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REVIEW

How rare bone diseases have informed our knowledge of complex diseases

Mark L Johnson

Department of Oral and Craniofacial Sciences, University of Missouri–Kansas City School of Dentistry, Kansas City, MO, USA.

Rare bone diseases, generally defined as monogenic traits with either autosomal recessive or dominant patterns of inheritance, have provided a rich database of genes and associated pathways over the past 2–3 decades. The molecular genetic dissection of these bone diseases has yielded some major surprises in terms of the causal genes and/or involved pathways. The discovery of genes/pathways involved in diseases such as osteopetrosis, osteosclerosis, osteogenesis imperfecta and many other rare bone diseases have all accelerated our understanding of complex traits. Importantly these discoveries have provided either direct validation for a specific gene embedded in a group of genes within an interval identified through a complex trait genome-wide association study (GWAS) or based upon the pathway associated with a monogenic trait gene, provided a means to prioritize a large number of genes for functional validation studies. In some instances GWAS studies have yielded candidate genes that fall within linkage intervals associated with monogenic traits and resulted in the identification of causal mutations in those rare diseases. Driving all of this discovery is a complement of technologies such as genome sequencing, bioinformatics and advanced statistical analysis methods that have accelerated genetic dissection and greatly reduced the cost. Thus, rare bone disorders in partnership with GWAS have brought us to the brink of a new era of personalized genomic medicine in which the prevention and management of complex diseases will be driven by the molecular understanding of each individuals contributing genetic risks for disease.

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Introduction

Complex genetic traits are defined as those phenotypes controlled by multiple genes, environmental factors and gene–environment interactions. In the decades leading up to the Human Genome Project, the identification of genes underlying bone traits was confined largely to the study of monogenic disorders of bone in which a particular trait segregated in a large family or several smaller families. In addition, a cadre of candidate gene association studies have been reported in the literature for complex traits. Not surprisingly these candidate gene association studies with few exceptions produced findings of both positive and negative associations depending upon the ethnicity of the population under study, the phenotype chosen and the sample size. In contrast, the identification of causal mutations in rare bone disorders has provided a wealth of knowledge regarding bone biology and provided a number of candidate genes and pathways whose components can be associated with complex traits such as osteoporosis and fracture. Just as important, as candidate genes are proposed that reside within chromosomal regions identified through genome-wide association studies (GWAS), these rare bone disorders can provide a critical validation of a role for those GWAS candidate loci in bone regulation.

The Human Genome Project established a variety of tools that have greatly accelerated gene discovery in complex bone traits such as bone mineral density (BMD), fracture and many other phenotypes that have often been associated with diseases such as osteoporosis. Also, large consortiums were established that began to provide adequate power in terms of subjects enrolled in the studies. In recent years, high throughput and relatively low cost DNA sequencing technologies, high density marker and physical maps, large genetic databases, and advances in statistical approaches, as well as multiple approaches using animal models to identify or more important biologically validate candidate genes, has greatly facilitated the identification of genes underlying complex bone traits. However, guidance for the study of complex bone traits from

Correspondence: Dr ML Johnson, Department of Oral and Craniofacial Sciences, University of Missouri–Kansas City School of Dentistry, 650 East 25th Street, Kansas City, 64108 MO, USA.
E-mail: johnsonmark@umkc.edu

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studies of rare, monogenic bone diseases still remains an important contributor to our molecular genetic dissection of complex diseases. In fact, many of the same technologies that have accelerated the genetic dissection of complex bone diseases have also facilitated the discovery of genes underlying rare diseases of bone.

