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Occasional Note

Growing bone knowledge

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Molecular dissection of genetic bone diseases continues to deliver exciting insights on developmental control of skeletal patterning and growth. But will diagnostic tests become available to the genetic community on a wide basis?

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Developmental biologists and geneticists met with pediatricians and radiologists in rural Virginia recently to report on advances in the field of genetic bone diseases (1). The study of those disorders known collectively as bone dysplasias and characterized by stunted growth and skeletal deformity has attained scientific and medical importance for the insights it provides into processes of morphogenesis, growth, and homeostasis of the skeleton.

Following the 2001 meeting, a molecular classification (2) had been developed to go along with the traditional phenotypic nosology (3), and additional genes have been reported in the meantime. Some of the genes reported at the 2003 meeting were unexpected guests, as natriuretic peptide receptor 2, mutated in acromesomelic dysplasia (M. Warman, Cleveland); and selectin-E ligand, the knockout of which results in dwarfism in mice (B. Lee, Houston), neither one having been previously associated with skeletal development.

Implication of a carbohydrate sulfotransferase in progressive kyphoscoliosis (S. Mundlos, Berlin) came as no surprise, the role of the sulfation pathway in proteoglycan synthesis being well known. As more genes are recruited, the paradigm is shifting – as one speaker simply put it, 'getting the gene used to be the hard part; today, it is figuring out what the gene does'. Because of nature's ability to use similar molecules in different tissues for different tasks, cloning a gene, and looking at its structure does not readily reveal its particular function.

As more and more single genes are added as tiles to the mosaic, pathways and patterns are recognized. A remarkable series of signaling genes (*IHH, GDF5, ROR2,* and *BMPR1*) may manifest either with dominant or recessive mutations; the milder manifestation in the heterozygous state being a form of brachydactyly, and the homozygous manifestation being a generalized skeletal dysplasia, as if the hand with its numerous and highly patterned bones would respond to even slight signal perturbations that spread to the whole skeleton only in presence of a mutation double dose (G. Mortier, Gent; S. Mundlos), and as more of the players come to light, models for limb patterning and segmentation have to become more refined – as another speaker put it, there is a need to 'sort out the signaling soup'.

The close loops between signals and biochemical effectors seem to explain how molecules belonging to unrelated classes – growth factors and structural components of matrix, such as *GDF5* and collagen 2, or transcription factors and enzymes such as *RUNX2* and alkaline phosphatase – are becoming integrated in pathways of bone morphogenesis and growth; and as this happens, developmental biologists, biochemists, and radiologists meet at the same table to synchronize their views.

Although the paradigm of one gene – one disease has been archived years ago upon discovery

of extensive phenotypic series, the notion of a single gene (*FMNA*; S. Robertson, Dunedin, NZ) giving rise to either a purely neurological phenotype, or three different malformation-skeletal dysplasia phenotypes, all phenotypes breeding true from mutations in distinct regions of the molecule, is exceptional, another notable example being *LMNA*. Opposing phenotypes from the same locus are also uncommon: the report of variants in the *LRP5* gene that are associated with high bone mass – unlike the rare recessive mutations causing osteoporosis that had revealed the gene's role in bone homeostasis – open exciting perspectives of tampering with the *wnt* signaling pathway to influence bone mass (W. van Hul, Antwerp; M. Warman). As more variants become known, interaction between genes as phenotype modifiers may be expected for the years to come.

Complementing the study of man's vast repertoire of genetic bone diseases, the mouse continues to deliver timely contributions – either as pathocopies of disorders seen in human, as the sulfate transporter knockout showing the bone and joint changes of diastrophic dysplasia that may serve as model for drugs inducing intracellular production of sulfate (A. Rossi, Pavia) or as tools to dissect the pathogenesis, such as mice carrying neomycin-silenced *FGFR3* mutations that become expressed selectively in chondrogenic or neurogenic tissue by an astute hookup of *cre* recombinase to tissue-specific promoters (S. Sandusky and C. Francomano, Baltimore). While cranial and spinal bone impingement has been believed to be at the origin of most neurological complications in achondroplasia, some of these might be intrinsic to brain and spinal cord development instead, casting questions on current surgical treatment. Subcellular localization studies suggest that notwithstanding molecular models for intrinsic activation, it is the intracellular misrouting and the ensuing gross accumulation of mutant receptors that may finally be the most important single factor in determining the antiproliferative effect of FGFR3 mutations (W. Horton, Portland).

More animal rescue may be out there as the mouse is being flanked by the chicken, whose relatively large embryo continues to contribute precious insights on limb patterning through gene microinjection or galactosidase-visualized expression patterns; the fruit fly, from which illumination is expected on the function of *DMC1*, a highly conserved but as yet functionally obscure gene responsible for dwarfism and developmental delay in man (D. Cohn, Los Angeles; V. Cormier, Paris); and the zebrafish that combines the advantage of good visibility of skeletal elements (its vertebrae are easier to count than those of either mouse or man) with short generation times and ease of cultivation. The notion that one of the spontaneous zebrafish mutants, a brittle bone fish afflicted by spontaneous fractures, is caused by a glycine substitution in collagen 1 (S. Fisher, Baltimore), is a remarkable example of interspecies pathohomology and must have provoked a nostalgic smile among bone dysplasia aficionados, remembering how in the early eighties, discovery of glycine substitutions in collagen 1 leading to osteogenesis imperfecta had been a major breakthrough and fostered concepts like molecular topology and the dominant negative effect (4).

Obliging to tradition – the meeting having been brought to life by a group of pediatricians and radiologists devoted to genetic bone disorders 20 years ago – the scientific presentations have been balanced by clinical reports and by a diagnostic contest – participants being challenged to diagnose bone dysplasias off the screen, within a few minutes and in public, a task capable of beating the wits out of even the most imperturbable of dysplasia experts and quite aptly highlighting the importance of evidence-based, as opposed to eminence-based, diagnostics. But it would be premature to predict the end of radioclinical diagnosis: only about a third of bone dysplasias have had their molecular basis worked out; and even as we will learn more, most patients in the world will not have access to molecular tests. What is needed is continuous education to refine the physicians' ability to recognize the molecular signature of a disorder and to direct the patient's samples to the correct analysis.

Making molecular diagnostics available is proving thorny. Given the limited treatability of most bone dysplasias, molecular diagnostics is one of the benefits to patients who participated in research (and others with the same disorders). In another feedback loop, molecular confirmation seems to be the only way to assemble patients' collectives that are homogeneous and large enough to learn on the natural course and complications of individual disorders – a further potential benefit to patients. Unless a way is found to deliver these services, patients will not have realized the benefits of participation, nor will society have had a return on its research investment. All too often, laboratories are not willing, or not permitted, to cross the line between research and diagnostics, and genetic tests go orphan once research interest abates. While commercial laboratories are growing west of the Atlantic, a non-profit, EC-sponsored network proposes itself as an alternative solution (5). Will this model prove successful in providing equal and adequate access to diagnostics of rare

diseases, and thus for transfer from research to diagnostics? The experiment is interesting as stakes are high.

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