American College of Rheumatology Research and Education Foundation—ASP—Junior Career Development Award in Geriatric Medicine

Award Recipient:

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Project:

Low-density Lipoprotein Receptor-Related Protein 5 (LRP_5) Mutations in Patients with Low Bone Mass, a Risk Factor for Osteoporosis

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Osteoporosis is a disease characterized by low bone mass and microarchitectural deterioration of bone tissue leading to enhanced bone fragility and an increase in the risk of fractures. Osteoporosis is one of the most common diseases affecting our aging population. More than 52 million US women and men aged 50 years and older will have either low bone mass or osteoporosis by the year 2010 and more than 61 million will be affected by the year 2020. Bone mass, a major determinant of the risk of osteoporotic fracture, increases during childhood and adolescence, reaching a peak at about the age of 20. Twin and family studies indicate that genetic factors account for approximately 80 percent of the variation in bone mass, although the exact genes that control this variation are largely unknown. The identification of molecular mechanisms that control bone mass is a task of utmost importance.

The LRP5 locus has a substantial effect on bone mineral density (BMD) compared to other identified loci at multiple skeletal sites. Inactivating mutations (loss-of-function) in the LRP_5 gene give rise to osteoporosis-pseudoglioma syndrome (OPPG). On the other hand, activating mutations (gain-of-function) in the LRP_5 gene have been described in phenotypically normal individuals with exceptionally dense bones or high bone mass (HBM) and other conditions with an increased bone density. OPPG carriers also have reduced bone mass. These results indicate that OPPG disease-causing mutations in LRP_5 can have dominant effects as well as recessive effects. Obligate carriers of OPPG mutations have increased incidence of osteoporotic fracture indicating a dominant effect of this gene on bone mass. These findings suggest that LRP_5 plays an important role in determining bone mass by regulating at least two aspects of osteoblast biology: proliferation and function of the differentiated osteoblasts.

In the proposed research, we plan to perform mutation analysis of the LRP_5 gene in a cohort of 37 patients with low bone mass in which other metabolic causes have been excluded. We also plan to perform functional assays of the identified mutations in the LRP_5 gene to understand its osteoblastic function on bone metabolism. The identification of mutations in the LRP_5 gene in this small cohort of patients with low mass will be significant. It will provide a specific genetic link between LRP_5 as an important determinant of BMD and the development of osteoporosis in the normal population.