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Bone Fragility Disorders Related to Mendelian Inheritance

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Abstract: ***Genetics is a discipline of study that can be traced back to Gregor Johann Mendel, making it unique among other fields. Mendel's investigations led to the discovery of three inheritance rules, now known as Mendel's rules of inheritance or Mendelism. The bone is unique among structural materials in that it can self-repair and modify its properties and configuration in reaction to changes. It also contains four types of cells: osteoblasts, bone lining cells, osteocytes, and osteoclasts. This study examines bone fragility illnesses linked to Mendelian inheritance. We briefly cover illnesses such as osteoporosis, osteopetrosis, osteogenesis imperfecta, and current results. Investigating Mendelian laws led to a better understanding of inherited bone fragility syndromes. Bone fragility is a pathological condition characterized by changed mineralized bone mass and degradation of bone tissue, leading to reduced bone strength and increased fracture risk, even without high-impact trauma. Primary osteoporosis is the leading cause of bone fragility in the older population. Bone fragility can occur at any age due to congenital uncommon bone metabolic illnesses caused by inherited genetic defects that disrupt proper bone structure.***

Keywords: ***Mendel, inheritance. bone, fragility, osteoporosis, osteogenesis imperfecta, osteopetrosis, genetics, cells, factors, dominance, segregation, alleles, traits, fractures, bone density, diagnosis, pathological, congenital, research***

I. INTRODUCTION

The mid-nineteenth century saw significant progress in the knowledge of inheritance [1]. Gregor Mendel conducted seven years of hybridization studies on garden peas (1856-1863) and suggested inheritance rules in living creatures [1]. He discovered the desired plant in the common pea (Pisum sativum) [2]. Pisum is a hardy annual that is prolific and easy to work. Additionally, it has the advantage of preventing cross-pollination by insects that typically visit flowers [2].



Fig: Gregor Johann Mendel

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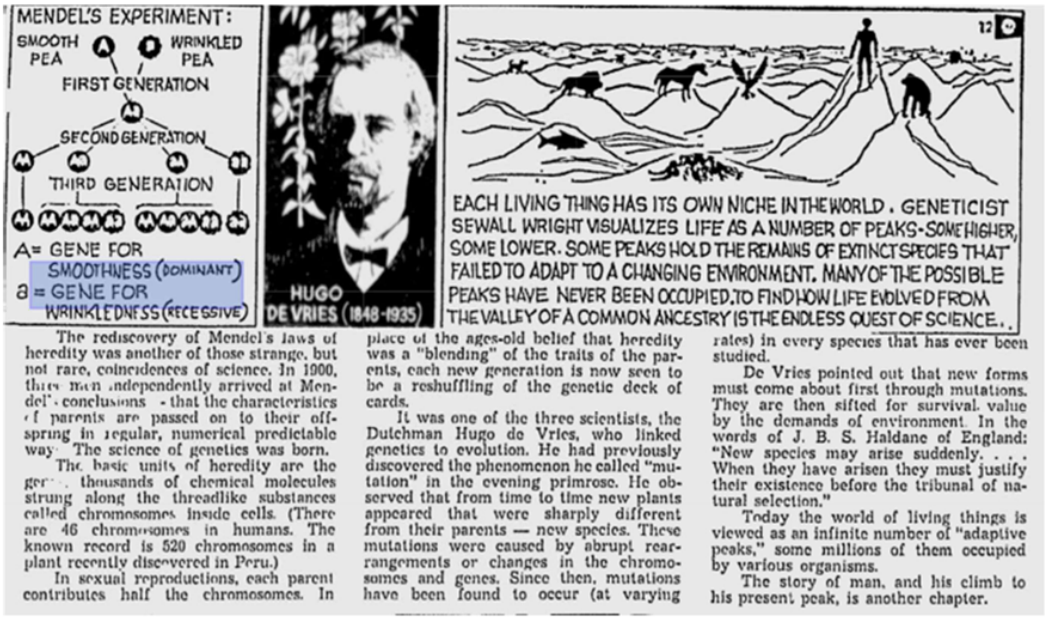


Fig: Newspaper: THE GADSDEN TIMES, Saturday, October 29, 1960, Page 3

A. Law of Dominance

The first law is the law of uniformity and dominance. The first law of heredity to be proposed from Mendel's works is the law of dominance [3]. According to the rules, each of a person's characteristics is governed by unique units known as factors that appear in pairs [3]. One of the factors dominate the other in heterozygous couples, which can be either homozygous or heterozygous [3].

(i) Discrete units known as factors govern characters [1].

(ii) Pairs of factors exist [1].

(iii) When two factors are distinct, one of them is dominant (dominant) and the other is recessive [1].

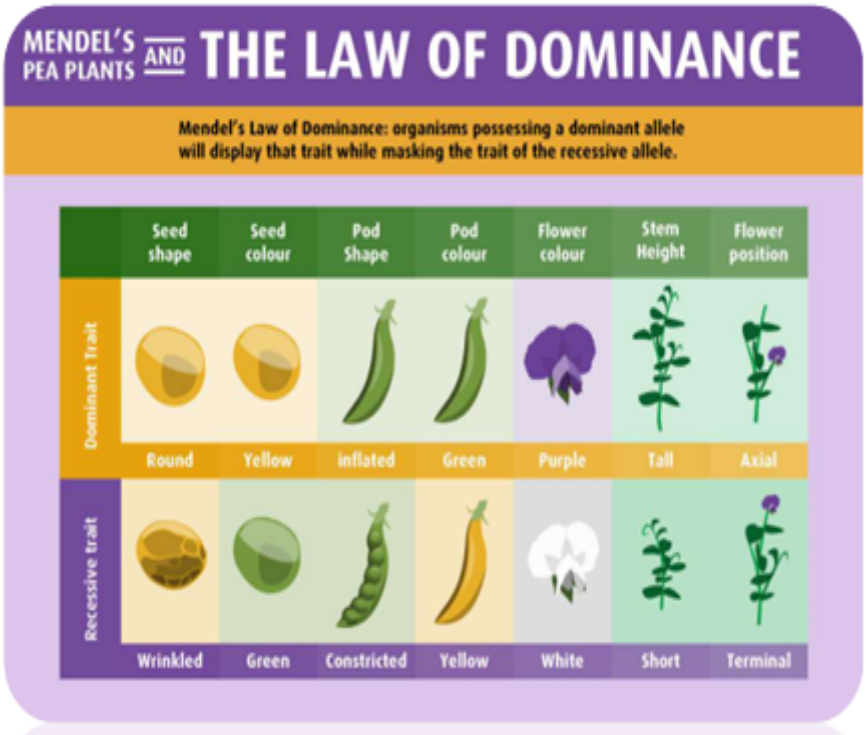


Fig: Characters and traits for dominant and recessive traits

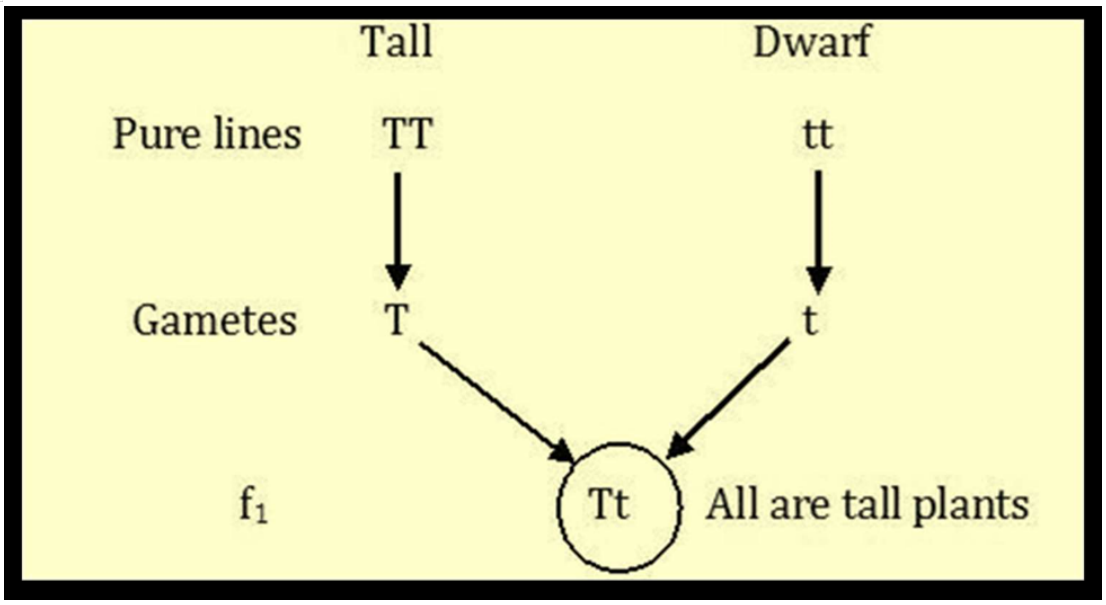


Fig: Picture represents dominating property of TT over tt to give offspring as Tt

