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SESSION TIME: 0815 - 0930, Tuesday 24 Oct 2006

Invited Plenary Abstracts
Plenary Lectures 3 - Epidemiology and Genetics

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Hongwen Deng (USA)

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Genetics of osteoporosis – what are the questions? How to answer them?

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People have different bone mineral density (BMD) and different susceptibility to osteoporotic fractures (OF), in any given population or across populations. BMD has been used as a major measurable phenotype for defining osteoporosis and (OP) for genetics studies of OP.

A few questions central for genetics studies of OP are listed in the following, and a brief discussion or simplified answer is also given for each question listed. The presentation will discuss these questions in more detail.

Q1: How much of this variation is determined by intrinsic genetic (G) factors, extrinsic environmental (E) factors and the interplay (interactions) of G and E (GXE) factors?
Answer: more than 60% due to G, less than 40% due to E and an uncertain amount due to GXE.

Q2: How to quantify the contribution to BMD variation from G, E and GXE factors?
Answer: By using the information from related individuals, such as families, relative pairs and large pedigrees. Some simple analysis methods will be introduced.

Q3: How much variation in risk to OF is determined by G factors?
Answer: ~50%.

Q4: Are genes for BMD variation at different skeletal sites the same?
Answer: No, but some are shared.

Q5: Are genes for BMD variation and OF the same?
Answer: No, evidence shows that they are largely NOT shared.

Q6: How to identify individual specific genetic factors (genes) for osteoporosis?
Answer: Gene mapping, DNA microarray, and/or proteomics in humans as well as model organisms.

Q7: What are the samples of subjects necessary and how to design experiments for identifying susceptibility genes?
Answer: Families based (linkage, transmission disequilibrium test) or use unrelated subjects (association for candidate genes or whole genome).

Q8: What exclusion or inclusion criteria should be considered in recruiting subjects?
Answer: Some examples will be given for excluding subjects with known abnormal conditions for high or low BMD variation.

Q9: What phenotypes should be studied for genetics of osteoporosis?
Answer: risk phenotypes such as BMD AND OF.

Q10: Can we bypass studying osteoporotic fractures forever?
Answer: No.

Q11: What modern technologies are available to identify osteoporosis genes and their functions?
Answer: Those with whole genome approach such as genome wide linkage/association, DNA microarray and proteomics, plus those with candidate gene studies.

P10

Genetics of osteoporosis – how to get the answers?

Matthew A. Brown
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To make progress in identifying genes causing osteoporosis, we need to determine what we are actually trying to find, and then pick the best of the available methods to achieve that goal.

Step 1 in this process is clearly to determine what are our goals and subsequently would be the best phenotypes to study. If we are trying to identify genes useful for prediction of those that fracture, then fracture itself would be the appropriate trait to study. If, however, we wish to understand the biology underlying how genes lead to fracture risk, then we will have a far greater chance of success if we study phenotypes closer to the site of action; otherwise noise from other covariates will make the task impossible. The phenotypes we study also need to be able to be measured in large populations robustly, non-invasively, and cheaply measurable, be highly heritable, and be correlated with fracture.

Step 2 is to choose the best available method to identify the genes determining the selected phenotype. The recent record in osteoporosis genetics shows that the following approaches are under-productive given the effort and cost involved: linkage studies in families in the absence of a clear major gene effect, candidate gene studies, and QTL-mouse mapping. These approaches have had some successes, but are not suited to providing a whole genome view of the genetics of osteoporosis. Whilst they will play niche roles, other high-throughput hypothesis-free approaches such as genomewide association studies and mouse mutagenesis offer the best chance of future success. Both these approaches have impressive track records in common diseases, which suggest that applied intelligently in osteoporosis they should be very productive.

Having robustly identified genes by these methods, the challenges will be to determine their role in bone disease, and their contribution to fracture risk in individuals and populations. Simple then! Off we go.

P11

Central control of bone mass

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Bone remodeling is controlled by local and systemic factors, the latter including direct central neural inputs involving critical hypothalamic relays. The details of such neural regulatory mechanisms are emerging. In particular, two distinct but interacting pathways regulated by the adipocytic hormone leptin and neuropeptide Y (NPY) are the subjects of intensive ongoing investigations.

Genetic ablation of leptin function in mice leads to a high cancellous bone mass phenotype associated with increased bone turnover. Binding of circulating leptin to its receptor on specific hypothalamic neurons inhibits cancellous bone formation via the sympathetic nervous system (SNS) and stimulates osteoclast differentiation via the SNS and a hypothalamic circuit involving cocaine- and amphetamine-regulated transcript (CART). Leptin-dependent sympathetic control of bone formation acts via β2-adrenergic receptors on the osteoblast to control cell proliferation by two antagonistic pathways that are mediated, in turn, by circadian *Per* genes and the AP-1 transcription factor. Sympathetic control of bone resorption, also via osteoblasts, relies on the above mechanisms as well as CART-mediated control of RANKL expression[1].

NPY is a downstream mediator of leptin in the control of energy homeostasis, and hypothalamic NPY-ergic neurons express both leptin and Y2 receptors. Y2 acts as an inhibitory auto-receptor, modulating NPY secretion and thus the effects of leptin on energy metabolism. In both leptin- and Y2-deficient (Y2KO) mice, hypothalamic NPY levels are elevated, suggesting a shared pathway for leptin and NPY in the central control of bone physiology. Germline or conditional hypothalamic deletion of the Y2 gene leads to increased cancellous bone formation similar to that in leptin-deficient *ob/ob* mice. Importantly, cortical bone mass is also increased in mice lacking hypothalamic Y2 receptor, but is reduced in *ob/ob* mice, a clear difference arguing against a shared pathway. Viral over-expression of NPY in the hypothalamus caused increases in fat mass and thus circulating leptin levels in both *ob/ob* and Y2KO mice. Consequently, decreases in osteoblast activity were observed in both models, but the Y2-associated elevation of bone formation relative to wildtype mice was maintained under this circumstance[2]. Thus, the Y2KO pathway can act consistently to stimulate bone formation, even as leptin continues to provide an opposing stimulus as obesity becomes more marked. NPY and leptin therefore act through distinct pathways to regulate bone remodeling.

Central control of bone remodeling therefore involves antagonistic mechanisms at several levels. Greater understanding of these mechanisms, and particularly of the peripheral osteoblastic responses to these central circuits, may facilitate targeting of these circuits for therapeutic advantage.

[1]Fu *et al.* 2005 Cell 122:803, Elefteriou et al. 2005 Nature 434:514 and refs therein.
[2]Baldock *et al.* 2005 J Bone Miner Res 20:1851 and 2006 *in press* and refs. therein.