Table 2 Risk estimates for the likelihood of VHL disease given a patient presenting with a single ocular angioma for differing combinations of clinical and molecular information

	Age group (y)			
Other negative information	*<20*	*21–40*	*41–60*	*>60*
None	0.30	0.30	0.30	0.30
DNA	0.11	0.11	0.11	0.11
Systemic screening	0.27	0.13	0.06	0.02
Parental history	0.19	0.13	0.09	0.09
Parental history + systemic screening	0.17	0.05	0.02	0.01
DNA + parental history	0.06	0.04	0.03	0.03
DNA + systemic screening	0.10	0.04	0.02	0.01
DNA + systemic screening + parental history	0.06	0.01	<0.01	<0.01

angioma after careful ophthalmic examination, and a combination of other negative information, are summarised in table 2.

Although some caution should be exerted when extrapolating these results to other populations (for example, the mutation detection sensitivity will depend on the precise investigations performed and the prevalence of sporadic ocular angioma might vary), this analysis does, for the first time, provide clinicians with risk estimates for the likelihood of underlying systemic disease in patients with a solitary ocular angioma. This information will help determine the most appropriate investigation and management of such patients.

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1 Maher ER, Yates JRW, Harries R, Benjamin C, Harris R, Ferguson-Smith MA. Clinical features and natural history of von Hippel-Lindau disease. *Q J Med* 1990;**77**:1151-63.
2 Webster AR, Moore AT, Maher ER. The clinical characteristics of ocular angiomatosis in von Hippel Lindau disease and correlation with germline mutation. *Arch Ophthalmol* 1999;**117**:371-8.
3 Maher ER, Iselius L, Yates JR, *et al*. Von Hippel-Lindau disease: a genetic study. *J Med Genet* 1991;**28**:443-7.
4 Webster AR, Maher ER, Bird AC, Gregor ZJ, Moore AT. A clinical and molecular genetic analysis of solitary ocular angioma. *Ophthalmology* 1999; **106**:623-9.
5 Rosner B. *Fundamentals of biostatistics*. 4th ed. Chapter 5. London: Wadsworth, 1995.
6 Maher ER, Webster AR, Richards *et al.* Phenotypic expression in von Hippel-Lindau disease: correlations with germline VHL gene mutations. *J Med Genet* 1996;**33**:328-32.

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Confirmation of the assignment of the Sanjad-Sakati (congenital hypoparathyroidism) syndrome (OMIM 241410) locus to chromosome lq42-43

EDITOR—Over the past 12 years, 26 patients with an unusual syndrome of congenital hypoparathyroidism associated with severe prenatal and postnatal growth retardation and a pattern of facial anomalies have been seen at the King Faisal Specialist Hospital and Research Centre, Saudi Arabia.[1 2] The disorder has been listed by McKusick in OMIM as "hypoparathyroidism-retardation-dysmorphism syndrome; HRD" as entry 241410. Recently, Parvari *et al*[3] reported the assignment of the gene for this disorder to chromosome 1 at 1q42-43. Their report was based on a study of consanguineous Bedouin families from Israel and their linkage analysis was based on homozygosity by descent.[4] This reports describes a study of three consanguineous Saudi families, which yielded results consistent with the 1q42-43 location of the responsible gene.

Blood samples were collected and DNA extracted from three Saudi families consisting of first cousin parents and their 14 children, five of whom manifested the Sanjad-Sakati syndrome. DNA samples were pooled from the five affected children and a separate pooled sample prepared from the DNA of their nine unaffected sibs. The initial analysis included PCR amplified DNA markers linked to genes involved either in parathyroid structure or function.[5] As no evidence of linkage was found, the analysis was expanded to the human genome screening set from Research Genetics (Huntsville, Alabama). The analysis proceeded from chromosome 22 to chromosome 1. A positive result was based on finding a single band in the pooled sample from the affected children indicating homozygosity, while the pooled sample from the unaffected sibs showed two or more bands. A positive result with marker DlS235 prompted analysis of all 20 samples separately with the additional markers D1S1656, D1S163, D1S179, D1S2712, D1S1540, D1S1680, D1S2678, D1S2680, D1S2850, D1S373, and D1S2670, all of which cluster around 1q42-43.