B. The Law of Segregation, or the Second Law

When two individuals who are heterozygous for a certain characteristic are crossed, such as in F1-generation hybrids, the Law of Segregation of Genes is applicable [4]. The F2-generation's children vary in genotype and phenotype in order for the grandparents' traits (P-generation) to recur frequently [4]. Half of heterozygous individuals in a dominant-recessive inheritance are homozygous for the dominant trait, 25% are homozygous for the recessive trait and hence express the recessive trait in the phenotype, and 25% are homozygous for the dominant trait [4]. Mendel came up with the concept of hereditary "factors" or components of heredity [4]. Mendel discovered that differences in inherited traits can be explained by different types of components, which are today referred to as genes [4]. For instance, there are two variations of the gene for bloom color in pea plants: one for purple and one for white [4]. For instance, pea plants have two different versions of the gene that determines seed color [5]. One allele or form is responsible for the yellow seed color (Y), while another is responsible for the green seed color (y) [5]. The allele for green seed color is recessive in this instance, while the allele for yellow seed color is dominant [5]. The dominant allele trait manifests and the recessive allele trait is concealed when a pair of alleles diverge (heterozygous) [5]. (YY) or (Yy) genotype seeds are yellow, whereas (yy) genotype seeds are green [5].

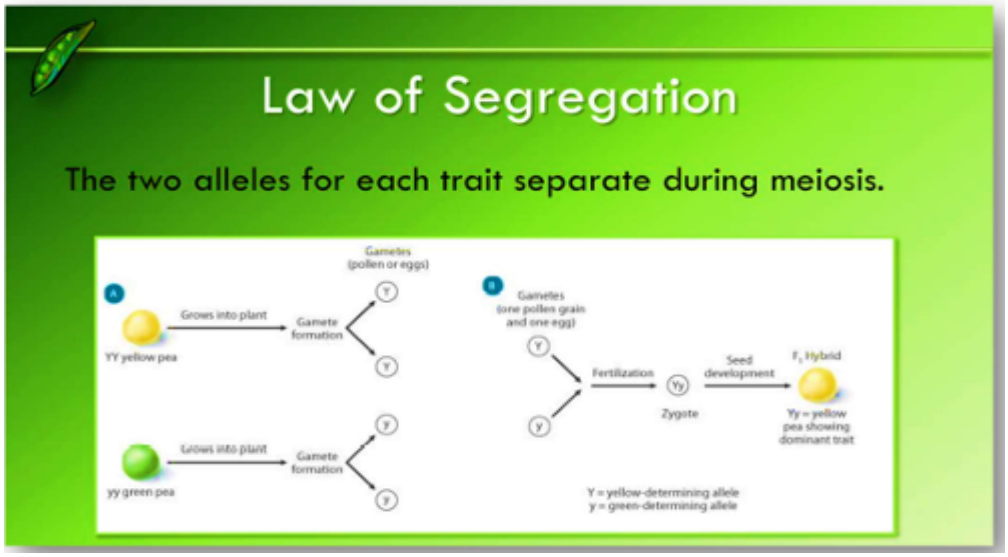


Fig: Mendel's Law of Segregation explained using dominant yellow pwa and recessive green pea

