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Primary Autosomal Recessive Microcephalies and Seckel Syndrome Spectrum Disorders – RETIRED CHAPTER, FOR HISTORICAL REFERENCE ONLY

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Summary

NOTE: THIS PUBLICATION HAS BEEN RETIRED. THIS ARCHIVAL VERSION IS FOR HISTORICAL REFERENCE ONLY, AND THE INFORMATION MAY BE OUT OF DATE.

Clinical characteristics

Primary autosomal recessive microcephalies (MCPH) and Seckel syndrome (SCKS) spectrum disorders are characterized by microcephaly and the absence of visceral malformations. Although MCHP and SCKS were previously distinguished by height (maximum height in SCKS was equivalent to the minimum height in MCPH), stature is no longer a discriminating feature, leading to the conclusion that these phenotypes constitute a spectrum rather than distinct entities.

Microcephaly is characterized by:

- Onset during the second trimester of gestation;
- Occipito-frontal head circumference (OFC) at birth equal to or less than -2 SD below the mean for sex, age, and ethnicity;
- Slower than average increase in OFC after birth.

Variable findings in the MCPH-SCKS spectrum disorders include:

- Brain structure (which is normal in the majority);

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- Degree of cognitive impairment (usually mild to moderate without significant motor delay in the majority of persons with MCPH and more severe in those with SCKS and MCPH with brain malformations);
- Degree of short stature;
- Craniosynostosis (which may be secondary to poor brain growth).

Diagnosis/testing

The diagnosis of MCPH-SCKS spectrum disorders is based on clinical findings, brain imaging that shows reduced brain volume with grossly normal architecture, family history consistent with autosomal recessive inheritance, and molecular genetic testing when available. The genes in which biallelic mutation is known to cause MCPH-SCKS spectrum disorders are separated into those that are currently known to be associated with:

- MCPH phenotype only: *MCPH1* (locus name MCPH1), *WDR62* (MCPH2), *CDK5RAP2* (MCPH3), *KNL1* (MCPH4), *ASPM* (MCPH5), *STIL* (MCPH7), *CEP135* (MCPH8), and *CDK6* (MCPH12);
- SCKS phenotype only: *ATR* (locus name SCKL1), *NIN* (SCKL7), and *ATRIP*; and
- MCPH, SCKS, and/or intermediate phenotypes: *RBBP8* (locus name SCKL2), *CEP152* (MCPH9/SCKL5), *CENPJ* (MCPH6/SCKL4), *CEP63* (SCKL6), and *PHC1* (MCPH11).

Of note, roughly one half to three quarters of western Europeans or North Americans with MCPH have no identified gene defect; in contrast, the proportion of individuals with identified pathogenic variants appears higher in persons from the Indo-Pakistan area.

Management

Treatment of manifestations: Supportive therapy including special education, speech and language therapy, behavioral therapy, occupational therapy, and community services for families. Ritalin® may be helpful in managing hyperkinesia. Seizures are usually responsive to monotherapy with standard antiepileptic drugs (AEDs).

Surveillance: Neurologic follow up from birth to adulthood to detect behavioral difficulties, hyperactivity, attention disorder, and motor problems (spasticity), and to monitor for evidence of seizures, which can be late onset. Periodic neuropsychological evaluation to adapt interventions and schooling to the individual's abilities.

Genetic counseling

MCPH-SCKS spectrum disorders are inherited in an autosomal recessive manner. At conception, each child of two carrier parents has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk relatives and prenatal diagnosis for pregnancies at increased risk are possible if the pathogenic variants in the family are known.

Diagnosis

Constant findings in the primary autosomal recessive microcephalies (MCPH) and Seckel syndrome (SCKS) spectrum disorders are microcephaly and the absence of visceral malformations.

The microcephaly is characterized by the following:

- Onset during the second trimester of gestation
- Occipito-frontal head circumference (OFC) at birth that is equal to or less than -2 SD (and often < -3 SD) below the mean for sex, age, and ethnicity. After birth, the OFC continues to increase, but at a slower rate than usual, so that microcephaly (expressed in SD) tends to worsen over time. After age six months OFC is at least -3 SD. In older individuals, OFC ranges between -4 and -12 SD (mean -8 SD). Note: "Mild microcephaly" refers to an OFC between -2 SD and -3 SD.

