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Osteogenesis Imperfecta

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Human Inherited Diseases

Bio 375

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Introduction

Osteogenesis imperfecta (OI), otherwise known as brittle bone disease, is an inherited disorder that causes varying degrees of bone fragility, and is associated with defects in several tissues rich in type I collagen. It is generally characterized by multiple bone fractures, blue sclerae and possible hearing loss, although considerable variability in the number of fractures and the degree of resulting disability has been observed. Using clinical, radiographic and genetic criteria, the disorder has been classified into four types. Type I is a dominant form that is mild, characterized by blue sclerae, and results in normal life expectancy. Type II is a perinatally lethal form that usually causes patient death in early childhood. Type III is a progressively deforming syndrome with decreased life expectancy, and Type IV is a moderately severe dominant form with normal sclerae and life expectancy (Korkko et al., 1995). Although biochemical and genetic studies provide a sound basis for diagnosis of the different types, even a detailed scheme could never predict correctly the OI in every individual because of the variability of expression. However, despite the differences in severity and certain phenotypic characteristics, all four types of the disease are ultimately caused by defects in the amount or structure of type I collagen, an important part of bone matrix. The incidence of osteogenesis imperfecta in the general population is an estimated 1 in 20,000 infants, and all ethnic and racial groups seem to be similarly affected. Over 200 mutations of various kinds have been detected, and it has been established that over 90% of patients with OI have a mutation in COL1A1 on chromosome 17 and/or COL1A2 on chromosome 7, which are genes that encode type I collagen (Korkko et al., 1995).

Mode of Inheritance

Osteogenesis imperfecta can be inherited in one of three ways. First, although rare recessive inheritance has been documented, the defect is more often inherited in an autosomal dominant pattern from an affected parent. This means that the affected parent, who carries a single gene for the disorder, has a fifty percent chance of having children with the disorder. In these cases, the blue sclerae characteristic shows 100% penetrance and associated hearing loss is age-dependent. Second, the defect may be acquired by a spontaneous mutation occurring in a parent's germ cell line. In such sporadic cases, neither parent is affected, but there seems to be a direct correlation between sporadic mutations and relatively advanced paternal age (Blumsohn, et al., 2001). Finally, the disorder may be acquired through germ line mosaicism. In this mode of inheritance, there are two possibilities: either a portion of a parent's germ cell line carries the mutation or the mutation occurs very early in a somatic cell before the separation to germinal cells and is therefore present both in somatic and germinal cells (Raghunath et al., 1995). It is estimated that about 2 to 7 percent of families with only one affected individual show the phenomenon of mosaicism, and this is a particularly important concept for genetic counseling, which will be discussed at continuation (Zlotogora, 1998).

Molecular Nature of OI

A myriad of structural mutations resulting in osteogenesis imperfecta have been discovered by PCR and verified by consequent DNA sequencing, varying from allele deletions, substitutions and splicing mutations to promoter and enhancer mutations, premature termination and duplications. However, as mentioned, COL1A1 and COL1A2 genes code for type 1 collagen, which is affected in OI patients, and it is in these genes where the majority of mutations are seen. Type I procollagen is a

heterotrimer comprised of two proalpha1 chains and one proalpha2 chain. Chain recognition, association and alignment of proalpha chains into correct registration are thought to occur through interactions between the C-terminal propeptide domains of the three chains. The C-propeptide of each contains a series of cysteine residues, the last four of which form intra-chain disulphide bonds. These residues are important for the folding and assembly of fully functional procollagen (Pace et al., 2001). Triple helix formation is a prerequisite for the passage of type I procollagen from the endoplasmic reticulum and secretion from the cell to extracellular fibrils that will support mineral deposition in bone. If the helical coding regions of the COL1A1 and COL1A2 collagen genes are modified by any number of mutations, type I procollagen alpha chains tend to be post-translationally overmodified, and the extracellular secretion is markedly reduced (Glorieux, 2001). The disruption of just one intra-chain disulphide bond in the propeptide of the proalpha1 chain of type I procollagen permits slow (or non-existent) assembly and secretion of these procollagen trimers, ultimately resulting in a diseased phenotype.

This explains why inheritance of osteogenesis imperfecta is of a dominant pattern: just one altered allele can result in an affected phenotype because two unaffected alleles are needed to produce *all* normal procollagen. Any type of mutation will most likely affect triple helix formation, and consequently, the folding of the collagen product. Also, the severity of the disorder depends on the kind of mutation involved. The most severe variants are caused primarily by single-base substitutions that convert a codon for an obligate glycine in the triple helix of the protein to a codon for an amino acid with a bulkier side chain that distorts the conformation of the triple helix. On the other hand, most mutations in the milder forms of OI cause decreased

expression of proalpha1 chains because of premature-termination codons or RNA-splicing defects in the COL1A1 gene (Pace et al., 2001).

Clinical Symptoms and Prognosis

In addition to being distinguished by multiple bone fractures, blue sclerae and eventual hearing difficulties, osteogenesis imperfecta patients can typically be characterized by a wide variety of symptoms: thin, easily bruised skin, moderate joint hypermobility, kyphoscoliosis, hernias, mitral valve prolapse, aortic valvular insufficiency and/or larger than normal aortic root diameter (Glorieux, 1998). Further complications may include: recurrent pneumonia, heart failure, brain damage due to skull fractures, permanent deformity and general breathing problems. Again, OI exhibits such variability in its mutational origin and symptoms, that diagnosis, treatment, family planning and prognosis become a difficult task. In a study by Widmann et al. (2001), the physical and mental health of a diverse adult cohort of patients with osteogenesis imperfecta was quantified using health assessment techniques. Demographic and functional assessments were evaluated in addition to the physical limitations imposed by the disease. The results revealed significantly lower physical function scores compared to the U.S. adult norms. However, the mental component scores were equal to the U.S. adult norms and high level of academic achievement, as well as employment, were evident, despite physical impairments. Although it is acknowledged that the physical limitations imposed by OI may influence social development, self-image and independence, the only significant limitation tends to be related mostly to ambulation (Widmann et al., 2001).

