

Invited Speaker Abstract

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Osteoporosis genomewide association studies – hope, hype and how to go forward from here

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The advent of genomewide association studies (GWAS) has revolutionized the study of complex human genetics. It is a disappointing fact that such studies of osteoporosis have lagged well behind the progress being made in most other major common diseases, something that can only be ascribed to funding issues given the wealth of well characterised cohorts available for genetic interrogation of determinants of osteoporosis risk. Several groups are now performing genomewide association studies in osteoporosis, mainly studying genetic determinants of bone density (BMD) or of fracture in general population cohorts.

Early studies have demonstrated that this approach will identify genes involved in BMD variation. Interestingly, fracture genes identified have all been more strongly associated with BMD than fracture, and nearly all BMD genes identified have been associated with fracture. This suggests that the evidence that genes controlling fracture and BMD were largely independent is incorrect and that the best design is to study BMD first, then test BMD associations for effects on fracture. Genetic heterogeneity is likely to be a problem for osteoporosis studies, but until we test the genomewide association approach in this field it is difficult to know whether phenotypes such as BMD are too complex genetically to identify other than the 'low-hanging fruit' identified by studies to date. A priori, it seems likely that designs that minimize heterogeneity related to age, gender, site of measurement (of BMD), hormonal status, and potentially environmental background, will be more likely to succeed. As many/most of the cohorts currently being studied are not designed to minimise these issues, it is quite possible that the early genomewide association studies in osteoporosis will not be as productive as we would hope. Cohorts of convenience may be therefore less helpful in unraveling the genetics of osteoporosis than those with recruitment designs aimed to address specific genetic questions.

GWAS are one step in the long process of translating the known high heritability of bone fragility to clinical outcomes. Nor will GWAS identify all variants of significance in common diseases such as osteoporosis. The strengths and weaknesses of GWAS, and how the results of GWAS can be carried forward towards impacts on clinical practice will be discussed.