- Small brain with small gyri. The volume of the cerebral hemispheres can be reduced to one third of normal, which is particularly evident in the cerebral cortex. The organization and topography of gyri are grossly normal; however, the pattern may be simplified.
- Hindbrain and cerebellum that are evenly reduced in size and normally shaped
- A significant correlation between the severity of microcephaly and both the degree of simplified gyration and the reduction of white matter volume

Variable findings in the MCPH-SCKS spectrum disorders are the following:

- **Brain structure** that is usually normal, but can be abnormal in a minority of patients:
  - When microcephaly is severe, the gyri may be shallow and the gyration pattern may be simplified.
  - The corpus callosum tends to be thinner when microcephaly is more severe [Adachi et al 2011].
  - Some affected individuals show abnormalities of neuronal migration, such as heterotopias, or focal pachygyria or polymicrogyria [Woods et al 2005, Passemard et al 2009].
  - Malformations are more common with mutation of certain genes, such as biallelic *WDR62* pathogenic variants. Strictly speaking, these individuals do not fit the definition of MCPH, but are nevertheless included in this *GeneReview* as no genotype-phenotype correlation exists to explain their malformations.

  See also Clinical Description, Autosomal Recessive Primary Microcephaly, **Neuroimaging.**

- **Cognitive impairment** in the majority of persons with MCPH is mild to moderate without major motor delay. More severe cognitive impairment has been observed in individuals with SCKS and in those with MCPH with brain malformations, such as those with biallelic *WDR62* pathogenic variants.

- **Short stature.** Previously MCHP and SCKS were distinguished by height: typically in MCPH stature was between -1 SD and -2 SD and in SCKS between -4 and -12 SD. However, loss-of-function variants in *CENPJ, CEP152*, and *PHC1* have been reported in classic SCKS and in persons with stature consistent with MCPH. Furthermore, height in individuals with pathogenic variants in *RBBP8*, *CEP152*, *CENPJ*, *CEP63*, and *PHC1* can be between -2 and -4 SD, which is between that observed in MCHP and SCKS. Note that the maximum height in persons with SCKS is equivalent to the minimum height seen in persons with MCPH.

- **Craniosynostosis.** Some individuals may develop craniosynostosis, probably secondary to slow, insufficient head growth. Although this rare feature was reported with mutation of *MCPH1* and *ATR*, it could be a nonspecific finding.

Testing

Cytogenetic testing. Click here for supplementary information (pdf).

Molecular genetic testing can be used to confirm the diagnosis of an MCPH-SCKS spectrum disorder in an individual with microcephaly, no malformations in other organs, and (usually) no major brain malformations (Table 1). Affected individuals have biallelic pathogenic variants in a single gene. Digenic inheritance has not been reported.

Of note: roughly one half to three quarters of western Europeans or North Americans with MCPH have no identified gene defect; in contrast, the proportion of individuals with identified pathogenic variants appears higher in persons from the Indo-Pakistan area.

The following genes (followed by locus name in parentheses) in which biallelic pathogenic variants are known to cause MCPH-SCKS spectrum disorders are separated into those that are currently known to be associated with:

- **MCPH phenotype only.** *MCPH1* (MCPH1), *WDR62* (MCPH2), *CDK5RAP2* (MCPH3), *KNL1* (MCPH4), *ASPM* (MCPH5), *STIL* (MCPH7), *CEP135* (MCPH8), and *CDK6* (MCPH12)
- **SCKS phenotype only.** *ATR* (SCKL1), *NIN* (SCKL7), and *ATRIP*
- **MCPH, SCKS, and/or intermediate phenotypes.** *RBBP8* (SCKL2), *CEP152* (MCPH9/SCKL5), *CENPJ* (MCPH6/SCKL4), *CEP63* (SCKL6), and *PHC1* (MCPH11)

Note: No gene has yet been identified for the locus designated SCKL3.

