npg

ARTICLE

Is the novel SCKL3 at 14q23 the predominant Seckel locus?

Mehmet Okyay Kılınç[1,6], Vasiliki Ninidu Ninis[1], Sibel Aylin Uğur[1], Beyhan Tüysüz[2], Mehmet Seven[3], Sevim Balcı[4], Judith Goodship[5] and Aslıhan Tolun*[,1]

[1]Department of Molecular Biology and Genetics, Boğaziçi University, Istanbul, Turkey; [2]Department of Pediatrics, Cerrahpaşa Medical School, Istanbul University, Istanbul, Turkey; [3]Genetic Research Center, Cerrahpaşa Medical School, Istanbul University, Istanbul, Turkey; [4]Department of Clinical Genetics, Hacettepe University, Ankara, Turkey; [5]Institute of Human Genetics, Newcastle University, Newcastle-upon-Tyne, UK

Seckel syndrome (SCKL) is a rare disease with wide phenotypic heterogeneity. A locus (SCKL1) has been identified at 3q and another (SCKL2) at 18p, both in single kindreds afflicted with the syndrome. We report here a novel locus (SCKL3) at 14q by linkage analysis in 13 Turkish families. In total, 18 affected and 10 unaffected sibs were included in the study. Of the 10 informative families, nine with parental consanguinity and one reportedly nonconsanguineous but with two affected sibs, five were indicative of linkage to the novel locus. One of those families also linked to the SCKL1 locus. A consanguineous family with one affected sib was indicative of linkage to SCKL2. The novel gene locus SCKL3 is 1.18 cM and harbors ménage a trois 1, a gene with a role in DNA repair.

Introduction

Seckel syndrome (SCKL) is characterized by microcephaly, low birth weight-type proportionate dwarfism, and a bird-like head (SCKL [MIM 210600]). Mental retardation is present, but to a much lesser degree than would be expected in view of the very small skull. Some patients exhibit additional clinical findings such as large bulging eyes, cleft palate, skeletal or dentition abnormalities, ocular manifestations, pancytopenia, and chromosome instability. In view of the wide clinical heterogeneity, Di Blasi et al[1] suggested that the syndrome was overdiagnosed and that only 19 of the 44 cases reported since HPG Seckel described the syndrome in 1960[2] were truly Seckel. On the other hand, Arnold et al[3] suggested that SCKL represented a spectrum of Seckel disorders. The syndrome is inherited in an autosomal recessive fashion and very rare, as only less than 25 families with two or more affected siblings have been reported.

Emergence of genetic heterogeneity was not a surprise, since the phenotypic heterogeneity was known to be high and a wide spectrum of clinical findings have been reported. Autozygosity mapping in two Pakistani families from the same village revealed the first gene locus SCKL1 in a 12-centi Morgan (cM) region at 3q22.1–q24,[4] while a second locus SCKL2 was identified at 18p11.31–q11.2 (30 cM) in a consanguineous family of Iraqi descent.[5] In addition, O'Driscoll et al[6] identified mutations in the DNA ligase IV gene in three unrelated patients, all with Seckel-like features and pancytopenia, and designated the locus LIG4. We studied 13 unrelated Turkish Seckel families, 10 of which were informative, and report here a novel locus at 14q23, which we designated SCKL3. Intriguingly, an affected sib pair was homozygous at both SCKL1 and SCKL3. Another family was indicative of linkage to SCKL2.