Two recent reviews on the genetics of bone mass have been published that the reader is referred to for additional details beyond the scope of this perspective. Boudin *et al.*[1] have published an excellent review of a number of genes that are central to the control of bone mass and their associated monogenic bone disorders and detailed descriptions of their human bone phenotypes. Karasik *et al.*,[2] summarized the current state of GWAS for bone traits and listed a total of 132 single-nucleotide polymorphisms (SNPs) with a genome level of statistical significance that have been identified for BMD, bone ultrasound and fracture. These SNPs are associated with ~144 neighboring candidate genes. Thirteen of these candidate genes have causal mutations identified in monogenic traits and have been found in GWAS based association studies as highly significant loci. Among these genes are those associated with Wnt/β-catenin signaling (*LRP5*,[3–10] *LRP4*[6,8,11–14] and *SOST*[6,8,15–19]), osteoclast differentiation or function (*TNFSF11*,[6–8,10,19–21] *TNFRSF11A*,[6,8,10,22,23] *TNFRSF11B*[6,8–10,19,23–27] and CLCN7[26,28–30]) and osteoblast differentiation or function (*RUNX*,[8,31–35] *SP7*[6,8,36,37] and *COL1A1*[38,39]), and other signaling pathways important in bone cell regulation (*JAG1*,[40–42] *ESR1*[6,7,9,27,39,43] and *PTHLH*[34,44]). The relationship between the key bone cells expressing these genes and their bone cell targets are illustrated in **Figure 1**.

In this review, I will discuss some of the key 'historical' gene discoveries that have greatly informed our biology of bone and some of the more recent gene identifications that continue to direct and validate our studies of complex traits. The focus of my discussions will be on three broad categories of monogenic bone syndromes/disorders; namely osteopetrosis, hyperostosis and osteosclerosis, and osteogenesis imperfecta. Presented in **Table 1** is a brief description of the skeletal and important clinical features associated with these rare bone disease that in the past have served to differentiate them from each other. However, as our molecular/genetic dissection of these conditions has evolved, it is interesting to note that the 'traditional' clinical categorization of many of these syndromes/disorders has been or needs to be reconsidered based upon our knowledge of the underlying genetic basis of the trait.

Osteopetrosis

Historically speaking the period from 1900–1990 provided a wealth of detailed clinical descriptions of rare diseases of bone. The decade of the 1990s and up to the present date, because of our enhanced abilities to genetically dissect monogenic traits, has yielded a detailed molecular understanding of these rare bone diseases and identified critical genes/proteins/pathways that in some cases confirmed, but in many instances identified, new components of bone mass regulation that clinical studies could not provide.

Osteopetrosis was first described in 1904 by Albers-Schönberg,[45] which generally occurs in adulthood and is less severe that the autosomal recessive (AR) forms. Radiographically it is distinguished by pronounced endplate thickening of the vertebrae and the 'bone within bone' appearance of the iliac wings. Collectively the autosomal dominant (AD) and AR forms of osteopetrosis represent a class of osteoclast defect diseases. Traditionally, each of the different types of osteopetrosis has been distinguished by clinical descriptions that relied heavily on radiographic features, severity of disease and age of onset, although oftentimes differences between disorders are very subtle. Our current ability to determine causal mutations has provided a means to more finely categorize these diseases and also provides valuable directions for clinical management of the disorders.

The gene for Albers-Schönberg disease or AD osteopetrosis type II (ADO II), as it is now classified, was shown by linkage studies of several families to reside on chromosome 16p13.3 and each these families carried mutations in the chloride channel 7 (*CLCN7*) gene.[46] At the same time, Kornak *et al.*[28] reported a patient with infantile malignant osteopetrosis that was a compound heterozygote with a nonsense mutation (Q555X) in exon 18 of one allele and a missense mutation (R762Q) in exon 24 of the other allele of the *CLCN7* gene. This suggests that CLCN7 can underlie different forms of osteopetrosis in a genotype–phenotype relationship that is not clearly understood. CLCN7 is an integral component of the ruffled membrane of osteoclasts involved in the transport of Cl^- ions into the resorption compartment on bone surfaces. Most cases of ADO II are due to heterozygous mutations in *CLCN7*, whereas a few cases of homozygous or compound heterozygous mutations have been attributed to AR osteopetrosis.[47]

AR forms of osteopetrosis (ARO) were first shown by clinical studies to be due to a deficiency in carbonic anhydrase II (CA II)[48] and subsequently a point mutation in the *CA2* gene[49] was identified in a Belgian family in 1991. We now identify eight different forms of ARO, each associated with different genes/mutations (see Review by Boudin *et al.*[1]) that encode several different proteins involved in osteoclast differentiation or function. Some of the major genes that have been identified are *TCIRG1* (the osteoclast specific vacuolar proton pump V-type ATPase a3 subunit)[50–52] and two members of the tumor necrosis factor (TNF) receptor superfamily; *TNFSF11* (encoding RANKL)[20] and *TNFRSF11A* (encoding RANK).[22] A closely related disease, Pycnodysostosis, is caused by mutations in *CTSK* (Cathepsin-K).[53,54] All of these studies of ADO and ARO have illustrated the critical role of the osteoclast and control of its differentiation and function in bone mass regulation. Somewhat surprisingly of all of the genes causal for various forms of osteopetrosis, GWAS studies to date have only identified *TNFSF11* and *TNFRSF11A* as candidate genes potentially underlying normal variation in BMD (at the lumbar spine).[2]

Hyperostosis and Osteosclerosis

Hyperostosis and osteosclerosis have generally been considered one large group of sclerosing bone diseases. These syndromes manifest clinically with generalized changes in bone density (decreased or increased) throughout the skeleton, but with varying degrees of involvement at specific skeletal sites and in many cases other tissue involvement that have served to distinguish them in the past. However as a result of our emerging molecular/genetic characterization we need to begin incorporating knowledge of the genes/pathways involved in the

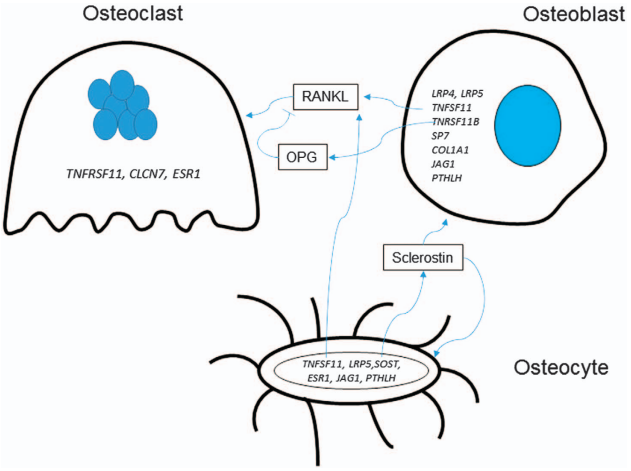

Figure 1 Major genes that are causal for rare bone disorders and have genome level significant single nucleotide polymorphisms for bone mass, bone ultrasound or fracture as identified by GWAS. Genes are associated with the bone cell in which the gene is expressed, although many have a site of action that affects a different bone cell. For example, the *SOST* gene is expressed in osteocytes, but its protein product sclerostin appears to act on any cell expressing the LRP4/5/6 co-receptors that regulate Wnt/β-catenin signaling, such as the osteoblast and the osteocyte. RANKL, the product of the *TNFSF11* gene is expressed in both osteoblasts and osteocytes and regulates osteoclast differentiation by binding to its receptor, RANK (product of the *TNFRSF11* gene). OPG, the product of the *TNFRSF11B* gene, is a decoy receptor for RANKL and blocks RANKL binding to RANK.

classification of these syndromes as clinical classifications do not fully discriminate the subtle differences that we now appreciate.