Two approaches to molecular genetic testing can be considered:

- **Single gene testing** involves sequencing of one or more genes listed in Table 1 based on the predominant features present in the affected individual and on the frequency of pathogenic variants in that gene in a given population:
    - In the European population, the genes in which pathogenic variants are most likely to be identified appear to be *ASPM* and *WDR62* for MCPH and *CEP152* for SCKL.
    - Pathogenic variants in *WDR62* are the most commonly associated with structural brain anomalies.
    - For individuals from a consanguineous mating, SNP-array technology can identify regions of homozygosity (homozygosity mapping) that allow prioritization of the gene or genes to be tested.
- **Multigene panels** include some or all the genes listed in Table 1. For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Table 1. Summary of Molecular Genetic Testing Used in MCPH-SCKS Spectrum Disorders

Gene [1] (Locus Name)	Proportion of the Phenotype Attributed to Mutation of This Gene		Test Method	Variants Detected [3]
	MCPH [2]	SCKS		
MCPH1 (MCPH1)	<10%	0%	Sequence analysis [4]	Sequence variants
			Deletion/duplication analysis [5]	Exon or whole-gene deletions or duplications
			Targeted analysis for pathogenic variants [6]	p.Ser25Ter
WDR62 (MCPH2)	<10%	0%	Sequence analysis [4]	Sequence variants
			Deletion/duplication analysis [5]	Exon or whole-gene deletions or duplications; none reported [7]
CDK5RAP2 (MCPH3)	<5%	0%	Sequence analysis [4]	Sequence variants
			Deletion/duplication analysis [5]	Exon or whole-gene deletions or duplications; none reported [7]
KNL1 (MCPH4)	<5%	0%	Sequence analysis [4]	Sequence variants
ASPM (MCPH5)	25%-50%	0%	Sequence analysis [4]	Sequence variants
			Deletion/duplication analysis [5]	Exon or whole-gene deletions [6]
CENPJ (MCPH6/ SCKL4)	<5%	1 family [8]	Sequence analysis [4]	Sequence variants
			Deletion/duplication analysis [5]	Exon or whole-gene deletions or duplications; none reported [7]

Table 1. continued from previous page.

Gene [1] (Locus Name)	Proportion of the Phenotype Attributed to Mutation of This Gene		Test Method	Variants Detected [3]
	MCPH [2]	SCKS		
STIL (MCPH7)	<5%	0%	Sequence analysis [4]	Sequence variants
			Deletion/duplication analysis [5]	Exon or whole-gene deletions or duplications; none reported [7]
CEP135 (MCPH8)	<5%	2 individuals [9]	Sequence analysis [4]	Sequence variants
CEP152 (MCPH9/ SCKL5)	<5%	Majority of SCKS	Sequence analysis [4]	Sequence variants
			Deletion/duplication analysis [5]	Exon or whole-gene deletions; none reported [5]
PHC1 (MCPH11)	1 family with intermediate phenotype [10]		NA	NA
CDK6 (MCPH12)	1 family [11]		NA	NA
ATR (SCKL1)	0%	4 families [12]	Sequence analysis [4]	Sequence variants
			Deletion/duplication analysis [5]	Exon or whole-gene deletions or duplications; none reported [7]
			Targeted analysis for pathogenic variants [6]	IVS9-57A>G
RBBP8 (SCKL2)	0%	1 family [13]	Sequence analysis [4]	Sequence variants
			Deletion/duplication analysis [5]	Exon or whole-gene deletions or duplications; none reported [7]
CEP63 (SCKL6)	0%	1 family [14] with intermediate phenotype	NA	NA
NIN (SCKL7)	0%	1 family [15]	NA	NA

Table 1. continued from previous page.

Gene [1] (Locus Name)	Proportion of the Phenotype Attributed to Mutation of This Gene		Test Method	Variants Detected [3]
	MCPH [2]	SCKS		
ATRIP	0%	1 family [15]	NA	NA

1. See Table A. Genes and Databases for chromosome locus and protein.
2. For the MCPH phenotype, few studies have addressed the relative importance of each locus or included all known genes. See Table 3.
3. See Molecular Genetics for information on allelic variants.
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Testing that identifies exon or whole-gene deletions/duplications not readily detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA; included in the variety of methods that may be used are: quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA) that includes this gene/chromosome segment.
6. Targeted pathogenic variants may vary by laboratory.
7. No exon deletions or duplications have been reported to date. (Note: By definition, deletion/duplication analysis identifies rearrangements that are not identifiable by sequence analysis of genomic DNA.)
8. Al-Dosari et al [2010]
9. Hussain et al [2012]
10. Awad et al [2013]
11. Hussain et al [2013]
12. O'Driscoll et al [2003], Ogi et al [2012], Mokrani-Benhelli et al [2013]
13. Qvist et al [2011]
14. Sir et al [2011]
15. Dauber et al [2012]

Clinical Characteristics

Clinical Description

All individuals with the primary autosomal recessive microcephalies (MCPH) and Seckel syndrome (SCKS) spectrum disorders have (1) microcephaly and (2) no malformations in other organ systems. More variable are:

- Brain structure (usually normal, but can be malformed at the severe end);
- Cognitive function (ranging from low-normal intelligence to severe cognitive impairment); and
- Linear growth (ranging from low-normal to extremely short).

Males and females are affected equally.

Historically SCKS has been distinguished from MCPH by intrauterine and postnatal growth retardation in the former; however, distinctions between MCPH and SCKS were blurred in 2010 when loss-of-function variants in *CENPJ* and *CEP152* were shown to result in either phenotype. Although these phenotypes represent a clinical spectrum in which the two extreme phenotypes (MCPH and SCKS) cannot be distinguished by genotype, the height-based distinction remains clinically useful, considering the severe growth retardation observed (by definition) in SCKS.

Furthermore, individuals with pathogenic variants in some genes (e.g., *MCPH1*, *PHC1* and *CEP135*) can have mild short stature (between -2 and -4 SD), in what is now described as an intermediate phenotype.

Autosomal Recessive Primary Microcephaly (MCPH)

Because MCPH5 (caused by mutation of *ASPM*) is the most common form of MCPH and the only one for which large series have been published, many clinical data are only available for this form of MCPH. Whether

the other MCPH types have the same clinical and radiologic spectrum of findings is largely unknown because of the small number of reported patients, selection bias, and (often) the lack of accompanying precise clinical information. Thus, in this *GeneReview*, MCPH5 is considered the prototypical form of MCPH to which the other types are compared.

Prenatal head growth. Microcephaly is a consequence of deficient brain growth [Aicardi 1998, Woods et al 2005, Cox et al 2006]. Microcephaly may be evident by the 24th week of gestation through ultrasonographic measurement or by fetal brain MRI [Tunca et al 2006]. Because of the pattern of deficient brain growth, OFC in some instances remains close to the lower limit of normal (i.e., ~-2 SD) and thus microcephaly may be undiagnosed until term (i.e., 40 weeks' gestation).

Postnatal head growth. OFC at birth is typically at least 2 SD below the mean for age and sex. The authors' experience with MCPH5 is that OFC lies between -2 SD and -4 SD at birth, and declines progressively, usually to -4 SD to -6 SD at the age of six months [Passemard et al 2009]. Hence, contrary to earlier assertions [Bond et al 2005], the diagnosis of MCPH may be overlooked in the perinatal period.

In adults with molecularly confirmed MCPH5, OFC varies between -3 SD and -13 SD [Bond et al 2003]. Intrafamilial correlation for OFC is strong; however, some sibs may show differences of 2 to 3 SD.

Growth. By definition, stature is normal in individuals with MCPH. Atypical MCPH designates individuals with stature between -2 and -3 SD.

Development. Developmental milestones are sometimes normal, but usually mildly delayed. Children are not hypotonic and, in the absence of associated brain malformations, usually walk unsupported before age two years.

Most children with MCPH have speech delay; they acquire language between ages three and four years when there are no associated brain malformations.

The majority of individuals with MCPH have mild to moderate cognitive impairment; however, few data have been published on the cognitive function of individuals with molecularly confirmed MCPH. In individuals with MCPH5, full-scale IQ scores range from less than 40 to 70 and do not correlate well with OFC [Passemard et al 2009]; however, severe cognitive impairment has been observed in some [Bond et al 2003]. Few individuals are able to read or write.

Individuals with MCPH have been described as cheerful, affable, and cooperative [Pattison et al 2000]; however, young children may show aggressive behavior [Passemard et al 2009].

Infants and children with MCPH often have severe hyperactivity. Hyperactivity decreases in late childhood and is usually not a problem in adolescence.

Seizures have been reported in approximately 10% of individuals with MCPH5 [Shen et al 2005, Passemard et al 2009]. Seizures often begin after age two years, are usually tonic/clonic in nature, and can occur during sleep. They are typically easily managed by anticonvulsant medications. In those with cortical malformations seizures are more common and may be resistant to drug therapy.