Materials and methods
Subjects
We studied 13 unrelated families. They originated from different parts of the country, with the exception that two originated from the same province, but different towns. There were 18 patients in total, nine males and nine females. The ages of the patients ranged from 5 months to 35 years. Appropriate informed consent was obtained from families for the study. Five of the families (Families 1–4 and 8) had two affected sibs each, and the number of unaffected sibs was 3, 3, 1, 0, and 1, respectively. Eight families had only one affected sib each, with two of them (Families 9 and 11) having, in addition, one unaffected sib each available for study. Parental consanguinity was reported in all except four: one with two affected sibs (Family 4) and three with one each (Families 6, 7, and 13). Facial appearances of patients in Families 1 and 2 are given in Figures 1 and 2. Clinical data were available from 15 patients in 11 of the families. The common clinical findings in those patients were short stature (both prenatal
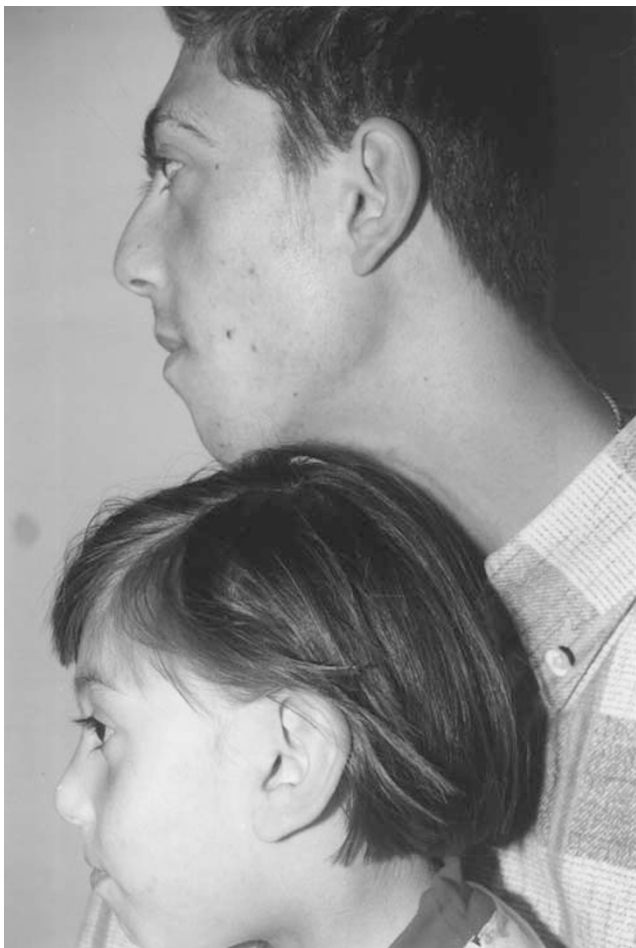

Figure 2 Facial appearance of Patients 3 (left) and 4 (right), Family 2.

and postnatal), head smaller with respect to the body, eyes not large or bulging, high nasal bridge, no malformations in ears, profound microcephaly with mental retardation, no pancytopenia or chromosome breaks, and normal karyotype. Some other phenotypic and clinical manifestations that are considered typical for SCKL but not shared by all patients studied as well as general information on families are given in Table 1 for Families 1, 2, 3, and 5. Additional findings for the patients were as follows: patients 3 and 4 (Family 2) had unilateral convergent strabismus and pes planus. In addition, Patient 3 had upslanting peribral fissures. Patient 9 (Family 5) was reported to have hyperactive and aggressive behavior. She had ptosis, bilateral iris coloboma, pectus carinatus, and bilateral camptodactyly between the third and fourth fingers/toes on the hands/feet. Multiple café-au-lait spots (maximum $1\,cm \times 1\,cm$) were present on her right shoulder. Patient 10 (Family 6) was reported to have seizures. Patient 12 (Family 8) had severe motor retardation, contractures, debility, and Rett-like behavior. She was not cooperative and had an IQ of 20. Computerized tomography (CT) results at age 9 years revealed craniosynostosis and bilateral frontotemporal and subarachnoid dilatation in addition to cerebral atrophy. The findings were confirmed 5 years later. Fundoscopic findings were normal. Patient 13 (also in Family 8) was hospitalized at 10 months of age due to convulsions not accompanied by fever. At age 7 years, she had severe motor and mental retardation, and teeth gritting was noted. She had Rett-like behavior.

Blood samples from Families 4 and 7 were kindly provided by Drs Y Aslan and FM Aynacı.

DNA analysis
DNA was extracted from peripheral blood samples using standard methods. The genome scan was performed using

Figure 1 Facial appearance of Patients 1 (above) and 2 (below), Family 1.