Multipoint lod scores were generated using MAPMAKER/HOMOZ.[6] Analysis of the data assumed equal frequencies of the alleles at each marker. The order of the markers was taken from the maps published by Broman *et al*.[7] The data showed that the affected sibs in the three families were homozygous for markers that clustered around the marker D1S235. A maximum lod score of 4.12 around D1S235 at 1q42-43 was obtained. Flanking markers D1S1656 and D1S2678 were consistent with those found by Parvari *et al*[3] and suggest a candidate region maximally at 1 cM.

The initial report of Sanjad *et al*[1] in 1988 and their definitive report in 1991[2] clearly established this as a distinct disorder with autosomal recessive inheritance. The consistency with which hypocalcaemic tetany or seizures or both occur in intrauterine growth retarded infants suggests that this is not a diagnosis likely to be missed. That this disorder has only been reported in consanguineous Arabic families suggests that a founder effect of a long standing mutation is responsible for this disorder.

Kenny-Caffey syndrome type 1 is clinically manifest as growth retardation, craniofacial anomalies, small hands and feet, hypocalcaemia, hypoparathyroidism, and radiological evidence of cortical thickening in the long bones with medullary stenosis and absent diploic space in the skull. The original reports of Caffey[8] and Kenny and Linarelli[9] suggested autosomal dominant inheritance and the condition is now referred to as Kenny-Caffey syndrome type 2. In 1997 Khan *et al*[10] reported on 16 affected children with Kenny-Caffey syndrome type 1 in six unrelated sibships born to healthy, consanguineous, Bedouin parents from Kuwait. From this group of patients, Diaz *et al*[11] in 1998 mapped the locus for this disorder to 1q42-43. All of this information taken together suggests

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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1 Sanjad SA, Sakati NA, Abu-Osba YK. Congenital hypoparathyroidism with dysmorphic features: a new syndrome. *Pediatr Res* 1988:**22A**.
2 Sanjad SA, Sakati NA, Abu-Osba YK, Kaddoura R, Milner RDG. A new syndrome of congenital hypoparathyroidism, severe growth failure and dysmorphic features. *Arch Dis Child* 1991;**66**:193-6.
3 Parvari R, Hershkovitz E, Kanis A, *et al*. Homozygosity and linkage disequilibrium mapping of the syndrome of congenital hypoparathyroidism, growth and mental retardation, and dysmorphism to a 1-cM interval of chromosome 1. *Am J Hum Genet* 1998;**63**:163-9.
4 Lander ES, Botstein D. Homozygosity mapping: a way to map human recessive traits with the DNA of inbred children. *Science* 1987;**236**:1567-70.
5 Shashi V, Golden WL, Allinson PS, Kelly TE. Molecular analysis of recombination in a family with a large pericentric X-chromosome inversion. *Am J Hum Genet* 1998;**58**:1231-8.
6 Kruglyak L, Daly MJ, Lander ES. Rapid multipoint linkage analysis of recessive traits in nuclear families, including homozygosity mapping. *Am J Hum Genet* 1995;**56**:519-27.
7 Broman KW, Murray JC, Sheffield VC, White RL, Weber JL. Comprehensive human genetic maps: individual and sex-specific variation in recombination. *Am J Hum Genet* 1998;**63**:861-9.
8 Caffey J. Congenital stenosis of medullary spaces in tubular bones and calvaria in two proportional dwarfs - mother and son coupled with transitory hypocalcemic tetany. *AJR* 1967;**100**:1-11.
9 Kenny FM, Lineralli L. Dwarfism and cortical thickening of tubular bones: transient hypocalcemia in mother and son. *Am J Dis Child* 1985;**111**:201-7.
10 Khan KTS, Uma R, Usha R, Al Ghanem MM, Al Awadi SA, Farag TI. Kenny-Caffey syndrome in six Bedouin sibships: autosomal recessive inheritance is confirmed. *Am J Med Genet* 1997;**69**:126-32.
11 Diaz GA, Khan KTS, Gelb BD. The autosomal recessive Kenny-Caffey syndrome locus maps to chromosome 1q42-43. *Genomics* 1998;**54**:13-18.

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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