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MINIREVIEW

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Genetic analysis of skeletal dysplasia: recent advances and perspectives in the post-genome-sequence era

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Abstract Skeletal dysplasia is a group of disorders of the skeleton that result from derangement of growth, development and/or differentiation of the skeleton. Nearly 300 disorders are included; most of them are monogenic diseases. Responsible genes for skeletal dysplasia have been identified in more than 150 diseases mainly through positional cloning. Identification of disease genes would improve patient care through genetic diagnosis as well as improving our understanding of the diseases and molecular mechanism of skeletal tissue formation. Studies of skeletal dysplasia would also help identify disease genes for common diseases affecting bones and joints. In this study, the author reviews recent advances and the current status of the genetic analysis of skeletal dysplasia and its impacts on research into skeletal biology.

Keywords Skeletal dylplasia · Classification · Mutation · Disease gene · Genetic diagnosis · Pseudoachondroplasia · Multiple epiphyseal dysplasia · Dysostosis

What is skeletal dysplasia?

Skeletal dysplasia is a group of disorders that are characterized by abnormal formation of the skeleton because of intrinsic derangement of the growth, development and/or differentiation. Nearly 300 disorders are included in this entity; most of them are heritable (monogenic) diseases. Most of the diseases in the category are rare, but skeletal dysplasia as an entity is a common disease.

There are two classes of skeletal dysplasia: osteochondrodysplasia and dysostosis. Osteochondrodysplasia results from abnormal growth and development of bone and/or cartilage; the lesions are generalized and progressive. Examples include osteogenesis imperfecta (OMIM 166200, 166210, 166220, 259440) and achondroplasia (OMIM 100800). In contrast, dysostosis is the disorder of individual bones, singly (skull, hand, arm, etc.) or in combination (e.g., skull and fingers). The lesions are local and nonprogressive. Poly/syndactyly and craniosynostoses are representative diseases. Previously it was believed that the two were different: osteochondrodysplasia was considered a genetic disorder and dysostosis an accidental derangement during embryonic development, unrelated to genes. However, now we know that both are caused by genetic abnormalities.

Classification of skeletal dysplasia and its significance

As there are so many diseases in the category, classification is necessary for better understanding of skeletal dysplasia. Therefore, in 1969, an international classification was first invented (McKusick and Scott 1971). There were minor revisions twice, until in 1992, drastic changes were introduced to the classification. In the major revision, the diseases were grouped according to radiographic similarities of their phenotypes (Beighton et al. 1992). The grouping is based on the concept of "family" proposed by Spranger (1985). The radiologist tried to group disorders based on presumed pathogenetic similarities with the underlying idea that the phenotypic similarity must reflect the causality. Representative diseases such as achondroplasia and spondylo-epiphyseal dysplasia congenital (SEDC; OMIM 183900) were selected, and diseases with similar radiographic phenotypes were gathered together into groups. This was to prepare for the progress of basic

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research; at the dawn of genome era, the radiologist must have recognized the importance of phenotyping. There are 33 groups for osteochondrodysplasia and three groups for dysostosis in the current classification (Hall 2002).

The grouping by clinical information provided a great deal of help in the basic research, in particular, in identification of disease genes. For example, *FGFR3* was first identified as a disease gene for achondroplasia, the prototype of the achondroplasia group (Shiang et al. 1994). Then, disorders in the group were examined for *FGFR3*, and mutations were found one after another. Similarly, *COL2A1* mutation was first found in SEDC (Tiller et al. 1990), and *COL2A1* was also found to be the disease gene for other members of the group (Ahmad et al. 1991; Bogaert et al. 1992; Winterpacht et al. 1993; Nishimura et al. 2004; Miyamoto et al. 2005). Thus, a radiologist's insight derived solely from clinical practice supported identification of a number of disease genes at the bench.

Identification of disease genes by clinical information

Let me review the process of gene identification with achondroplasia, the most common skeletal dysplasia, taken as an example. By linkage analysis, the gene for achondroplasia was the localized to chromosome 4p (Le Merrer et al. 1994; Velinov et al. 1994). *FGFR3* in the region was examined, and a Gly380Arg mutation in its transmembrane domain was found (Shiang et al. 1994). The mutation was so recurrent that chondroplasia was considered to be defined by the single mutation (Bellus et al. 1995a). We examined *FGFR3* mutation in an "atypical," milder achondroplasia (Nishimura et al. 1995) and found a mutation in its transmembrane domain; however, it was not Gly380Arg, but Gly375Cys (Ikegawa et al. 1995).

Thus, we know *FGFR3* mutations produce similar phenotypes. Then, how about a "similar" disease with a milder phenotype? The second fox is caught in the same snare. Hypochondroplasia (OMIM 146000) is also caused by *FGFR3* mutation in the intracellular tyrosine kinase domain (Bellus et al. 1995b). The achondroplasia group contains a similar condition with a more severe phenotype, thanatophoric dysplasia (OMIM 187600, 187610), and the same snare still worked very well. The disorder is also caused by *FGFR3* mutations (Tavormina et al. 1995). Furthermore, the list of the achondroplasia group included still other diseases including Crouzon syndrome with acanthosis nigricans (OMIM 100600), SADDAN dysplasia (Francomano et al. 1996), Muenke syndrome (OMIM 602849) and Saethre-Chotzen syndrome (OMIM 101400). The radiologist's prediction was right. All these similar phenotypes are caused by the *FGFR3* mutation.

With the help of such clinical information, more than 150 disease genes have been found to date. The list is updated almost weekly. We are in the middle of the cloning rush. The speed of cloning of the disease genes will surely be accelerated further by the recent progress in genome analyses and by establishment of a worldwide database for human DNA sequences.

Genetic diagnosis of skeletal dysplasia

If you find a disease gene, you can make genetic diagnosis. We have a strong need for genetic diagnosis of skeletal dysplasia because there are so many diseases with complex phenotypes and many individual variations according to age, treatment and environment. No powerful diagnostic tools and reliable biochemical markers are currently available. Current diagnosis largely depends on radiographic examinations, which are very subjective and often error-prone. For example, pseudoachondroplasia (PSACH; OMIM 177170) resembles achondroplasia, as its name shows (Fig. 1a). Both disorders present short-limbed short stature and limb deformity. Diagnosis of PSACH is easy before skeletal maturity because of a characteristic radiographic feature, the "anterior tongue-like protrusion" (Fig. 1b). However, it is a disease of the skeleton. Skeletal features change with age (Fig. 1c): after the skeleton reaches maturity, the pathognomonic feature disappears (Fig. 1d), and with age, secondary changes such as osteoarthritis (OA) and fractures make the diagnosis very difficult.

Let me show the current status and problems of genetic diagnosis using PSACH as an example. Its disease gene is cartilage oligomeric matrix protein (*COMP*; Hecht et al. 1995), which encodes an extracellular matrix protein specific to cartilage. The COMP protein has characteristic motifs including calmodulin-like repeat (CLR). *COMP* mutations are also found in multiple epiphyseal dysplasia (MED; OMIM 601560; Briggs et al. 1995), which is not similar to PSACH at first glance. The clinical abnormalities of PSACH are severe. The adult height is sometimes below 1 m. Radiographic abnormalities are seen in the spine, epiphyses and metaphyses. In contrast, MED is a mild dysplasia. Many patients are of normal height. Radiographic abnormalities are limited to epiphyses with little or no spinal involvement (Haga et al. 1998).

They look apparently different, but are the same in essence. Transitional cases have been known (Hall and Dorst 1969). Therefore, they have been grouped together in the international classification, and molecular studies confirmed that they are nothing but a part of the continuous spectrum of the *COMP* mutation (Unger and Hecht 2001). The mildest end of the spectrum may be common idiopathic OA. We have experienced a family with mild dysplasia harboring a *COMP* mutation that was diagnosed as having familial OA (Kawaji et al. 2002).

To clarify the spectrum of the *COMP* mutation and its phenotypes, we examined the *COMP* mutation in 35 consecutive Japanese patients (Itoh et al., unpublished).

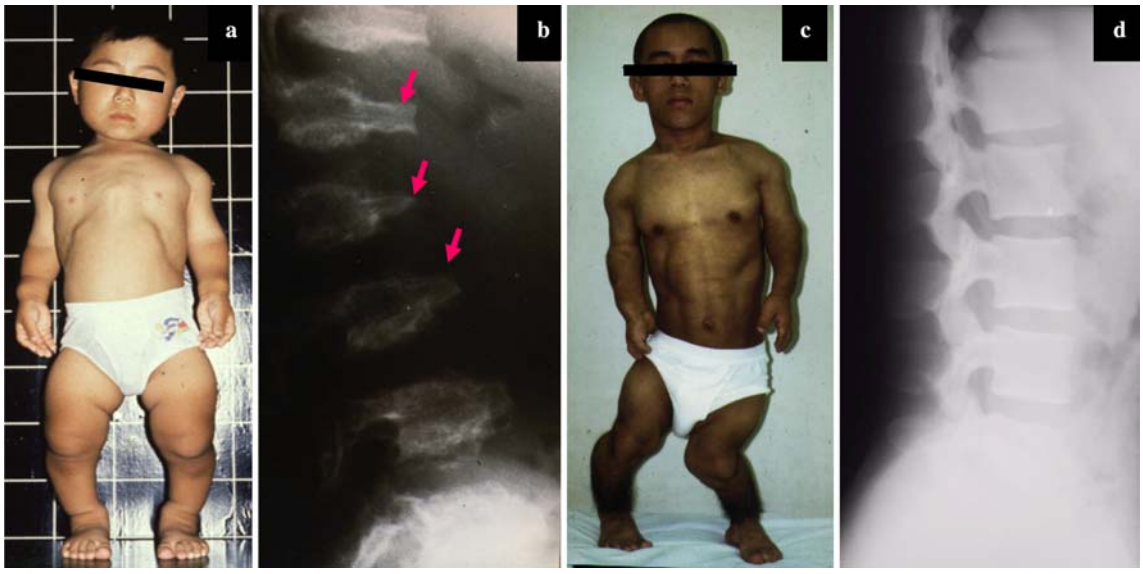

Fig. 1a–d Skeletal features change with age. **a** A pseudoachondroplasia patient aged 6. Short-limbed short stature resembling achondroplasia, but the patient is of normal facies. **b** Lateral radiograph of the spine aged 6 showing the "anterior tongue-like protrusion" appearance (*red arrow*). **c** The same patient aged 17. The short stature and deformity of extremities have become more conspicuous. **d** Lateral radiograph of the spine aged 17. The characteristic feature has disappeared

Detection rate of the *COMP* mutation is very high in cases with clinical diagnosis of PSACH. Mutations are clustered in CLRs, especially in the seventh CLR (Ikegawa et al. 1998a, b). Then, we examined genotype–phenotype association and found correlation between the position of *COMP* mutations and the severity of short stature. Mutations in seventh CLR cause extremely severe short stature, while mutations elsewhere show relatively mild phenotype (Mabuchi et al. 2003). In contrast to PSACH, *COMP* mutation is found in only 1/5 of MED patients. This is due to genetic heterogeneity in MED. Five other genes have already been recognized: for the dominant-type MED, *COL9A1–A3* encoding α1–3(IX) chains of type IX collagen (Muragaki et al. 1996; Paassilta et al. 1999; Czarny-Ratajczak et al. 2001), respectively, and *MATN3* encoding matrilin 3 (Chapman et al. 2001); and for the recessive-type MED, *DTDST* encoding diastrophic dysplasia–sulfate transporter (Superti-Furga et al. 1999). As there are many MED genes, genetic diagnosis is difficult and inefficient.

If we could differentiate them a priori, we would be able to reduce time and labor so much. The hint was in pathology. Chondrocytes from *COMP* diseases have intracellular inclusion bodies (Stanescu et al. 1992). This is the enlarged rough-surfaced endoplasmic reticulum containing COMP. We hypothesized that the *COMP* mutation impairs the protein's secretion into the cartilage matrix, and we tested whether COMP in blood is decreased in the patients. Plasma COMP level is decreased in patients with *COMP* mutation, indicating that we can screen the presence of *COMP* mutations by a blood test (Mabuchi et al. 2004b).

MATN3 mutation is the most common MED mutation in Japanese (Mabuchi et al. 2004a). Mutations are clustered in the von Willebrand factor type A domain, suggesting the importance of this region in vivo. Type IX collagen mutations are not common in Japanese MED. Interestingly, all type IX collagen mutations result in loss of the third collagenous domains by skipping of a single exon. Previous studies reported that double-layered patella is specific to *DTDST* mutation; however, we found it in a case with type IX collagen mutation (Nakashima et al. 2005). Systematic examination by integration of such clinical and genetic information en-

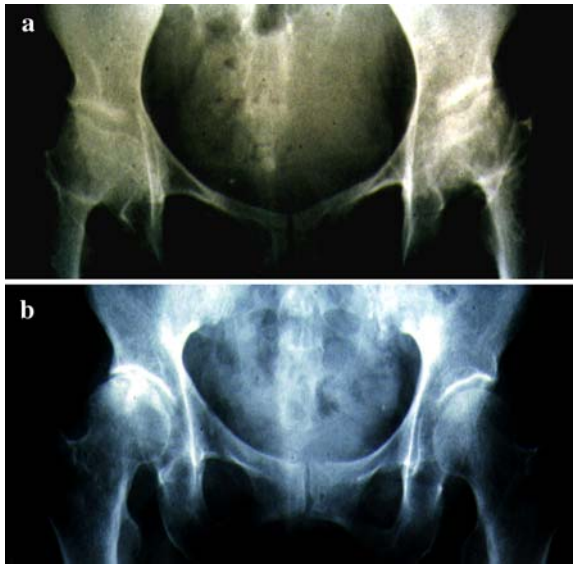

Fig. 2a, b Radiographs of hip osteoarthritis (OA). **a** Multiple epiphyseal dysplasia (MED). Severe, early-onset OA at the age of 30. **b** Common idiopathic OA at the age of 66

ables the efficient genetic diagnosis of MED. Of course, further identification of unknown MED genes is necessary for this system. Known gene mutations were found in fewer than half of the MED patients (Jackson et al. 2004; Jakkula et al. 2005). Familial cases not linked to known MED loci exist (Jakkula et al. 2005; our unpublished experience).

Identification of disease genes

We have to identify the disease genes in order to make genetic diagnosis possible. Due to the Human Genome Project, the task has become much easier. To identify the genes, integration of clinical and genetic information is important, also. Before the Project, there were so many steps that were all time and labor consuming. Even after the gene to be examined was determined, there remained so many tasks, including determination of sequences of cDNA and genomic DNA, determination of gene structures, construction of the mutation detection system, designing of PCR, determination of sequence of patients and exclusion of polymorphisms. In the post-genome-sequence era, most of the tasks have disappeared; a huge amount of information is available. After you determine the candidate gene, all you have to do is check the DNA sequence of the patients.

If you successfully integrate clinical and genetic information, identification of disease genes is easy. The best example is the identification of the gene for metaphyseal chondrodysplasia, Schmid type (OMIM 156500; Warman et al. 1993), followed by that for spondylometaphyseal chondrodysplasia, Japanese type (Hasegawa et al. 1994; Ikegawa et al. 1998a, b). Furthermore, by integration of information on humans and mice, we can speed up the identification of disease genes. Linkage in humans can not narrow down the critical region, but we can do it in mice because we can freely enlarge the family in mice. The comparative genomics approach including synteny mapping could further localize the gene. Phenotyping of mice is difficult, but in humans a huge list of phenotypes are collected in the medical record. Many probands are available in human. Thus, the integrated approach could make gene identification and subsequent functional analysis much easier.

Advances in classification

Based on the genetic information, reclassification of skeletal dysplasia is rapidly progressing. The most significant progress is found in the group of lethal skeletal dysplasias. Previously, the spondylodysplastic and other perinatally lethal group consisted of achondrogenesis type 1A (OMIM 200600) and lethal platyspondylic skeletal dysplasias (LPSD). Four subtypes of the LPSD group are known: thanatophoric dysplasia, and LPSDs, San Diego type (OMIM 270230), Torrance type (OMIM 151210), and Luton type (OMIM 151210). *FGFR3* mutations were found first in thanatophoric dysplasia (Tavormina et al. 1995) and then in LPSD, San Diego type (Brodie et al. 1999), transferring them to the achondroplasia group. Accumulation of cases and the presence of intermediate forms of LPSD, Torrance and Luton types, indicated that they are an identical entity and their phenotypes are reminiscent of severe forms of SEDC. Therefore, we examined the *COL2A1* mutation in LPSD, Torrance type, and found mutations specifically in its C-terminal region (Nishimura et al. 2004). LPSD, Torrance and Luton types, will be moved to the SEDC group. Classification based on molecular pathogenesis, such as "type II collagenopathy" and "type X collagenopathy," has already been included in the current classification (Hall 2002), and this trend will continue in the future classification.

Table 1 Skeletal dysplasias and their disease genes associated with osteoarthritis

Skeletal dysplasia	Disease gene (gene symbol)
SED congenita	*COL2A1*
SED tarda	*COL2A1, SEDL*
Stickler dysplasia	*COL2A1, COL11A1-A2*
Pseudoachondroplasia	*COMP*
MED	*COMP, COL9A1-A3, MATN3, DTDST*
PPRC	*WISP3*

SED Spondyloepiphyseal dysplasia, *MED* multiple epiphyseal dysplasia, *PPRC* progressive pseudorheumatoid chondrodysplasia

Significance of genetic research for skeletal dysplasia

The genetic study of skeletal dysplasia helps us to provide better care and treatment for patients who are suffering from this disabling condition. In addition, through its study, we can approach the molecular mechanism of the skeletal formation of humans because all the disease genes are associated with skeletal formation in human. The list of the disease genes includes a huge variety of molecules including extracellular matrix proteins, enzymes, hormones, cytokines and their receptors, and transcription factors. The variety reflects the complexity of skeletal formation in vivo. Using the human disease genes as starting points, we can clarify the complex mechanism. Best examples are *SOX9* for campomelic dysplasia (Foster et al. 1994) and *CBFA1*/*RUNX2* for cleidoclanial dysplasia (Otto et al. 1997).

Furthermore, skeletal dysplasias are genetic models for common bone and joint diseases, including OA, osteoporosis, rheumatoid arthritis, scoliosis and disc herniation. For example, there are many skeletal dysplasias associated with OA (Table 1). These diseases are nothing but severe, early onset, hereditary forms of OA (Fig. 2). Their disease genes are being identified, and are all good candidate genes for common idiopathic OA.

The study of the rare monogenic diseases can bring a breakthrough for clarifying the genetic aspects of common diseases.

Thus, as regards medicine and basic science, research into skeletal dysplasia will give us a lot of knowledge. Integration of clinical and genetic information is the key to success for research in the genome era.

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