II. BONE FRAGILITY DISORDERS

A. *Osteogenesis* Imperfecta (OI)

Patients with osteogenesis imperfecta (OI) frequently experience recurrent fractures of the limbs and vertebrae [6]. Brittle bone disease, another name for OI, is a hereditary connective tissue illness with significant clinical and genetic variability [6]. With an incidence of one in 10,000–20,000 newborns, OI is an uncommon condition [6]. Low bone mass and increased bone mineralization density are characteristics of OI from the standpoint of bone material, leading to brittleness, frequent fractures, skeletal abnormalities, and extra-skeletal symptoms [6]. These latter include cranial abnormalities (such as basilar invagination), pulmonary hypoplasia with decreased lung capacity in severe cases, blue sclerae, dentinogenesis imperfecta, joint laxity, and hearing loss [7]. Mobility impairment ranges from minor to severe, depending on the clinical severity. Although fractures are more common in children, the risk of fractures increases throughout life [7]. Genetic variations linked to monogenic bone fragility disorders frequently have effects that are orders of magnitude greater than those found by genome-wide association studies (GWAS) [8]. Only in adulthood or never at all can people with moderate types of heritable bone fragility experience fractures [8]. However, the majority of knowledge regarding monogenic bone fragility disorders comes from pediatric research, and these problems typically appear in childhood [8].

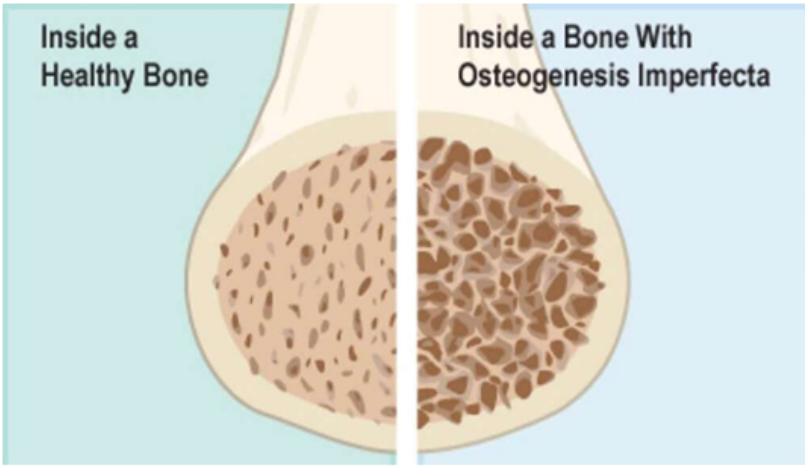


Fig: Difference between Healthy bone and bone affected by Osteogenesis Imperfecta