Neurologic findings are limited to a mild pyramidal syndrome (i.e., mild spasticity of the lower limbs).

Facial features are normal except for the non-specific narrow, sloping forehead often noticed in infants with very reduced cranial size of any cause. When OFC is severely reduced, the midface tends to be relatively prominent, with a big nose.

Life expectancy. No data have been reported on life expectancy, but anecdotal reports document survival (without obvious complications) in persons older than age 50 years.

No information on cancer risk in MCPH is available.

Neuroimaging. In addition to the findings discussed in Diagnosis, the following may be observed.

- A simplified gyral pattern is frequently observed in MCPH5 [Mochida & Walsh 2001, Desir et al 2008, Passemard et al 2009], which corresponds to microcephaly with simplified gyral pattern type 1 in Barkovich's neuroradiologic classification [Barkovich et al 1998] and to group 1 in Basel-Vanagaite's system [Basel-Vanagaite & Dobyns 2010] (see Nomenclature).
- A wide spectrum of severity (ranging from the "classic" small brain with simplified gyral pattern to severe brain disorganization) can be seen in individuals with pathogenic variants in *WDR62* [Bilguvar et al 2010, Nicholas et al 2010, Bhat et al 2011].

Neuropathologic findings. Severe depletion of neurons in superficial cortical layers II and III has been reported in fetuses or infants with clinically diagnosed primary autosomal recessive microcephaly of unknown genotypes [Evrard et al 1989].

Neuropathologic findings in genetically characterized MCPH have not been reported to date.

Seckel Syndrome (SCKS)

SCKS was probably overdiagnosed in the past in individuals with microcephaly and short stature. Critical review of the literature prior to 2010 can be found in Anonymous [2011]. According to this review, fewer than 50 convincing cases of SCKS have been reported. It must be stressed that the nosology prior to 2010 distinguished clearly between MCPH (aka *microcephalia vera*) and Seckel syndrome based on stature, but overlooked those individuals with intermediate growth patterns. The clinical description that follows is based on the classic clinical criteria.

Head circumference. In SCKS, prenatal and postnatal head growth is similar to that described for MCPH. Mean OFC in children and adults is around -9 SD. Microcephaly is more severe (expressed in SDs) than height in half of affected individuals.

Growth. By definition, infants with SCKS have low birth weight and short birth stature, but consensus criteria do not exist. In historic series, the mean birth weight was about 1500 g, but ranged from 1000 g to 2000 g. No reliable data for birth length exist. For the authors of this *GeneReview*, birth length at or below -4 SD is necessary for a diagnosis of SCKS.

Children with height between -3 SD and -4 SD persisting after age one year may be considered to have an intermediate phenotype between MCPH and SCKS.

Postnatal growth is severely restricted. The mean height is around -7 SD, but height as short as -13 SD has been observed.

Development. Intellectual disability is usually moderate to severe, with full-scale IQ scores below 50 in 50% of affected individuals; some affected individuals may show milder intellectual disability.

Facial features. In early reports SCKS was said to have a characteristic 'bird-headed' appearance (features are similar to those observed in individuals with severe MCPH), i.e., facial features that result from the relative sparing of the midfacial structures compared to the rest of the head. The forehead is narrow and sloping, the eyes are proportionally prominent or bulging, the palpebral fissures have an upward slant, the nose is proportionally large and convex, the lower jaw is receding, and the teeth are small. The pinnae are small but proportionate to head size, and usually lack the lobule.

Other. Jawad syndrome (OMIM 251255) is the name proposed for a family with primary microcephaly, short stature, tetramelic polydactyly, II-III syndactyly, and total absence of nails. The finding of biallelic *RBBP8* (SCKL2) pathogenic variants in this family suggests that the phenotype is intermediate SCKS with a few additional features.

Malignancies. Some individuals with non-molecularly confirmed SCKS appear to develop myelodysplasia [A Verloes, personal observation]. Such a patient was reported with acute myeloid leukemia at age 26 years [Hayani et al 1994].

Life expectancy. Data on life expectancy in SCKS have not been reported; however, anecdotal reports document survival without obvious complications in persons over age 50 years. The risk for hematologic complication has not been assessed; no data link those with hematologic problems to a specific genotype.

Radiographs. Skeletal radiographs typically demonstrate severely delayed bone maturation and the presence of cone-shaped or ivory epiphyses [Poznanski et al 1983].

