) usually present in toddlers. They present as gait disturbances, excessive drooling, and elevated levels of hepatic alpha-fetoprotein. Telangiectasias usually appear in the whites of the eyes by age 8 years as illustrated in the left figure. Progressive cerebellar degeneration with Purkinje cell depletion leads to dystonia with tremors and myoclonic movements. The atrophic cerebellum (red arrows in the figure) of an A-T patient can be appreciated when comparing to a non- A-T individual (Black arrow). Immunodeficiency is associated with low levels of immunoglobulins and T-cells. Telomeric shortening can be appreciated through specific molecular diagnostic assays. Patients with A-T usually die from pulmonary infections or cancer before their mid-20s, and autopsy findings include an embryonic-like thymus, neurofibrillary tangles, and neuronal lipofucin pigments.

Slide 10:

A-T is an autosomal recessive condition with more than 400 pathogenic truncating or splice site mutations. The ATM gene is located on chromosome 11 at 11q22 codes for a serine/threonine protein kinase that is normally activated by double stranded breaks in DNA. Activation of the ATM gene phosphorylates proteins that regulate cell-cycle check points that normally initiate repair and/or apoptosis in cells with damaged DNA. ATM mutations lead to immunodeficiency, leukemia, and/or lymphoma and is cytogenetically associated with subsequent translocations between chromosomes 7 and 14 as illustrated in the examples on this slide.

Slide 11:

Nijmegen breakage syndrome (NBS) is another rare genetic chromosome instability disorder. NBS is associated with short stature, progressive microcephaly, beaked nose, and micrognathia as illustrated in the photos of the same individual in infancy and adulthood. Intellectual disability

is evident by 3-years old and is often progressive. NBS is also associated with primary amenorrhea, infertility, immunodeficiency, and about 50 times increased cancer risk when compared to the general population. Common malignancies include non-Hodgkin's lymphoma, gliomas, and rhabdomyosarcomas.

Slide 12:

NBS is an autosomal recessive condition caused by mutations in the NBS1 gene at 8q21, disrupting the structure of the nibrin protein that is normally responsible for DNA repair processes. NBS has been reported to be more common in individuals of Polish (or Slavic) ancestry). Non-functional nibrin leads to decreased immune cell proliferation, spontaneous chromosome breakage and fusion (arrows in the figure) as well as tetraploidy that is evident in bone marrow cells.

Slide 13:

Immunodeficiency, Centromere instability, & Facial anomalies Syndrome (ICFS) is often cytogenetically associated with rearrangements in chromosomes 1, 9, and 16, with typical "star-burst" chromosome appearances as illustrated in the figure. Patients with ICFS have flattened, dysmorphic facial features, small birth weight, hypotonia, and recurrent infections due to immunoglobulin deficiencies. The genetic lesion is due to a mutation in the DNA methyltransferase gene, DNMT3B, leading to epigenetic hypomethylation.

Slide 14:

Werner syndrome (WS) is a chromosome instability syndrome usually first associated with a growth failure at puberty and accelerating age changes starting in the mid-20s. Phenotypic features include hair graying, hair loss, voice hoarsening, sclerotic/ulcerating skin with sclerodermic changes that can lead to gangrene, bird-like dysmorphic facial features, cataracts, atherosclerosis, osteoporosis, diabetes, and lipodystrophy. Multiple forms of cancer begin in the early 40s, and life-expectancy is rarely beyond 50 years. Patients may appear to be in their 80s or 90s when they are chronologically 50 years old. The man in the picture illustrated on this slide was 37-years old at the time of this photo.

Slide 15:

WS is an autosomal recessive condition caused by a mutation in RECQL2 at 8p12 that codes for the wernin protein (WRNp). WRNp resembles a RecQ helicase that normally functions to replicate DNA, protect against oxidative damage in the aging process, and repair DNA damage. Altered WRNp is unable to be transported to the nucleus, which allows the accumulation of DNA damage typically seen in age-associated methylation processes. These increased rates of DNA methylation and epigenetic changes has been described as a hypothetical molecular biomarker known as the “epigenetic clock”. Multiple cancers usually are detected by the time the individual with Werner Syndrome is 40 years old, and life- expectancy is in the mid-50s.

Slide 16:

Rothmund Thompson syndromes is a chromosomal instability syndrome that shares some phenotypic and molecular genetic features with WS. RTS is associated with poikiloderma skin changes, premature aging, skin atrophy, telangiectasia, sparse hair, dental and hair abnormalities, gastrointestinal disorders, cataracts, absent or malformed bones with osteoporosis, and radial ray bone malformations. Osteosarcomas are common in childhood as are basal and squamous cell skin cancers. RTS is an autosomal recessive condition caused by a mutation in RECQL4, a DNA helicase at 8q. Many documented cases of RTS identify compound heterozygous point mutations in the DNA helicase.

Slide 17:

In summary, chromosome breakage syndromes are a group of mostly autosomal recessive inherited conditions that present with failures to repair breaks in chromosomes. Patients with chromosome breakage syndromes usually do not have intellectual and developmental delays, but they do have dysmorphic facial features, numerous cancers, and skeletal malformations. Characteristic cytogenetic findings are often associated with the numerous and various malignancies seen these patients.

Slide 18: References

These references summarize many of the salient characteristics discussed in this presentation.

Slide 19: Disclosures

I have no disclosures or conflicts of interest.

Slide 20: Thank You from www.TraineeCouncil.org

Thank you for your time and attention to this Pearl of Laboratory Medicine on Chromosome Instability Syndromes.