Is SCKL3 the predominant Seckel locus?
MO Kılınç *et al*

853

Table 1 Additional phenotypic features for patients and general information on four of the families indicative of linkage to SCKL3

	Family 1		Family 2		Family 3		Family 5
Parental consanguinity	First cousin		Second cousin		Third cousin		First cousin
# Affected sibs	2		2		2		1
# Surviving normal sibs	3		3		1		5
# Deceased sibs	0		2[a]		0		0
Patient no.	1	2	3	4	5	6	9
Sex	M	F	M	M	F	M	F
Age (years)	24	6	35	29	12	9	12
Beaked nose	Yes	No	Yes	Yes	Yes	Yes	Yes
Long nose	Yes	No	Yes	Yes	Yes	Yes	No
Bird face	No	No	Yes	Yes	Yes	Yes	No
Small face	No	Yes	Yes	Yes	Yes	Yes	Yes
Facial asymmetry	No	No	Yes	Yes	No	No	No
Micrognathia	Yes	No	Yes	No	No	No	Yes
Narrow and high palate	No	No	Yes	Yes	No	No	Yes
Clinodactyly (fifth finger)	No	No	No	No	Yes	Yes	No
Simian crease	No	No	One hand	One hand	No	No	No
Can speak	Yes	Yes	No	Yes	Yes	Yes	Yes
Ophtalmological findings	None	None	Yes	Yes	None	None	Yes
Brain CT	Cortical hypoplasia	Agenesis of corpus callosum	NP[b]	NP	Normal	Normal	NP

[a]The family reported that one of the two girls had Seckel phenotype. [b]Not performed.

the low-density (about 25-cM spacing) microsatellite set Version 8 with 156 autosomal markers (Research Genetics). The alleles for the markers were resolved on 8% denaturing polyacrylamide gels and visualized by staining with silver nitrate, as described previously.[7]

Statistical analysis

Linkage analysis was performed under the assumption of autosomal recessive inheritance, full penetrance, a disease gene frequency of one in 100 000, consanguinity, and equal frequencies of marker alleles. The number of alleles for each marker was the number of different alleles observed in all families together. Two-point lod scores were calculated using the MLINK program of the FASTLINK 4.1 package. The LINKMAP program of the same package was used for multipoint parametric linkage analysis at SCKL3 allowing for locus heterogeneity. GENEHUNTER version 2.0 beta was used for calculating the multipoint lod score of Family 1 at SCKL1 and construction of haplotypes of all families, allowing minimum number of recombination events.

Results

We first carried out autozygosity mapping in the affected sib pairs of Families 1 and 2, both with parental consanguinity, for the purpose of localizing the gene responsible for the syndrome. The loci for all markers exhibiting shared homozygosity in a sib pair were further analyzed to investigate whether the parents were informative, the unaffected siblings had different genotypes than the patients, and the patients were also homozygous for

the nearby markers. Marker D14S592 in the screening set and the close-by marker D14S586 pointed out to a novel gene locus. Each sib pair shared haplotypes, while the genotypes of the unaffected siblings were different, supporting linkage to this locus at 14q, which we designated SCKL3. All remaining markers for which the patients were homozygous turned out to be identical in state.

Genotyping with markers that flanked D14S586 and D14S592 narrowed down the maximum region of homozygosity to 1.18 cM between markers D14S1429 and D14S997. Marker D14S586 had not been assigned to a contig (GenBank), but reported by GDB to be 0.66 Megabases (Mb) away from D14S592 and 0.49 Mb by UCSC Genome Bioinformatics. We analyzed the remaining families for the locus also. Two other sib pairs, one in Family 3 (with parental consanguinity) and the other in Family 4 (with reportedly nonconsanguineous parents who had their origins in the same geographical region) were also found homozygous for both the markers. The remaining sib pair (Family 8) was homozygous for D14S592 only, while both parents (first cousins) and the unaffected sister were heterozygous. All available unaffected sibs in these families that suggested linkage to SCKL3 (Families 1–5) had genotypes different from those of their affected siblings. The remaining families all had single affected sibs and were genotyped for the two markers delineating the maximum homozygosity region and the two markers that flanked them. Two of the single affected sibs (Families 5 and 6) were homozygous for both markers and one (Family 7) for D14S592 only. Only one of those (Family 5) was reported to have parental consanguinity. The haplotypes