Details of the MCPH-SCKS Spectrum Disorders by Gene

See references cited in Table 2 for studies related to MCPH/SCKS types by gene.

Table 2. Studies Related to MCPH/SCKS Types

Gene	MCPH/SCKS Type	References
MCPH1	MCPH1	Tommerup et al [1993], Jackson et al [2002], Trimborn et al [2004], Trimborn et al [2005], Woods et al [2005], Garshasbi et al [2006], Darvish et al [2010], Farooq et al [2010], Leung et al [2011], Ghani-Kakhki et al [2012], Sajid Hussain et al [2013]
WDR62	MCPH2	Bilguvar et al [2010], Nicholas et al [2010], Yu et al [2010], Bhat et al [2011], Kousar et al [2011], Murdock et al [2011], Bacino et al [2012], Memon et al [2013], Sajid Hussain et al [2013]
CDK5RAP2	MCPH3	Bond et al [2005], Hassan et al [2007], Pagnamenta et al [2012], Issa et al [2013], Tan et al [2014]
KNL1	MCPH4	Genin et al [2012]
ASPM	MCPH5	Bond et al [2002], Bond et al [2003], Passemard et al [2009]
CENPJ	MCPH6/SCKL4	Bond et al [2005], Gul et al [2006a], Al-Dosari et al [2010], Darvish et al [2010], Sajid Hussain et al [2013]
STIL	MCPH7	Kumar et al [2009], Darvish et al [2010], Papari et al [2013]
CEP135	MCPH8	Hussain et al [2012]
CEP152	MCPH9/SCKL5	Guernsey et al [2010], Kalay et al [2011]
PHC1	MCPH11	Awad et al [2013]
CDK6	MCPH12	Hussain et al [2013]
ATR	SCKL1	O'Driscoll et al [2003], Ogi et al [2012], Mokrani-Benhelli et al [2013]
RBBP8	SCKL2	Borglum et al [2001], Hassan et al [2008], Qvist et al [2011]
CEP63	SCKL6	Sir et al [2011]
NIN	SCKL7	Dauber et al [2012]
ATRIP		Ogi et al [2012]

Genotype-Phenotype Correlations

The discovery of the genetic basis of the primary autosomal recessive microcephalies (MCPH) and Seckel syndrome (SCKS) has led to these two entities being considered part of a clinical spectrum, called the MCPH-SCKS spectrum disorders.

The gene products implicated in both phenotypes cooperate in the basic and universal cellular processes that regulate the cell cycle (monitoring of DNA damage, mitosis kinetics and checkpoint control, centrosome cycle, organization and function of the mitotic spindle). Not surprisingly, alteration of these proteins results in similar

phenotypes. Nevertheless, gene-based analysis has shown more or less subtle differences in the manifestations of the phenotype associated with mutation of each gene. MCPH and SCKS remain rare disorders; only *ASPM* and *WDR62* pathogenic variants have been reported in large series and clinical data by gene are often limited to a small number of individuals and thus are potentially highly biased (see Table 2).

Note: Some individuals with biallelic pathogenic variants in genes associated with MCPH-SCKS spectrum disorders have distinctive brain findings that could lead to their being considered separate entities (see Differential Diagnosis).

Nomenclature

The abbreviation MCPH stands for *m*icrocephaly, *p*rimary, *h*ereditary.

MCPH4 and MCPH9. *CEP152* (locus name MCPH4 prior to 2012 and locus name MCPH9 after 2012) and *KNL1* (locus name MCPH4 after 2012) are located close together on the same chromosome.

When *CEP152* was discovered, it was assigned the locus name MCPH4, despite the fact that no *CEP152* pathogenic variants were found in the original MCPH4 family. Subsequently when *KNL1* pathogenic variants were identified in the original MCPH4 family in 2012, the *CEP152* locus name was changed to MCPH9. Hence, publications that refer to MCPH4 between 2005 and 2012 are in fact referring to MCPH9.

Microcephalia vera. Primary autosomal recessive microcephaly (MCPH) was previously called "microcephalia vera," "true microcephaly," or "radial microbrain." However, in the past this diagnosis was usually made without the benefit of neuroimaging studies. Thus, it is likely that the entity referred to as microcephalia vera in the literature published before the availability of brain MRI was much more heterogeneous than MCPH as defined here.

