Introduction to the Summary of Scientific Evidence:

Osteoporosis is a major public health threat in the U.S. and worldwide. It affects approximately 10 million Americans, with an additional 34 million at risk. Women are more frequently affected with a prevalence rate of 55% after the age of 50 (1-3). Osteoporosis is a disease of the skeletal system and is characterized by reduced bone mass and structural deterioration of bone tissue. These conditions cause bones to become fragile and more likely to break.

One common type of broken bones occurs in the spine and is called vertebral or spinal fracture (4). Spine fractures may cause back pain, disabilities, kyphosis or stooped posture, and loss of height. They are associated with much higher risk of subsequent fractures and can lead to increased risk of death.

Since osteoporosis can progress painlessly until a bone breaks, it is very challenging for disease management. Knowing one’s risk for developing the disease will help adoption of appropriate measures to prevent onset or progression of the disease. Both genetic and environmental factors contribute to osteoporosis. Despite the fact that we are all exposed to similar environmental factors, not everyone has fragile or broken bones. This could be attributed to individual genetic differences.

Genetics determines not only an individual’s susceptibility to osteoporosis but also possibly the individual’s response to (preventative) treatment. There have been multiple reports that describe...
the heritability of osteoporosis and also utilize genetic studies to identify gene variations associated with osteoporosis. These studies have identified a small number of single nucleotide polymorphisms (SNPs) that are associated with clinical manifestation of osteoporosis.

Interleukin Genetics has developed a genetic test panel in the area of Bone Health (BH), which includes the genes that are associated with increased risk for low bone mass or spine fracture. The genes were selected based on the results from numerous clinical studies, including one large study that Interleukin Genetics conducted in collaboration with leading academic institutions (5).

**Process Used to Develop the Bone Health Genetic Test Panel:**

1. A team of experts at Interleukin Genetics identified genes that either were associated with osteoporosis-related conditions, such as low bone mass and bone fractures, or had a documented role in bone turnover, which underlies the development of osteoporosis. These genes included interleukin 1 (IL1) cluster, estrogen receptor 1 (ESR1), and vitamin D receptor (VDR). These three genes are in metabolic pathways known to influence bone metabolism (mineralization and inflammation).

2. Interleukin Genetics sponsored a large 2355-person clinical study to identify or validate genetic association between osteoporosis and candidate genes.

3. Variations in each of the three genes were determined to be associated with osteoporosis-related conditions. Two of these gene variations are associated with increased risk for spine fracture. The other variation is associated with increased risk for low bone mass (low mineralization).

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The Bone Health test panel genes and variants include:

a. Interleukin 1 beta (IL1B) rs16944 (C/T)
b. Vitamin D receptor (VDR) rs1544410 (A/G)
c. Estrogen receptor 1 (ESR1) rs9340799 (A/G)

The Bone Health test panel is designed to assess the risk for osteoporosis and assist with prevention of this disease by guiding diet and exercise programs based on genetic differences. Following are summaries of scientific evidence for each of the polymorphisms included in the Bone Health Genetic Test.

**Interleukin 1 beta (IL1B) rs16944 (C/T) Polymorphism:**

IL1B gene encodes the interleukin-1 beta (IL-1β) member of the IL-1 family of cytokines, which are major regulators of inflammation and have been implicated in osteoporosis. IL1 family members are key regulators of bone turnover, which is critical to the overall health of the bone (6-8). A polymorphism in the promoter region of IL1B gene (IL1B rs16944 (C/T) or IL1B (-511)) was found to be associated with increased risk for spine fracture in a large clinical study conducted by Interleukin Genetics in collaboration with a major University (5). Carriers of T/T genotype of this IL1B polymorphism have 44% increased risk for spine fracture as compared to non-carriers. Consistent with this result, Nemetz, et al (9) found that carriers of allele T of the IL1B (-511) polymorphism had significantly lower bone mass as measured by bone mineral density (BMD) at the lumbar spine and femoral neck. The association of allele T of this IL1B (-511) polymorphism with increased risk for osteoporosis-related conditions is likely due to chronic hyper-inflammation. This allele is associated with increased transcriptional activity of the IL1B gene promoter (10). In addition, a haplotype defined by IL1B (-511) and 3 other SNPs is associated with increased levels of serum IL1B protein and C-reactive protein (11), an inflammatory biomarker.
Vitamin D receptor (VDR) rs1544410 (A/G) Polymorphism:

Vitamin D receptor is important for bone health, as it regulates calcium absorption and mineralization of bone matrix. Association between common variants of VDR gene and osteoporosis has been well-documented. About 180 SNPs have been identified in the human VDR gene. Among these SNPs, the VDR rs1544410 (A/G) is one of the most studied polymorphisms. This SNP was determined to be associated with spine fracture in the large clinical study sponsored by Interleukin Genetics (5). Carriers of allele A of this SNP are predisposed to a higher risk of spine fracture. Compared to individuals who do not carry the allele, carriers of one copy of the allele have 18% increased risk and carriers of two copies of the allele have 136% increased risk. Consistent with this observation, the SNP was also reported to be associated with increased bone turnover and reduced bone mass. For example, Morrison et al. identified an association between this SNP (A/G) and bone turnover, measured by serum osteocalcin levels (12). They subsequently reported that VDR gene variants were a major contributor to the BMD genetic determination and that carriers of allele A of this VDR SNP had lower BMD (13). Although not all studies agree that VDR SNPs are a significant determinant of bone density (14,15), a meta-analysis of 39 studies confirmed the association between the VDR rs1544410 (A/G) SNP and BMD and further showed that this SNP was associated with greater bone loss over time (16). In addition, this SNP influences efficacy of anti-osteoporotic treatments (17), and has recently been shown to influence the positive skeletal response (increased BMD) to Vitamin D3 supplementation in healthy adolescent girls (18).
**Estrogen receptor 1 (ESR1)**

Estrogen receptor 1 (ESR1) plays important roles in regulating bone homeostasis and regulating postmenopausal bone loss. Association between common variants of the ESR1 gene and osteoporosis has been well documented. The SNP rs9340799 (A/G) is located in intron 1 of the ESR1 gene and is one of the major polymorphisms associated with osteoporosis. This SNP was associated with low BMD in a large clinical study sponsored by Interleukin Genetics (5). Carriers of allele A of this SNP are predisposed to a higher risk for low BMD. Compared to individuals who do not carry the allele, carriers of one copy of the allele have 26% increased risk and carriers of two copies of the allele have 152% increased risk. Although some studies fail to detect the association between this SNP and BMD (19,20), the association was confirmed in a meta-analysis of 30 studies involving more than 5000 women (21). Consistent with the observation that this SNP is associated with BMD, two meta-analysis studies showed that this SNP was associated with bone fractures (20,21). In addition, a haplotype defined by ESR1 rs9340799 (A/G) and another ESR1 SNP was shown to be associated with increased risk for spine fractures (22).

For more on the science behind genetic testing, visit [InherentHealth.com](http://InherentHealth.com)
References:


