that the Sanjad-Sakati syndrome and type 1 Kenny-Caffey syndrome are at least allelic disorders if not the same condition. Despite the multiplicity of abnormalities, including intrauterine growth retardation, mental retardation, and facial dysmorphism with congenital hypoparathyroidism, there is currently no information about the nature of the underlying molecular defect in either disorder. Mapping of the locus responsible now offers promise for analysis of candidate genes or positional cloning as likely methods to delineate the molecular basis.

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J Med Genet 2000;**37**:64–65

Molecular diagnosis is important to confirm suspected pseudoachondroplasia

EDITOR—Pseudoachondroplasia (PSACH) is an autosomal dominant chondrodysplasia. In the majority of clinically defined cases, mutations have been identified in the gene encoding cartilage oligomeric matrix protein (*COMP*).[1] Mutations in the *COMP* gene have also been identified in some forms of multiple epiphyseal dysplasia (MED), a related skeletal dysplasia.[1] All of the mutations associated with PSACH and MED have been found in exons encoding the type III repeat region or C-terminal domain of *COMP*.

Clinically, PSACH is characterised by short limbed dwarfism, which first becomes apparent in infancy, short fingers, ligamentous laxity, scoliosis, and early onset osteoarthritis (OA).[2] Radiographic features include small irregular epiphyses with delayed ossification, flared metaphyses, anterior beaking of the vertebral bodies, and delayed maturation of the triradiate cartilage and acetabulum.[3]

We report three patients who had previously been given erroneous diagnoses, in whom mutations in exon 13 of the *COMP* gene have been identified. This emphasises the utility of molecular diagnosis, particularly in adult patients where radiological diagnosis can be difficult.

All three affected subjects were born to unaffected parents. Each was of normal intelligence and normal facial appearance.

Case 1 presented at 5 years because of pain in both hips. Numerous diagnoses, including spondyloepiphyseal dysplasia congenita with coxa vara and Morquio's syndrome, were considered following *x* ray examination. Extensive surgery over the following years included a left femoral osteotomy and bilateral Girdlestones operations to treat her osteoarthritis. She has had two unaffected children. Examination at 65 years showed her height at 136 cm (<3rd centile), reduced extension at the elbows, short, stubby fingers, and severe kyphosis. Radiological examination showed rhizomelic limb shortening, a prominent deltoid insertion, brachydactyly, metaphyseal broadening, extensive degenerative changes of the knee and elbow, femoral head destruction with formation of pseudoacetabula superiorly bilaterally, a thoracolumbar kyphosis with anterior wedging of the lower thoracic vertebral bodies, and a horizontal sacrum.

Case 2 first presented at 3 years with short stature (87.5 cm, <3rd centile) and bowed legs. Clinical and radiological examination suggested a diagnosis of spondylometaphyseal dysplasia type Kozlowski. Eight operations had been performed to effect tibial lengthening and straightening. Examination at 16 years showed a height of 124 cm (<3rd centile), genu varum, a waddling gait, and short stubby fingers. *X* ray appearances showed ovoid vertebral bodies, epiphyseal involvement, hypoplasia of the iliac bone, splayed irregular metaphyses, and evidence of the multiple operations, with pins and a plate in situ.

Case 3, a 36 year old woman initially presented at 18 months with an intermittent limp. Radiological assessment at this time was normal. Referral at 9 years for investigation of bilateral hip and left knee pain confirmed short stature, 107 cm (<3rd centile), with rhizomelic limb shortening, short fingers, and a waddling gait. Radiological assessment showed abnormal epiphyses and metaphyses, but normal vertebral bodies. At this time diagnoses of multiple epiphyseal dysplasia, PSACH, and Morquio's syndrome were all considered. At 21 years she had surgery to correct a subluxated left patella. She was recently referred to our department with a diagnosis of achondroplasia. She is awaiting bilateral total hip replacements for treatment of osteoarthritis. Examination showed a height of 125.5 cm (<3rd centile), short fingers, mild ligamentous laxity, and a waddling gait. *X* ray appearances showed marked epiphyseal involvement of the knees, hips, and wrists bilaterally, anterior beaking of the vertebral bodies, and metaphyseal changes in the metacarpals.

All three cases presented during infancy, had height below the 3rd centile, and rhizomelic limb shortening, normal skulls, and short, stubby fingers. Cases 1 and 3 both had severe osteoarthritis affecting their hips bilaterally and necessitating surgery. Case 1 also had a severe dorsolumbar kyphosis and case 2 genu varum. The features are all within the recognised spectrum associated with PSACH and although radiological investigations were compatible with this diagnosis they were not definitive. Previous *x* rays

taken in childhood were not available from the three patients. In view of this, the clinical presentation, and the previous difficulty in diagnosis, molecular confirmation was sought.