Microcephaly with premature chromosome condensation (PCC). PCC is synonymous with MCPH1. Neitzel et al [2002] reported two sibs with severe intellectual disability whose parents were first cousins. They had low birth weight, short stature, microcephaly, and, on karyotype, an excess of prophase-like cells and metaphases with poor banding quality. They were shown to habor biallelic *MCPH1* pathogenic variants [Trimborn et al 2004].

Neuroradiologic classification of microcephaly with simplified gyral pattern (MSG). In addition to the clinically based classification of primary microcephalies used in this *GeneReview*, the two MRI-based classification systems are that of Barkovich et al [1998] (updated in Adachi et al [2011]) and Basel-Vanagaite & Dobyns [2010]. Both classify small brains with simplified gyral pattern on the basis of gyral pattern, alterations of white matter, involvement of infratentorial structures, and the degree of brain atrophy. Note: When the gyral pattern of MCPH and SCKS is simplified, the MRI findings fit the mildest type (MSG1) according to Barkovich, or type 1 according to Basel-Vanagaite.

Prevalence

Primary microcephaly has an incidence of 1:30,000 to 1:250,000.

MCPH-SCKS spectrum disorders have been confirmed by molecular genetic testing and reported in fewer than 200 families.

Mutation of *ASPM* is the most common genetic cause of MCPH in all populations. More than 100 families with affected individuals have been reported worldwide. In Pakistan and India, mutation of *ASPM* accounts for 33%-50% of MCPH. Reliable figures for the general incidence and relative proportion of the genes most likely to be mutated are not available for other parts of the world, as large regional and ethnic variations exist.

Table 3 summarizes published data on Pakistani [Woods et al 2005, Gul et al 2006b, Sajid Hussain et al 2013] and Iranian families [Darvish et al 2010].

Table 3. Proportion of the Genes Most Likely to be Mutated in the Populations Studied

Study		Woods et al [2005]	Gul et al [2006b]	Darvish et al [2010]	Sajid Hussain et al [2013]
Origin of the population		North Pakistan	Pakistan	Iran	Central and southern Punjab or Khyber Pakhtunkhwa
Number of probands		58	33	112	57
Molecular basis unknown		20 (37%)	10 (30%)	81 (72%)	23 (40%)
Gene (Locus Name)	*MCPH1* (MCPH1)	10 (18%)	2 (6%)	8 (7%)	1 (2%)
	WDR62 (MCPH2)	2 (4%)	0	3 (3%)	7 (12%)
	CDK5RAP2 (MCPH3)	2 (4%)	0	0	0
	ASPM (MCPH5)	24 (44%)	18 (55%)	13 (12%)	18 (14%)
	CENPJ (MCPH6/SCKL4)	NA	1 (3%)	5 (4%)	5 (9%)
	STIL (MCPH7)	NA	NA	2 (2%)	0
	(MCPH8)	NA	NA	NA	NA
	CEP152 (MCPH9/SCKL5)	0	2 (6%)	0	3 (5%)
	CEP135 (MCPH8)	NA	NA	NA	0

NA (not available) means that a gene was not investigated.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with mutation of *WDR62, CDK5RAP2, CEP152, ASPM, CENPJ, STIL, CEP63, CEP135, ATR, RBBP8, KNL1, NIN, ATRIP, PHC1,* or *CDK6.*

MCPH1. One Danish individual with craniosynostosis, microcephaly, ptosis, "bird-like" facies, and moderate intellectual disability reported to have the craniosynostosis-microcephaly with chromosome breakage (CMCB) syndrome [Tommerup et al 1993] was later found to be homozygous for a pathogenic *MCPH1* missense variant [Farooq et al 2010]. Cytogenetic studies showed a high proportion of endomitoses and endoreduplications, a high spontaneous chromosome breakage rate, increased sensitivity to alkylating agents and x-ray, and spontaneous coiling and banding patterns, but not premature chromatin condensation (PCC). Although considered to be an allelic disorder, CMCB syndrome may just represent variable expression of MCPH.

WDR62 **(MCPH2).** Mutation of *WDR62* can be associated with cerebral dysplasia and more severe structural brain anomalies than those typically seen in MCPH-SCKS spectrum disorders [Bilguvar et al 2010, Yu et al 2010]. Those patients often have severe to profound intellectual disability.

