Symposium II:  
S2-1  
Integrated Approach toward Bone and Joint Diseases using Human and Mouse Genetics  
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One of the challenges in the “post-genome sequence” era is to utilize the genome information to the research associated diseases in bone and joint, including disease and osteoporosis. These diseases are serious concern for the world health and economy, as exemplified by the WH0 campaign of “Bone and Joint Decade” (2001-2010); however, most of their etiology are unknown and their pathogenesis are unclear, resulting in lack of effective and fundamental treatment.

Recent advance in molecular genetics and genome medicine has revealed that genetic factors play a critical role in etiology and pathogenesis of these common bone and joint diseases. Identification of the genetic factors (i.e., susceptibility genes) is the first, mandatory step toward the innovative treatment and “order-made” medicine. To identify susceptibility genes, we have been performing systemic large-scale association studies followed by linkage–disequilibrium mapping in various diseases. Though these projects, we have found genes for OA, ASPN [1], GDF5 [2] and DWVA [3], which are supported by functional evidence and replication in different ethnic populations, as well as genes for lumbar disc disease, CILP [4], COL11A1 [5], TBSP2 [6] and MMP9 [6]. Identification of these genes gave us many insights into the molecular mechanism of the diseases, which would lead to the logical invention of innovative treatment.

In this talk, I explain the detail of our approach for the common diseases, using OA study as an example.

References:

S2-2  
The New Paradigm for OI Genetics and the Functional Effects of Recessive CRTAP and P3H1/LEPRE1 Mutations  
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Osteogenesis Imperfecta is a well-known autosomal dominant bone dysplasia caused by mutations in either of the genes that encode type I collagen, COL1A1 or COL1A2. Most clinically significant cases of dominant OI are caused by point mutations that result in substitutions for glycine residues in the collagen helical region. More recently, the genes responsible for recessive OI have been identified; these cases comprise 5-7% of OI. Recessive OI is caused by deficiency of either of two proteins, CRTAP and P3H1, involved in the prolyl 3-hydroxylation of types I, II and V and components of the ER 3-hydroxylation complex along with cyclophilin B. The phenotype of recessive OI types VII and VIII ranges from severe to lethal, similar to types II/III OI, except with white sclerae. A founder mutation from West Africa was identified in the LEPRE1 gene, with a prevalence of >1% in contemporary West-Africans and 1:200-300 in African-Americans. Recessive OI is characterized by the loss of CRTAP or P3H1 message and protein and lack of 3-hydroxylation of type I collagen. In contrast, collagen from these probands is overmodified and their collagen secretion is increased. P3H1 and CRTAP protein is absent or minimally detectable in CRTAP-null or LEPRE1-null fibroblasts, despite normal levels of LEPRE1 or CRTAP transcripts in these cell lines, respectively. This suggests that CRTAP and P3H1 are mutually protected in the ER prolyl-3-hydroxylation complex. Transfection of full length CRTAP expression constructs into CRTAP-null cells can rescue P3H1 protein and reduce overmodification of type I collagen. Protein degradation pathways were also investigated using proteasome inhibitors. Examination of ER stress in proband fibroblasts showed increased expression of IRE1, BiP and EDEM1, while HSP47 protein levels were increased to help relieve the ER stress burden. Loss of the 3-hydroxylation complex and ER stress adaptation may contribute to the recessive OI phenotype.