One of the most significant pathways to be identified as a result of the genetic dissection of rare bone diseases is the Wnt/β-catenin signaling pathway that was identified within the past 20 years as critical for many aspects of bone biology and particularly bone mass regulation. In 1996, Warman and colleagues[55] described the localization of the loci responsible for Osteoporosis Pseudoglioma Syndrome (OPPG) (Online Mendelian Inheritance in Man (OMIM) #259770), a rare human disease characterized by juvenile onset osteoporosis and progressive blindness, to human chromosome 11q12-13. The next year, Johnson and colleagues[56] localized the loci responsible for an AD high-bone mass (HBM) (OMIM #601884) trait to the same 11q12–13 chromosomal region and suggested that perhaps these two opposite phenotypes resulted from allelic variants in the same gene. Follow-up work to identify the gene in both of these traits led to the discovery of inactivating mutations in the low-density lipoprotein-related protein 5 (*LRP5*) by Warman and colleagues published in November of 2001[57] and a G171V missense mutation in *LRP5* as causal for the HBM kindred phenotype by Johnson and colleagues that was published in January of 2002.[58] A few months later Boyden and colleagues[59] published the identification of the same LRP5 G171V mutation in another, extreme high bone mass family that was unrelated to the Johnson and colleagues kindred. Critical to the discoveries of the *LRP5* mutations in these monogenic disorders were studies by other groups demonstrating the role of LRP5 and its close homolog, LRP6, in the Wnt/β-catenin signaling pathway.[60–63] The Wnt/β-catenin pathway was known to be an oncogenic pathway since the studies by Nusse and colleagues in the 1980s demonstrating that the mouse mammary oncogene *int-1* was identical to the *Drosophila* segment polarity gene Wingless (*Wg*).[64] Thus, the role of this pathway in bone mass accrual and regulation of adult mass came as a complete surprise. The convergence of these studies identifying LPR5 and its associated Wnt/β-catenin signaling pathway, served as a catalyst for the thousands of studies that followed over the last 15 years into this pathway's role in bone. However, although common allelic variants and SNPs of *LRP5* have consistently correlated with different bone phenotype in many association studies and in several GWAS analysis, the best estimates indicate that they explain only 2–3% of the variation in bone mass in any given population.

Also in 2001–2002 there were a number of papers published that identified *SOST* gene mutations as causal for Van Buchem's disease (OMIM #239100) and Sclerosteosis (OMIM #269500).[65–68] The importance of *SOST* was not fully recognized until 2005 when sclerostin, the product of the *SOST* gene, was shown to inhibit Wnt/β-catenin signaling by binding to LRP5/LRP6,[69,70] although one study suggested sclerostin was a BMP antagonist.[71] This second convergence which brought *SOST* and *LRP5* together created a broader landscape of regulation of bone mass by the Wnt/β-catenin signaling pathway and brought into focus the potential role of several other regulators of the pathway such as the Dkk and sFRP families of proteins. *LRP5* mutations have now been described in several bone related phenotypes.[72–74]

LRP4 is another member of the Wnt pathway family of proteins important in bone mass regulation. It was first identified in genome-wide studies[6,9,19] and in both mice[75,76] and humans[11,12] and shown to regulate bone mass. *LRP4* functions as a binding or docking protein for sclerostin.[11,12,75] Thus, while LRP4 was first identified as a candidate gene for bone mass from GWAS studies, the identification of human mutations with the rare bone disorders provided important confirmatory evidence for its role in human bone mass regulation.

Recently, from a GWAS study of the Icelandic population[77] a rare nonsense variant in *LGR4* (leucine-rich-repeat-containing G-protein-coupled receptor 4) was identified as being strongly associated with low BMD and osteoporotic fracture. LGR4 binds the R-spondin family of proteins that are known to potentiate Wnt/β-catenin signaling (see review[78]). Zhu *et al.*[79] have shown that LGR4 is a key receptor for R-spondin 2. What these *LRP4* and *LGR4* findings clearly illustrate is that the recognized importance of the Wnt/β-catenin pathway in regulating bone mass has enabled investigators to scrutinize regions that reach genome level significance in GWAS studies and focus on genes whose proteins regulate or interact with the pathway.

Several other diseases that have a bone associated phenotype related to the Wnt pathway family of genes have been described. *WNT5A* mutations have been reported in patients with autosomal dominant Robinow Syndrome (OMIM #180700).[80] *WNT7A* appears to be important in limb development as evidence by reports relating to Al-Awadi-Rass Rothchild syndrome (OMIM #276820) and Fuhrmann syndrome (OMIM #228930).[81,82] Several other members of the Wnt/β-catenin signaling pathway in bone have been identified as causal for rare bone disorders and this list is likely to grow as the genetic dissection of rare traits becomes more commonplace in the clinical characterization of these diseases. Conversely, GWAS studies have also identified *WNT16*