Is SCKL3 the predominant Seckel locus?
MO Kılınç et al

854

Table 2 Map distances for markers and haplotypes for seven families at 14q

Locus	cM[b]	Kb[c]	Family 1 (1st cousin)[a]						Family 2 (2nd cousin)							Family 3 (3rd cousin)						Family 4 (none)			Family 5 (1st Cousin)		Family 6 (none)		Family 7 (none)	
			F1	M1 P1 P2	S1	S2	S3		F2	M2 P3 P4	S4	S5	S6	S7		F3	M3 P5 P6	S7				F4	M4 P7	P8	F5	P9	F6	M6 P10	F7	M7 P11

[a]Parental consanguinity. [b]Marshfield map. [c]GenBank sequence map. [d]GDB map.

---

for Families 1–7 and the positions of the markers at and around the locus are given in Table 2. Two-point lod scores were positive for Families 1–5 for both D14S586 and D14S592 and were as follows, respectively: Family 1, 1.58 and 1.18; Family 2, 1.55 and 1.58; Family 3, 1.01 and 1.31; Family 4, 0.00 and 0.60; and Family 5, 0.55 and 0.46. Families 6 and 7 with single affected sibs were uninformative, as no parental consanguinity had been reported. Family 8 was negative for the former marker and positive for the latter. It was considered not linking to the locus, since multipoint analysis yielded a negative lod score. The reason for this result was that a crossover between the two closely located markers was unlikely in first-degree consanguinity. The highest multipoint lod score between D14S586 and D14S592 was for Family 2 (2.99). All 13 families were subjected together to linkage analysis. Assuming homogeneity, a maximum lod score of 0.89 was obtained with D14S592 (Table 3), and allowing heterogeneity, 4.23. Multipoint analysis using four markers at a time produced additional support for locus heterogeneity: the maximum multipoint lod score under homogeneity was <2; whereas, when heterogeneity was allowed, a maximum Lod2 of 3.6 was obtained between D14S586 and D14S592 (alpha = 0.55). The gene locus was identified as the 1.18-cM interval between markers D14S1429 and D14S997.

While autozygosity mapping was in progress, the first locus for Seckel syndrome (SCKL1) was reported.[4] We had already detected autozygosity at the locus in the affected sib pair in Family 1 and used markers at 1–1.5-cM spacing to determine the extent of homozygosity. The maximum region of homozygosity was larger than that reported for the two Pakistani families[4] and spanned 11.07 cM or 9.2 Mb delineated by D3S3617 and D3S1608, and the minimal critical region was 8.42 cM or 5.95 Mb between D3S1316 and D3S2394. The haplotypes and the map positions of the markers at the locus are given in Table 4. The maximum two-point lod score obtained for the family was 1.65 at a recombination fraction of zero for marker D3S2326 (Table 4). Multipoint analysis gave a lod score of 1.91 around D3S1301. The maximum lod scores obtained in the analyses were much lower than the threshold value of three for accepting linkage; however, the available family members were too few to yield scores above 3.00. Nevertheless, this score was higher than that obtained for SCKL3 (1.12). Thus, Family 1 was very strongly indicative of linkage to SCKL1 as well. The patients in the other families were also analyzed for the entire SCKL1 locus and found not to exhibit any autozygosity for more than one marker for which the parents were informative. The exception was Patient 3 in Family 2, who was homozygous at the entire locus, but shared genotype with two of his unaffected brothers. His affected brother had a heterozygous genotype that was the same as the remaining unaffected brother.