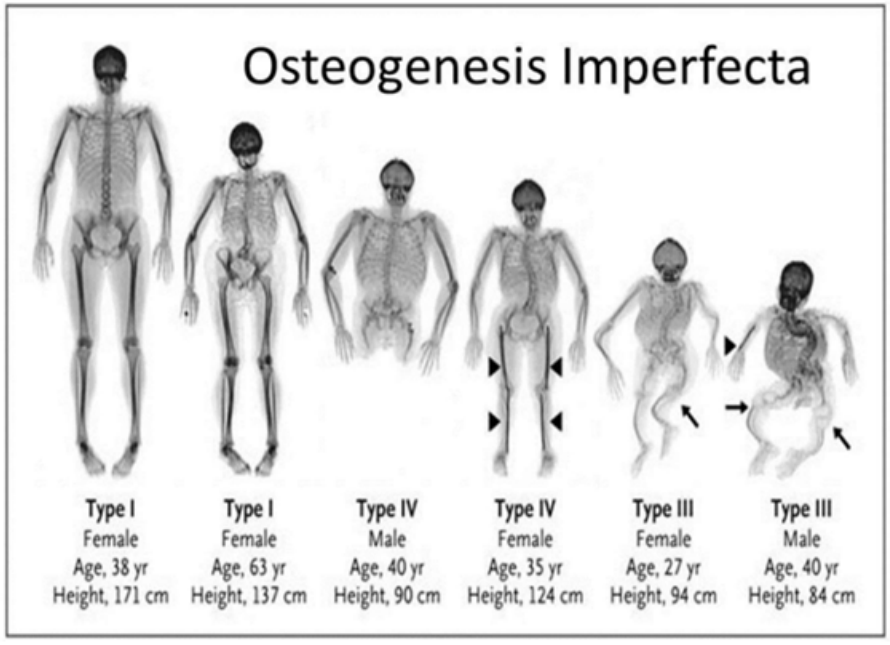


Fig: Six different types of Osteogenesis Imperfecta seen in varied age groups

B. Osteoporosis

In order to get the best possible care of this complex condition, a multidisciplinary approach is necessary [9]. Bone mineral density (BMD) with a T-score 2.5 standard deviations below the peak mean bone mass of young, healthy adults is considered osteoporosis by the World Health Organization [9]. Men and patients of all ages and races are susceptible to osteoporosis, a widespread bone ailment that primarily affects menopausal women [10]. The reduced bone mass accompanied with deterioration of the bone's microarchitecture and a higher propensity to fracture [10]. Vertebral fractures, femoral neck fractures, distal radius fractures, and sub capital humeral fractures are common osteoporotic fractures [10]. It is believed that these fractures are insufficiency fractures [10]. Idiopathic osteoporosis of the elderly is the most prevalent clinical cause of bone fragility [10]. The primary cause of increasing loss of bone mass is aging, which works in concert with exogenous (diet and lifestyle) and endogenous (genetic and epigenetic markers) risk factors that already exist [10]. The clinical endpoint of this pathological condition is fragility fractures, which are most common at the wrists, vertebrae, and proximal femur but can also occur at the ribs and humerus [10]. Furthermore, bone fragility can appear at any age due to a variety of uncommon congenital metabolic bone disorders, where the inherited genetic deficiency impairs proper bone tissue modeling and remodeling, resulting in fragility fractures and bone abnormalities [10]. Despite progress in understanding the pathogenesis and developing diagnostic techniques, identifying patients with elevated fracture risk remains a challenging aim [11].

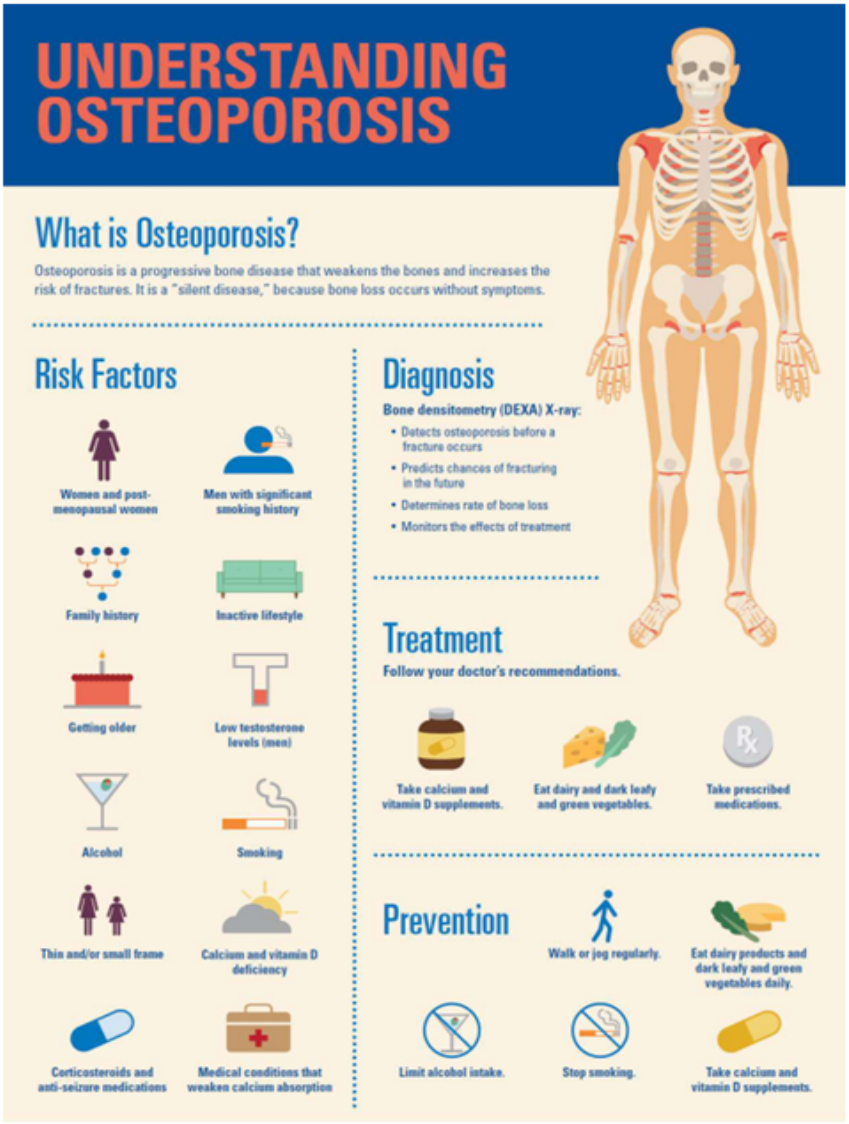


Fig: Definition, prevention, risk factors, diagnosis and treatment for osteoporosis