Table 1 Skeletal features of monogenic bone syndromes/disorders

Syndrome/disorder	*General skeletal and other important clinical features*	*Defective bone cell (s)*	*OMIM reference ID*[a]
Osteopetrosis			
Autosomal dominant osteopetrosis type II (ADO II) (Albers-Schönberg Disease)	Endplate thickening of vertebrae, Increased cortical thickening, Compromised marrow space, Diffuse increased bone density but associated with multiple fractures, 'Marbled' or bone-within-bone in the pelvis	Osteoclasts	166600
Autosomal recessive osteopetrosis			
Type 1 (severe neonatal or infantile form)	Osteomyelitis, Uniform increase in bone density, Increased fracture incidence, thick dense skull, sandwich appearance of vertebrae, Coxa vara in the hip	Osteoclasts	259700
Type 2	Hyperostosis of the skull, osteosclerosis of the skeleton, increased number of multiple fractures, tendency for osteomyelitis particularly in the jaw, mandible prognathism	Osteoclasts	259710
Type 3	Osteosclerosis of the skeleton, short stature, renal tubular acidosis and elevated serum acid phosphatase	Osteoclasts	259730
Type 4	Severe osteopetrosis and associated multiple fractures	Osteoclasts	611490
Type 5	Severe osteopetrosis, *in utero* fractures, hydrocephaly and stillborn cases reported	Osteoclasts	259720
Type 6	'Erlenmeyer flask' deformity of distal femur	Osteoclasts	611497
Type 7	Large areas of cartilage retention and trabecular structures	Osteoclasts	612301
Type 8	Macrocephaly of skull, open fontanels, dense bones with reduced marrow cavity, anemia	Osteoclasts	615085
Pycnodysostosis	Dense skull with open anterior fontanelle, aplastic clavicle, delayed tooth eruption, scoliosis of the spine	Osteoclasts	265800
Hyperostosis and osteosclerosis			
Osteoporosis pseudoglioma syndrome	Low bone density (childhood osteoporosis), early onset blindness, kyphosis	Osteoblast/ osteocyte	259770
High bone mass (HBM)	Generalized increased in bone density across skeleton with thick cortices	Osteoblast/ osteocyte	601884
Van Buchem's	Cranial hyperostosis and generalized increased in bone density throughout skeleton, hearing loss	Osteoblast/ osteocyte	239100
Sclerosteosis	Increased bone density with asymmetric/prominent mandible, cranial hyperostosis, sclerotic vertebral endplates, high cortical density of long bones	Osteoblast/ osteocyte	269500
Endosteal hyperostosis	Increased bone density, skull particularly affected with elongated mandible, mild sclerosis of spine and long bones with thickened cortices	Osteoblast/ osteocyte	144750
Robinow syndrome	Macrocephaly, frontal bossing and other facial features common. Short limbs and small hands also common.	Osteoblast	180700
Al-Awadi-Rass Rothchild syndrome	Asymmetric, long face. Hemivertebrae with shortened forearms and aplastic fibula and tibia		276820
Fuhrmann syndrome	Bowing of forearm and femur, missing patella, short stature, congenital hip dislocation		228930
Autosomal dominant osteopetrosis type I (ADO I)	Increased bone density, generalized skeletal sclerosis particularly pronounced in the cranial vault. No 'Rugger-Jersey spine' (vertebral end-plate thickening) observed in ADO II	Osteoblast/ osteoclast	607634
Camurati-Engelmann or progressive diaphyseal dysplasia	Sclerosis of skull and mandible. Progressive diaphyseal widening and 'Erlenmeyer' appearance, long bone marrow cavity narrowing	Osteoblast	131300
Raine syndrome	Neonatal generalized sclerosis, short stature, usually results in death within first few weeks after birth. Severe craniofacial anomalies common	Osteoblast	259775
Craniofacialmetaphyseal dysplasia	Sclerotic skull base and cranial vault with normal spine and pelvis. Limb metaphyses are widened and 'Erlenmeyer' appearance in childhood and club-shaped appearance in adulthood of distal femur	Osteoblast	123000
Occulodentodigital dysplasia	Skull and vertebrae hyperostosis with broad tubular long bones. Dental issues and cleft lip/palate, microcephaly, various eye problems	Osteoblast	164200
Osteogenesis imperfecta[a]			
Type I	Blue sclerae throughout life, mild osteopenia, multiple fractures during childhood to puberty	Osteoblast	166200
Type II	Multiple fractures present at birth. Soft calvaria. Perinatal lethal	Osteoblast	166200
Type III	Blue sclerae at birth but becomes normal as patient ages. Multiple fractures at birth. Sciolosis/kyphosis of spine, hypomineralized cranium. Long bone deformity at birth and bowing of limbs due to fractures.	Osteoblast	259420
Type IV	Mild to moderate skeletal deformities with varying degrees of fractures, scoliosis/kyphosis and biconcave and flattened vertebrae with limb bowing due to fractures.	Osteoblast	166220