Is SCKL3 the predominant Seckel locus?
MO Kılınç *et al*

855

Table 3 Two–point lod scores between Seckel syndrome and four markers on chromosome 14q

Marker and statistic	Lod score at theta =						
	0	*0.01*	*0.05*	*0.1*	*0.2*	*0.3*	*0.4*
D14S1429							
Lod1	−13.56	−5.29	−1.80	−0.66	−0.05	0.01	−0.02
Lod2	0.00	0.00	0.00	0.00	0.0001	0.01	0.00
Alpha	1.00	1.00	1.00	1.00	0.10	0.82	1.00
D14S586							
Lod1	−3.06	1.31	2.67	2.72	2.01	1.13	0.39
Lod2	2.76	2.76	2.76	2.72	2.01	1.13	0.39
Alpha	0.55	0.55	0.80	1.00	1.00	1.00	1.00
D14S592							
Lod1	0.89	3.58	4.17	3.80	2.58	1.41	0.48
Lod2	4.23	4.22	4.17	3.80	2.58	1.41	0.48
Alpha	0.70	0.75	1.00	1.00	1.00	1.00	1.00
D14S997							
Lod1	−9.55	−1.90	0.82	1.44	1.28	0.71	0.20
Lod2	0.42	0.52	1.03	1.44	1.28	0.71	0.20
Alpha	0.22	0.32	0.70	1.00	1.00	1.00	1.00

Lod1 = standard lod score; Lod2 = analysis under locus heterogeneity; alpha = proportion of families linked when Lod2 is maximized.

Table 4 Genetic positions for 14 markers at 3q, two-point lod scores, and haplotypes for Family 1

Locus	cM[a]	Kb[b]	F1	M1	P1	P2	S1	S2	S3	Z^c_{max}	θ_{MLE}
D3S2460	134.64	117,031	1 2	3 1	2 3	1 3	2 1	2 1	2 1	0.00	0.500
D3S3528	151.49	136,875	2 −	1 2	2 1	2 1	− 2	− 2	− 2	0.00	0.500
D3S2453	151.49	137,029	3 1	3 3	3 3	3 3	1 3	1 3	1 3	1.24	0.000
D3S1549	151.49	137,126	3 −	2 3	3 2	3 2	− 3	− 2	− 3	0.00	0.500
D3S3617	149.97	137,352	3 2	5 3	3 5	3 5	2 3	2 3	2 3	0.00	0.500
D3S1316	152.62	140,462	2 2	2 2	2 2	2 2	2 2	2 2	2 2	0.40	0.000
D3S1301	−	141,335	1 4	1 4	1 1	1 1	4 4	4 4	4 4	1.54	0.000
D3S3694	153.74	143,020	1 1	1 1	1 1	1 1	1 1	1 1	1 1	0.40	0.000
D3S2326	159.80	145,074	2 1	2 3	2 2	2 2	1 2	1 2	1 3	1.65	0.000
D3S1557	161.04	146,030	3 1	3 3	3 3	3 3	1 3	1 3	1 3	1.24	0.000
D3S2394	−	146,408	4 1	4 4	4 4	4 4	1 4	1 4	1 4	1.24	0.000
D3S1608	161.04	146,560	2 −	1 −	2 1	2 1	− 1	− 1	− −	0.00	0.500
D3S1744	161.04	147,977	4 2	4 5	4 4	4 4	2 4	2 4	2 5	1.65	0.000
D3S3705	165.02	149,932	2 1	2 1	2 2	2 2	1 2	1 2	2 2	0.42	0.105

[a]Marshfield map. [b]GenBank sequence map. [c]Maximum two-point lod score.

The linkage of Family 1 to both SCKL1 and the novel SCKL3 prompted us to analyze for SCKL3 the two consanguineous Pakistani families with two and three affected sibs who had been used to identify SCKL1. We wanted to rule out the possibility that SCKL1 might be a modifier locus only, rather than a locus that was responsible on its own for SCKL. Both families were found not to link to SCKL3.

Lastly, we investigated all families for linkage to SCKL2 at 18p, delineated by markers D18S78 and D18S866. We genotyped the patients using markers spread throughout the locus. The markers and their sequence map positions in kb are: D18S843 (8678), D18S1158 (10 799), D18S542 (11 550), D18S453 (13 001), D18S869 (19 814), D18S1107 (21 860), and D18S866 (23 101) in the order of telomeric to centromeric. The two outermost markers were outside the

homozygosity region. Only two patients (Families 7 and 11), both single affected, were homozygous for two consecutive markers, (D18S1158 and D18S542) in both cases. The lod scores for Family 11 were 0.67 and 0.56, respectively, for the markers. For Family 7, one parent was informative for one of the markers and the other for neither. With no known parental consanguity, the lod scores were zero. Thus, only Family 11 was considered indicative of linkage to this locus.