Mutation screening in exons of the *COMP* gene using SSCP and sequence analysis has been described previously.[1] In addition to mutation screening in genomic DNA from all three patients, we also screened for a *COMP* mutation in RNA isolated from a skin fibroblast cell line established on case 3. In this instance, cDNA was PCR amplified using primers flanking the type III repeat region and C-terminal domain of *COMP*. The oligonucleotide primers used were CaMF (5'-ggt cgc gac act gac cta gac-3') and CaMR (5'-ggt gag cgt gac ttc cag cgt t-3'), which amplified a 789 bp fragment containing the entire type III repeat region, and CtF (5'-gaa gtc acg ctc acc gac-3') and CtR (5'-cta ggc ttg ccg cag ctg atg g-3'), which amplified a 702 bp fragment containing the entire C-terminal domain.

Each patient was found to have a mutation in exon 13 of COMP. Case 1 was heterozygous for an in frame 3 bp deletion of GAG between nucleotides 1394-1397, which is predicted to result in the deletion of glutamic acid at residue 457. Case 2 was found to be heterozygous for an in frame 3 bp deletion of GAC between nucleotides 1430-1444, which is predicted to result in the deletion of an aspartic acid residue from between residues 469-473. Case 3 was found to be heterozygous for a G to T transversion at nucleotide 1418, which is predicted to result in the substitution of glycine by serine at residue 465. All of the mutations affect residues within the seventh repeat of the type III repeat region and are predicted to result in a qualitative defect in the COMP protein. The in frame deletion of one or more residues from the type III repeats of *COMP* have been described previously.[1] The G465S substitution affects a highly conserved glycine residue and the substitution of equivalent glycine residues in the second, fourth, and sixth type III repeats have previously been identified in patients with PSACH. Previous work has determined that in approximately 40% of cases of PSACH, deletion mutations in exon 13 of the *COMP* gene are responsible.[1] Our work (present study and M D Briggs, unpublished data) suggests that approximately 50% of all PSACH results from various mutations, either deletions/duplications or point mutations, in exon 13 of the *COMP* gene and we propose that analysis of this exon would be an appropriate initial step in the evaluation of a patient with suspected PSACH. We have also shown that it is possible to screen for *COMP* gene mutations in mRNA isolated from skin fibroblast cell lines using RT-PCR. This approach will allow for the rapid screening of mutations and used in conjunction with genomic analysis of the *COMP* gene will help provide molecular diagnosis to confirm a clinically suspected diagnosis of PSACH.

Diagnosis of PSACH has previously been based on the clinical assessment and the characteristic radiological features of people with short stature. These three cases show the difficulty in making a definitive diagnosis of PSACH in the absence of molecular confirmation. Accurate diagnosis is important, not only so that reproductive options may be considered in an informed context, but also so that accurate information about the prognosis of the condition may be provided.[4] In case 1 the erroneous differential diagnoses had been made 50 years ago and had not been re-evaluated in the interim, despite the improved and expanded classification of the skeletal dysplasias. Molecular diagnosis can be especially helpful in adulthood when radiological diagnosis is more difficult owing to concomitant changes resulting from osteoarthritis.

This work was supported by grants from the Arthritis Research Campaign (MDB is an ARC Post-Doctoral Research Fellow) and Wellcome Trust (BN is a Wellcome Trust Clinical Training Fellow).

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J Med Genet 2000;**37**:65–67

Biallelic expression of *IGFBP1* and *IGFBP3*, two candidate genes for the Silver-Russell syndrome

EDITOR—Silver-Russell syndrome (SRS) is a condition characterised by intrauterine and postnatal growth retardation with relative sparing of cranial growth, triangular facies, fifth finger clinodactyly, and facial, limb, or truncal asymmetry.[1 2] The molecular basis of SRS remains elusive and seems likely to be heterogeneous. However, maternal uniparental disomy of chromosome 7 (mUPD7) has been found in approximately 10% of SRS patients, suggesting that at least one gene on chromosome 7 is imprinted and involved in the pathogenesis of this condition.[3 4] Interest has surrounded the human chromosomal region 7p12-13, which is homologous to mouse proximal chromosome 11, since mUPD for this region in mice leads to prenatal growth failure.[5] Within this region lie the genes for insulin-like growth factor binding proteins 1 and 3 (*IGFBP1* and *IGFBP3*). Both are involved in regulation of fetal growth via the insulin-like growth factor axis.[6] *IGFBP1* and *IGFBP3* are therefore obvious candidates for a role in the SRS phenotype associated with mUPD7.[3 4]

In order to determine whether *IGFBP1* and/or *IGFBP3* are likely to be implicated in SRS, we have investigated their imprinting status in normal fetal tissues collected from termination of pregnancies. Samples were obtained from Queen Charlotte's and Chelsea Hospital with the approval of the Research Ethics Committee of the Royal Postgraduate Medical School (96/4955) and from the MRC Tissue Bank at Hammersmith Hospital (L Wong). Genomic DNA and total RNA was extracted from these tissues and RT-PCR performed as previously described.[7] The primers used in this study are listed in table 1. PCR was carried out for 35 cycles for all reactions. Products