Recent Osteoporosis Research: New Device

The University Hospitals of Geneva (HUG) and the University of Geneva (UNIGE) have been praised for the recent discovery of a bone fragility diagnostic gadget that has been approved for marketing in the European Economic Area and Switzerland [12]. The gadget is based on a novel way to evaluate bone quality via blood sampling [12]. This test is more specific than current approaches, leading to improved diagnosis and advancement of osteoporosis treatments [12]. Diagnosing bone fragility before a fracture is crucial since it can cause significant chronic pain and increase the risk of mortality, depending on age and bone type [12]. This idea is based on the periosteum, a membrane that supports bone growth and repair [12]. It secretes periostin, a protein that regulates bone diameter and strength [12]. A matricellular protein called periostin is mostly expressed by bone's osteocytes and periosteal cells, although it is also found in a number of other tissues [13]. The specificity of the antibodies used in the available immunoassays is unknown [13].



Fig: Periostin seen in human bone

It is broken down by the cathepsin K enzyme during the bone resorption process [13]. Bone fragility is reflected by the digested periostin fragment, known as k-POSTN, which is also present in the blood [13]. This fragment is of relevance because it is bone specific, in contrast to whole periostin, which has long been recognized by scientists but can also be elevated in cancer and cardiovascular illnesses [13].An ELISA test, a commonly used technique for measuring molecules in a biological sample, is utilized in the lab to determine the amount of k-POSTN after a blood sample has been drawn [13]. Health care providers may be able to use the new tool to monitor and identify patients with various bone-weakening conditions as well as those who are most at risk of osteoporotic fractures [13]. The imaging method now used to evaluate bone fragility, bone densitometry, is meant to be supplemented by this instrument [13]. Diabetes-related weight and fat mass increases make it difficult to evaluate bone mineral density, which may seem normal despite the presence of weak bone tissue [12].

C. Osteopetrosis

Another name for osteopetrosis is "Marble bone disease" [14]. The alternative names include "Albers-Schonberg disease" and "Brittle bone disease," which are named for the German radiologist who is credited with describing the disorder for the first time in 1904 [14]. Osteopetrosis literally translates to "stony bone" and is derived from the Greek words "Osteon," which means bone, and "Petros," which means stone [14]. Autosomal recessive osteopetrosis (ARO), sometimes referred to as malignant infantile osteopetrosis, is one type of osteopetrosis [15]. Malignant infantile osteopetrosis, which is identified at birth or in the early stages of infancy, exhibits the most severe symptoms [16]. The majority of variants of autosomal recessive osteopetrosis (ARO), a genetically and phenotypically diverse disease, are caused by late endosomal trafficking abnormalities that inhibit the creation of osteoclast ruffled borders [15]. Generalized bone sclerosis and osteopetrosis are characterized by thickening of the cortical bones; the increased bone mass obliterates bone marrow space and results in hematopoietic insufficiency [17]. Additionally, it may result in nerve entrapment syndromes, cranial nerve palsies, and irregular tooth eruption [17]. The most severe types of these disorders are autosomal recessive, while they can also be inherited as dominant, X-linked, or autosomal recessive features [17]. Although hematopoietic stem cell transplantation is used for the most severe forms linked to bone marrow failure and now gives the highest chance of longer-term survival in this group, the majority of osteopetrotic disorders are treated symptomatically [17].

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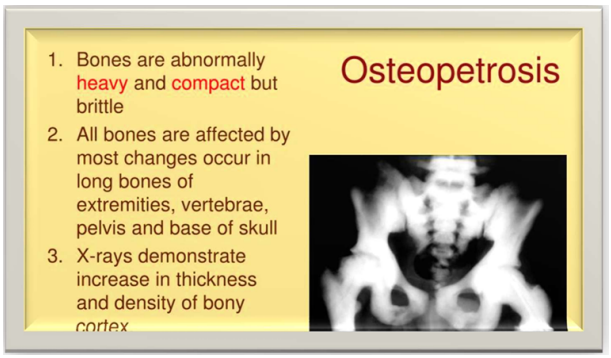


Fig: Image shows points regarding osteopetrosis and an X-ray image of an Osteopetrosis patient