Discussion
We investigated all 13 families for linkage to all three SCKL loci. Three of the four families that had denied parental consanguinity were uninformative, each having a single affected sib. The reason why we included these families

in the linkage analysis was that, in our experience, most parent pairs originating from the same small geographical region have a high probability of having some degree of consanguinity, especially if they have sibs afflicted with a rare genetic disorder. Our results indicated that the novel locus was predominant. Patients from two pairs of families shared haplotypes, and these families originated from different parts of the country. Thus, a founder mutation should not be expected. Four of the consanguineous families did not link to any of the three SCKL loci. Therefore, further genetic heterogeneity for the disorder is evident. Recently, six informative families (one European and five African) were shown not to link to SCKL1 or SCKL2,[8] consistent with our findings that these loci were not predominant. However, whether SCKL3 is a dominant locus only in the Turkish population is an open question at present.

Only one of our families (Family 1) was consistent with linkage to SCKL1, and intriguingly, it also linked to SCKL3. One of the patients (Patient 3) in Family 2 was also homozygous at SCKL1. Whether this intriguing observation has any molecular basis cannot be resolved until both genes are identified.

The small size of the novel locus in the majority of the families was intriguing. Patients from all five families indicative of linkage to the locus were homozygous for at most two markers, except for Family 3, where homozygosity was 9 cM in one patient and at least 21 cM in the other. A narrow region of homozygosity is generally taken to indicate that there was also parental consanguinity a large number of generations ago, allowing several meiosis after the common ancestor carrying the original mutation. In that case, either a higher disease incidence or high embryonic lethality would be the underlying cause for the very low incidence. But only Family 2 reported miscarriages (three in total), and the fetuses had not been diagnosed. Underdiagnosis for the disease is another hypothesis; patients with no bird-face appearance could easily escape diagnosis.

Several observations on the phenotypes of the patients were worth noting. Some features typical for Seckel, such as the bird-head described originally by Virchow[9] as a prominent beaked nose, receding forehead and chin, and large bulging eyes, were not present in about half (8/15) of the patients. The patients in Families 2 and 6 had enhanced bird-head appearance, due to the way the head was positioned on the neck and to the much smaller size of the head in comparison to the neck and the body (Figure 2). This peculiar position of the head was not due to ptosis, as ptosis was not present. Also, the phenotypes of our patients were strikingly different than those of the SCKL2 patients, who had no receding forehead and heads not smaller as compared to other parameters.[5] However, a similarity was noted: Patient 9 in this study had café-au-lait spots as were also reported in all three patients in the SCKL2 family. The

patients in Family 8 stood apart from the others with the severe mental and motor retardation that they exhibited.

We noted a great variation in the phenotypes of the patients that linked to the novel locus. Great differences were also observed in brain CT investigation performed for five of our patients, who indicated linkage to SCKL3: cortical and cerebral atrophy in Patient 10 (Family 6), cortical hypoplasia in Patient 1 and agenesis of corpus callosum in Patient 2 (Family 1), and normal (apart from the small size) in the sibs in Family 3 (Patients 5 and 6). Various brain abnormalities have been reported for other Seckel patients; however, the gene locus was not known.[10]

Marker D14S586 that delineates the homozygosity region telomerically has not been assigned to a contig yet; therefore, its exact distance to the other markers at the locus is not known. Both GDB and UCSC Genome Bioinformatics reported it to be just telomeric to D14S592. Thus, we evaluated the 1.18-cM region between D14S1429 and D14S997 for candidate genes. The two markers have been assigned to the same contig with 1.8 Mb in between (GenBank). Among the numerous genes reported to reside in the region, we assessed ménage a trois 1 (MNAT1) as the best candidate to be responsible for SCKL3. The reasons were that MNAT1 was known to have a role in DNA repair and marker D14S592 for which the highest lod score was obtained was located within the gene. The gene codes for a ring finger protein that is one of the three components of CAK kinase and functions in the assembly of the complex.[11] It has eight exons and codes for a 309 amino-acid peptide. Seckel and Seckel-like syndromes are suspected to arise from defects in DNA repair genes. Genes for two Seckel-like diseases, namely LIG4[6] and Nijmegen Breakage syndrome,[12] as well as the only Seckel gene[13] have been shown to indeed have such roles.