Summary of key skeletal and/or clinical features of rare bone syndromes/disorders discussed in this review. The Online Mendelian Inheritance in Man (OMIM) database (http://omim.org) Accession number is listed for further detailed clinical and genetic information related to these diseases. The major bone cell type involved in each disease is also indicated.

[a]Only the forms of osteogenesis imperfecta that involve either the *Col1A1* or *Col1A2* genes are listed. For a complete description of all osteogenesis imperfecta types refer to the recent review by Forlino and Marini.[102]

polymorphisms with bone mass and osteoporotic fracture,[83,84] but no rare syndrome has yet been identified due to mutations in this gene.

Interestingly, the ADO I form presents with a more generalized sclerosis (not the bone-within-bone typical of ADO II), which is especially pronounced in the cranial vault, and has been shown to be due to a number of different mutations in *LRP5*.[72,85] The fact that a bone formation gene/pathway, which principally acts in the osteoblast lineage, calls into question whether ADO I is correctly associated with osteopetrosis? Studies in mice and bone cell lines[86–93] have shown that Wnt/β-catenin signaling in osteoblasts/osteocytes controls the expression regulators of osteoclastogenesis (for example, osteoprotegerin and RANKL). Thus while ADO I has the appearance of an osteopetrotic condition,[85] the primary defect is acting at the osteoblast/osteocyte cell level, which begs the question of how best to classify the disease. Given the genetic basis of ADO I, perhaps it should be more appropriately categorized as an osteosclerotic phenotype as suggested by de Vernejoul.[47]

Other sclerosing bone diseases that have had causal genes identified include Camurati-Engelmann disease (OMIM #131300), which has been shown to be due to mutations in *TGFB1* (transforming growth factor *β-1* gene),[94] Raine Syndrome (OMIM #259775) that is caused by mutations in *FAM20C*,[95] and craniofacialmetaphyseal dysplasia (OMIM #123000) that has been shown to be due to mutations in *ANKH*[96,97] and interestingly to a rare mutation in *GJA1*.[98] Mutations in *GJA1* have been more commonly reported in association with occulodentodigital dysplasia (OMIM #164200).[99] Several other sclerosing diseases have been described and excellent reviews have been published in the literature that details these syndromes.[1,47,100,101]

At present, other than the Wnt/β-catenin pathway-associated genes, GWAS has yet to identify variants of these genes as underlying normal variation in bone traits. This highlights one of the limitations of GWAS studies, namely that common allelic variants are generally covered by GWAS and not rare variants that contribute to monogenic diseases. However, as the speed of genome sequencing increases and costs decrease, the potential exists for performing complete genome sequencing of all individuals within a population. Such was the case for the above mentioned Icelandic population study,[77] which identified *LGR4* as being associated with low BMD and osteoporotic fracture in that population.