NEW RESULTS CONNECTED TO OSTEOPETROSIS: GENETICS' PART IN OSTEOPETROSIS

Autosomal dominant, autosomal recessive, and X-linked inheritance patterns are among the several patterns of inheritance for osteopetrosis, a monogenic disorder [18]. The range of molecular abnormalities causing osteopetrosis has been further broadened by recent reports of novel mutations in recognized genes as well as problems in unknown genes [18]. There is significant genotypic and phenotypic variability in human osteopetrosis [18]. A less severe type of ARO is called Intermediate Autosomal Recessive Osteopetrosis (IARO) [19]. Individuals with IARO exhibit hepatosplenomegaly, mandibular prognathism, sporadic osteomyelitis, and a propensity for fractures [20].

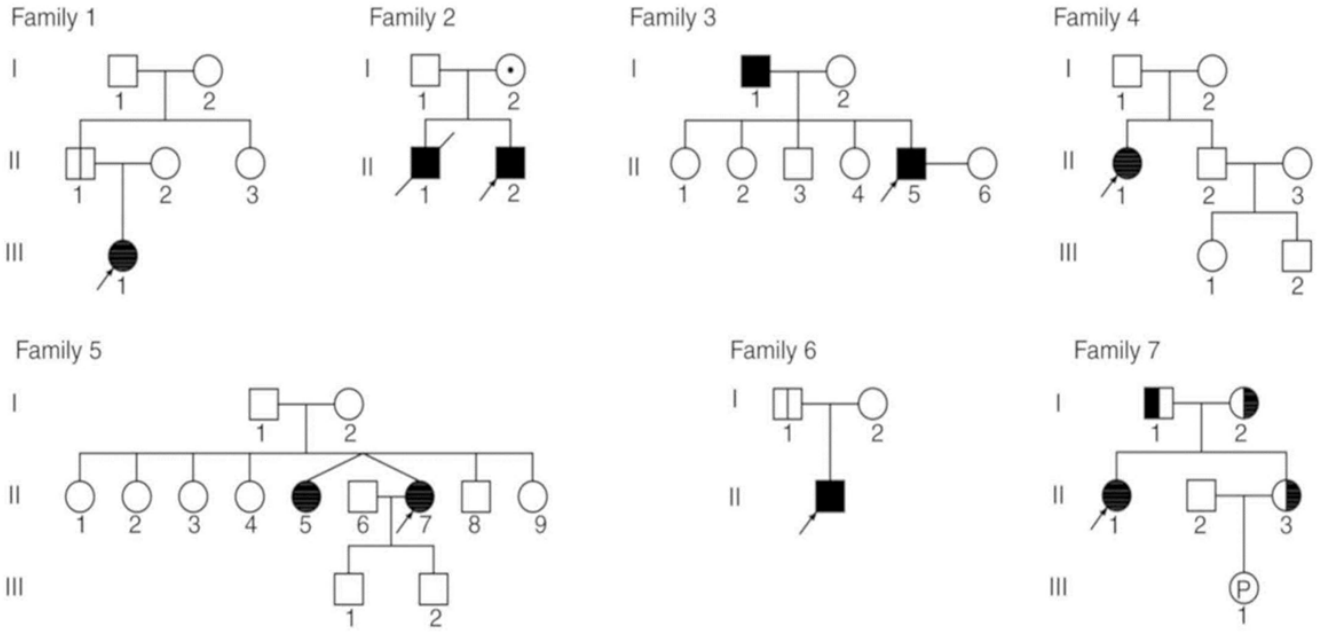


Fig: Pedigree analysis of seven osteoporotic families. Males are represented by squares, and females by circles.

Patients with osteopetrosis are indicated by filled black shapes. ADO-II non-penetrant carriers are indicated by shapes with a trunk line. Obligate carriers of IARO are indicated by shapes with a dot. Obligatory carriers with various heterozygous mutations are represented by half-black forms. P stands for subjects who are pregnant. Deceased subjects are represented by diagonal lines

III. CONCLUSION

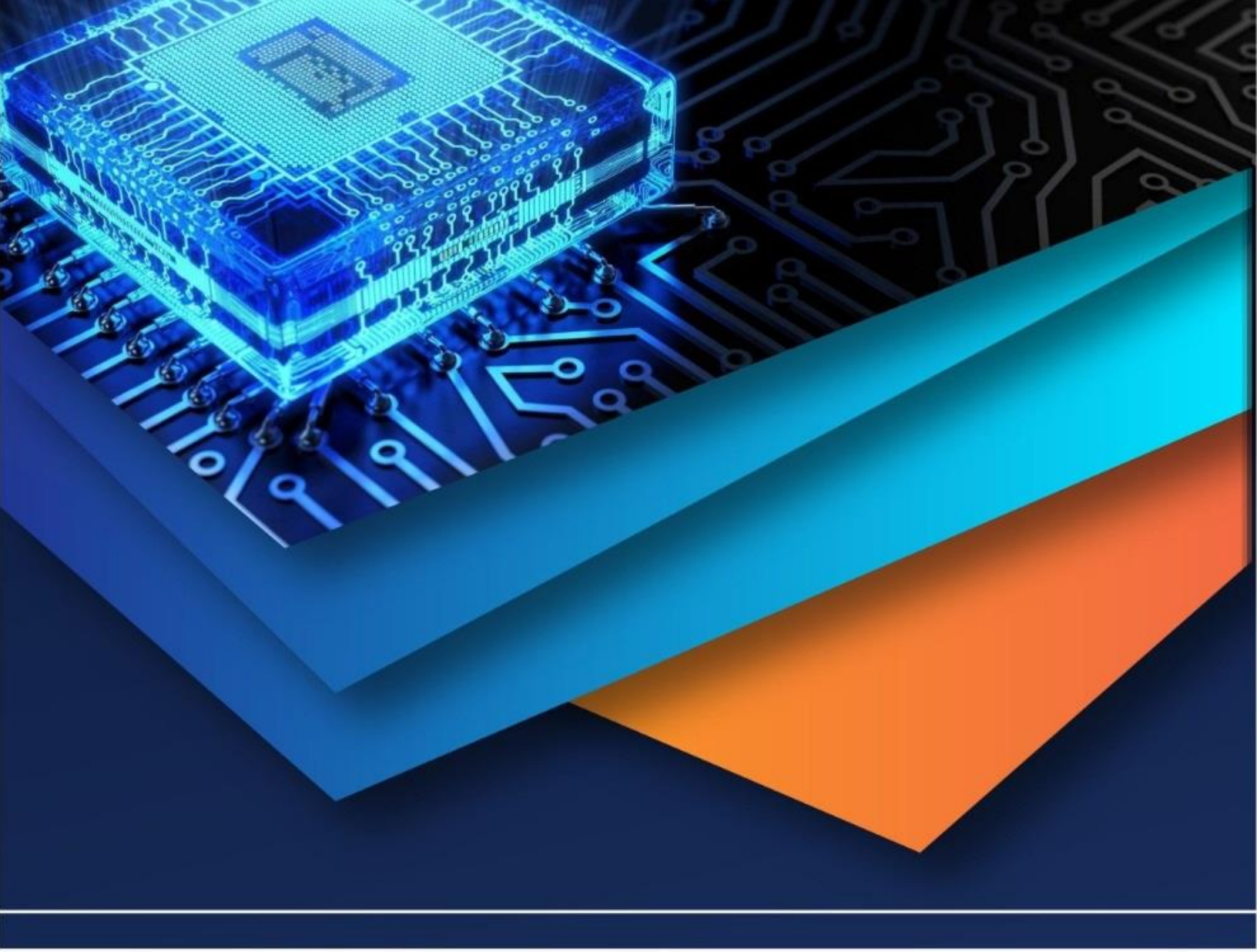
Known as the "Father of Genetics," Gregor Johann Mendel, an Austrian monk, was the first to finish experiments and study heredity for any reason (1822-1884). He provided the two well-known laws of inheritance, the Law of Segregation and the Law of

Dominance. Important bodily processes like movement, storing calcium and phosphate, and housing bone marrow are all facilitated by the human bone.

Although bone appears to be inert, it is actually a dynamic organ that is constantly being reabsorbed by osteoclasts and renewed by osteoblasts. Although inheritance varies among diseases, the bone disorders under discussion are linked to mendelism. In rare instances, they may follow X-linked patterns, or they may be autosomal dominant or autosomal recessive. This paper accessed all routes wherein mendelian inheritance and roles of Mendel's laws contributed to similar characteristics in bone fragility disorders like osteoporosis and osteopetrosis.

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