Our results indicate that SCK3 is more common than SCKL1 and SCKL2 in the Turkish population. This report will contribute to testing of Seckel cases for linkage to SCKL3. As the novel locus is rather narrow, the gene responsible for the disorder might be identified in the near future. Identification of the gene responsible for the disorder would facilitate elucidation of the molecular basis of the disease and screening patients for gene mutations.

Electronic-Database Information
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for SCKL [MIM 210600])

Center for Medical Genetics, http://research.marshfieldclinic.org/genetics/ (for genetic mapping information)

The Genome Database (GDB), http://www.gdb.org/ (for genetic mapping information)

National Center for Biotechnology Information (NCBI), http://www.ncbi.nlm.nih.gov/ and UCSC Genome Bioinformatics, http://www.genome.ucsc.edu/ (to access GenBank)

References

1 Di Blasi S, Belvedere M, Pintacuda S *et al*: Seckel's syndrome: a case report. *J Med Genet* 1993; **24**: 75–96.

2 Seckel HPG: *Bird-headed dwarfs: studies in developmental anthropology including human proportions.* Springfield, IL: Charles C Thomas, 1960.

3 Arnold SR, Spicer D, Kouseff B, Lacson A, Gilbert-Barness E: Seckel-like syndrome in three siblings. *Pediatr Dev Pathol* 1999; **2**: 180–187.

4 Goodship J, Gill H, Carter J, Jackson A, Splitt M, Wright M: Autozygosity mapping of a Seckel syndrome locus to chromosome 3q22.1–q24. *Am J Hum Genet* 2000; **67**: 498–503.

5 Borglum AD, Balslev T, Haagerup A *et al*: A new locus for Seckel syndrome on chromosome 18p11.31–q11.2. *Eur J Hum Genet* 2001; **9**: 753–757.

6 O'Driscoll MK, Cerosaletti M, Girard PM *et al*: DNA ligase IV mutations identified in patients exhibiting developmental delay and immunodeficiency. *Mol Cell* 2001; **8**: 1175–1185.

7 Kavaslar GN, Önengüt S, Derman O, Kaya A, Tolun A: The novel genetic disorder microhydranencephaly maps to chromosome 16p13.3–12.1. *Am J Hum Genet* 2000; **66**: 1705–1709.

8 Faivre L, Le Merrer M, Lyonnet S *et al*: Clinical and genetic heterogeneity of Seckel syndrome. *Am J Med Genet* 2002; **112**: 379–383.

9 Virchow R: Vorstellung der birmesischen Zwerge mit einem Salzburger Riesen. *Z Ethnol* 1896; **28**: 524–528.

10 Capovilla G, Lorenzetti ME, Montagnini *et al*: Seckel's syndrome and malformations of cortical development: report of three new cases and review of the literature. *J Child Neurol* 2001; **16**: 382–386.

11 Tassan JP, Jaquenoud M, Fry AM, Frutiger S, Hughes GJ, Nigg EA: *In vitro* assembly of a functional human CDK7–Cyclin H complex requires MAT1, a novel 36 kDa RING finger protein. *EMBO J* 1995; **14**: 5608–5617.

12 Varon R, Vissinga C, Platzer M *et al*: Nibrin, a novel DNA double-strand break repair protein, is mutated in Nijmegen breakage syndrome. *Cell* 1998; **93**: 467–476.

13 O'Driscoll M, Ruiz-Perez VL, Woods CG, Jeggo PA, Goodship JA: A splicing mutation affecting expression of ataxia–telangiectasia and Rad3-related protein (ATR) results in Seckel syndrome. *Nat Genet* 2003; **33**: 497–501.