Diagnosis and Genetic Testing

Diagnosis of osteogenesis imperfecta is made based on a physical examination that might confirm the presence of fractures, deformities or other symptoms. Also,

bone x-rays are often utilized to detect multiple healed fractures, and since procollagen abnormalities are expressed in various tissues, including epidermal tissues, skin punch biopsies are often implemented. Genetic testing can be complicated since there are so many different mutations that can cause the disease. Once the specific molecular diagnosis is known, family members can be tested by a DNA blood test and prenatal chorionic villus samples (CVS) can be used for the diagnosis of new family members. Severe OI is visible on prenatal ultrasound as early as 16 weeks. Another strategy for the prenatal diagnosis of osteogenesis imperfecta is by linkage analysis to the type I procollagen loci COL1A1 and COL1A2. The segregation of polymorphic DNA markers closely linked to the procollagen genes are analyzed, and patterns seen in affected family members are used as a comparison to determine prenatally if the baby will be affected (Benuslene and Kucinkas, 2000). Genetic counseling and family planning is often directed by the evaluation of known mutations in the family, germ line mosaicism and the age of the father (Zlotogora, 1998).

Treatment and Therapy

Fractures resulting from osteogenesis imperfecta must be repaired quickly and strengthened by surgical rod implementations (or by other means) in order to avoid permanent deformities. In addition to good nutrition, directed exercise and physical therapy is often beneficial in the optimization of bone and muscle strength. Growth hormone (GH) therapy has been used in different studies of patients with OI, including that of Kanaka-Gantenbein et al. (2001), in order to ameliorate bone density. Despite existing concerns about disproportionate growth, GH administration to OI patients has significantly increased bone density. Also, another prospective study was performed by Lee et al. (2001) to determine the efficacy and safety of pamidronate (biphosphonates) in improving bone mineralization and reducing fracture incidence in patients with

osteogenesis imperfecta. Intravenous pamidronate was administered at 1.5 mg/kg bimonthly to six children with OI, over 12-23 months. The number of fractures decreased from median of 3 (range 1-12) to 0 fractures/year (range 0-4). After 12 months of treatment, there was a significant improvement in bone mineral density (BMD).

Prospective Therapies

There are two main therapies for which investigation is underway: stem cell therapy and gene therapy. Mesenchymal stem cells reside in bone marrow and when these cells are incorporated into porous ceramics, the composites exhibit osteochondrogenic phenotypic expression in ectopic or orthotopic sites. *In vitro* cell culture technology can be used to mitotically expand these cells without the loss of their developmental potency. In certain culture conditions, these stem cells differentiate into osteoblasts, which make bone matrix on the ceramic surface. Such *in vitro* prefabricated bone within the ceramic provides immediate new bone-forming capability after *in vivo* implantation. Combining *in vitro* manipulated mesenchymal cells with porous ceramics can be expected to create sufficient newly formed bone, which can thereby provide tissue engineering approaches to patients with skeletal defects, like OI, in order to regenerate skeletal tissue (Ohgushi and Caplan, 1999). Gene therapy has also been considered in the treatment of osteogenesis imperfecta, and to explore the feasibility of this therapy, oim mouse models of human OI, such as that of Niyibizi et al. (2001), have been designed. In this particular experiment, the OI mouse model shows deficient synthesis of pro α 2 chains and cells isolated from the oim mice synthesize α 1 procollagen homotrimers that accumulate in tissues. A murine pro α 2 cDNA was inserted into an adenovirus vector and transferred into bone marrow stromal cells isolated from oim mice femurs. The murine cDNA under control of the

cytomegalovirus early promoter was expressed by the transduced cells. Analysis of the collagen synthesized by the transduced cells demonstrated that the cells produced stable type I collagen comprised of alpha1 and alpha2 heterotrimers. The collagen was efficiently secreted and the cells also retained osteogenic potential. These preliminary data demonstrate that collagen genes can be transferred into bone marrow stromal cells as well as into fibroblasts *in vivo* and that the genes are expressed. Studies such as these encourage further investigation of gene replacement for osteogenesis imperfecta (Niyibizi et al., 2000).

Conclusion

Osteogenesis imperfecta is an inherited disorder that results in varying degrees of bone fragility and defects in other tissues with high concentrations of type I procollagen. Mutations of the COL1A1 and COL1A2 collagen coding genes on chromosomes 17 and 7, respectively, are the cause of the phenotypic characteristics associated with the disorder. Such mutations can be of autosomal dominant inheritance, of sporadic origin or the consequence of a mosaic condition of one of the patient's parents. Osteogenesis imperfecta causes certain physical limitations, but does not affect intellectual competency or employment of affected individuals. OI can be diagnosed by various methods, including x-ray, skin punch biopsy, DNA blood tests and linkage analysis. Although there is currently no cure for OI, treatments and therapies, such as surgical repair, physical therapy, Growth hormone (GH) therapy, and intravenous pamidronate treatment are available. Stem cell and gene therapy research are underway, ensuring a promising and effective cure for patients affected by osteogenesis imperfecta.

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