Osteogenesis Imperfecta

Perhaps one of the best examples of how rare bone disorders has propelled our understanding of bone biology is illustrated by the studies from several groups who have provided a detailed molecular/genetic dissection of various forms of osteogenesis imperfecta. Several excellent reviews have been published and the reader is referred to one of the more recent reviews by Forlino and Marini[102] for detailed information. What has evolved is a detailed understanding of the molecular events necessary for collagen synthesis (*COL1A1* and *COL1A2*), post-translational processing/modification (*CRTAP*, *LEPRRE1*, *PPIB* and *TMEM38B*), folding and crosslinking (*SERPINH1*, *FKBP10* and *PLOD2*) and many of the key genes/proteins involved in this pathway.[102] Interestingly, of the studies to date, for these collagen associated genes only the *COL1A1* gene has been shown to reach a genome wide level of significance in GWAS studies.[2] What this perhaps suggests is that the numerous players involved are so finely tuned to their associated roles in collagen production that variants in these genes all lead to disease, rather than more subtle variations in bone density or fracture susceptibility as in the case of osteoporosis.

Recently, there has been a report of mutations in *WNT1* have been shown to cause bone fragility in one family specifically diagnosed with osteogenesis imperfecta.[103,104] Many other non-collagen genes[105] have been implicated in osteogenesis imperfecta including *CREB3L1*[106] and *SP7*,[36] which have roles in osteoblast differentiation. To account for this rapidly growing list of new genes associated with osteogenesis imperfecta, Forlino and Marini have proposed a functional metabolic classification scheme that incorporates both clinical and genetic information to subtype the disease.[102]

Conclusions

In this review I have focused on a few of the rare bone diseases that have contributed some of the greatest impact on our body of molecular/genetic knowledge with respect to bone biology. A complete listing of all rare diseases of bone is not possible in this short review. A simple search of the OMIM (http://www.ncbi.nlm.nih.gov/omim) database using terms such as bone dysplasia, osteopetrosis, osteosclerosis, osteogenesis imperfecta, Paget's Disease of Bone yielded a list of over 700 disorders in the catalog, and easily over one-third of which still have yet to have a causal gene identified. The advances made in recent years with exomic and whole genome sequencing, for example, now make it possible to identify the casual mutation in a single patient and it seems likely that the causal genes/mutations for these currently unknown disorders will be identified within the next decade.

However, once this catalog is created we still will have much work to do in the area functional studies aimed at understanding how common allelic variants in genes mutated in rare bone disease contribute to bone mass traits. For example, the types of studies that are needed include defining whether these common allelic variants contribute to changes in gene expression, mRNA stability, or induce subtle changes in protein conformation that alter protein function or interactions with other regulatory proteins (for example, inhibitors or activators). Another critical aspect that needs to be understood in the cases of many noncoding (exonic) allelic variants is if/whether they contribute to altered epigenetic regulation of the gene.

Given that our catalog of loci from GWAS studies now includes hundreds of potential genes, all with small effect sizes, and the relative contributions of any given gene to variation in a given bone trait in any one patient is likely to be highly variable; individual genetic profiling is ultimately going to be required to provide personalized diagnosis. The ability to rapidly sequence genomes at relatively low cost means that we are at the threshold of this reality. How these polymorphisms alter function remains a big challenge and this knowledge is essential. Once we can equate genetic changes to functional consequences, we will be one step closer to personalized molecular/genetic diagnosis for common diseases such as osteoporosis and customized treatments that will be maximally effective in any given individual.

So currently how have rare bone diseases informed our understanding of complex traits? Rare bone disorders have revealed molecular pathways whose members are strong candidates for variation in normal bone traits. These monogenic trait gene discoveries have provided a focusing lens for prioritizing candidate genes for further biological validation in intervals of genome level significance that are identified in GWAS studies. Conversely, GWAS studies have also provided clues as to genes underlying rare bone disorders. Currently there are several genes that represent a convergence between having a mutation that causes a rare bone disease and variants that contribute to variation in bone density in the population (summarized in **Figure 1**). The rapid evolution of technologies that has occurred in the genome/post-genome era including DNA sequencing, bioinformatics and model systems to study gene/protein function has provided us with the tools needed to genetically define causal mutations for any monogenic disease. Partnered with the growing wealth of knowledge gained from GWAS studies, it seems highly likely that genetic risk assessment for complex diseases such as osteoporosis will be possible in the very near future for every individual in the population. This will be a paradigm shift for both prevention and management of complex diseases.

Conflict of Interest

The author declares no conflict of interest.

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