ATR **(SCKL1).** Mutation of *ATR* causes the familial cutaneous telangiectasia and cancer syndrome (FCTCS) (OMIM 614564), which is characterized by cutaneous telangiectasias, patchy alopecia, mild dental and nail abnormalities, and increased risk of oropharyngeal and other malignancies.

Differential Diagnosis

Microcephaly can be considered primary (resulting from intrauterine reduced brain growth) or secondary (resulting from postnatal reduced brain growth caused by decreased cell proliferation and/or increased cell death). Although primary microcephaly and secondary microcephalies theoretically result from distinct pathogenic mechanisms, their etiologies can overlap. Moreover, processes that interfere with brain development

prenatally may occasionally be insufficient to give rise to microcephaly prenatally (i.e., primary microcephaly) and thus result in what appears to be postnatal reduced brain growth (i.e., secondary microcephaly).

Both primary microcephaly and secondary microcephaly can be:

- Associated with malformations of the central nervous system (CNS) or grossly normal CNS anatomy;
- Syndromic (i.e., associated with malformations occurring in other parts of the body) or isolated (i.e., not associated with malformations in other organ systems);
- Associated with disorders of DNA repair such as chromosome instability syndromes and syndromes with secondary onco-hematologic or immunologic disorders;
- Common in genomic rearrangements. Deletion or duplication involving multiple genes results in copy number variations (CNVs) which are commonly associated with microcephaly and short stature.
- Caused by teratogens. Well-known teratogens associated with microcephaly are alcohol and maternal hyperphenylalaninemia (usually the consequence of poor dietary control in a mother affected by PKU); see Phenylalanine Hydroxylase Deficiency.

Information useful for the differential diagnosis of microcephaly can be obtained through detailed past medical history (including history of the pregnancy and perinatal events), review of growth charts for head size and length, and physical examination (possibly with the help of someone trained in dysmorphology/clinical genetics).

Basic investigations for suspected primary microcephaly. Investigation of the differential diagnosis of MCPH-SCKS spectrum disorders requires, at a minimum, the following in all cases:

- **Brain MRI** to document the anatomy of the forebrain, brain stem, and cerebellum for the purpose of guiding the approach to molecular genetic testing. Views that allow the detection of calcification should be included. Note: When prenatal infection remains a possibility, CT scan (which detects intracranial calcifications more reliably) could be performed.
- Evaluation by a child neurologist
- **Fundus examination** to detect asymptomatic retinal anomalies
- **Chromosomal microarray analysis (CMA)** to identify chromosome rearrangements associated with nonsyndromic microcephaly

When MCPH seems likely:

- **Exclude maternal phenylketonuria** (if there are no sibs with a normal OFC).

When primary microcephaly is associated with short stature:

- **Skeletal** survey to identify anomalies that could suggest microcephalic osteodysplastic dwarfism, type II (MOPD2; OMIM 605925) (see Syndromes with Severe Short Stature)
- **Bone age**
- **IGF1 level**

Microcephaly with Brain Malformations

Microcephaly with Cortical Migration or Organization Defects

Microcephaly with simple gyri and other brain abnormalities: clinical vs radiologic classifications. The gyral patterns in individuals with MCPH-SCKS spectrum disorders vary from quasi-normal to severely simplified. Prior to the discovery of the molecular basis of the MCPH-SCKS spectrum disorders, a simplified gyral pattern (i.e., secondary and tertiary gyri are shallow or not developed) was considered to be central to the diagnosis.

Microcephaly with a normal gyral pattern was distinguished from microcephaly with a simplified gyral pattern (MSG) by Barkovich et al [1998], who subdivided the latter into five groups. (This classification has been recently updated [Adachi et al 2011].)

- MSG type 1 has a simplified gyral pattern, normal myelination, normal neonatal course, mild pyramidal signs, and no seizures, and is likely to correspond to the severe expression of the MCPH phenotype described in this *GeneReview*.
- MSG types 2-5 (delineated based on the presence of white matter defect, the severity of the neurologic impairment, presence of seizure, and survival) are probably distinct disorders.

A new classification of severe microcephalies was proposed by Basel-Vanagaite & Dobyns [2010].

- Group 1. Microcephaly with simplified gyri only (which includes individuals with MCPH and SCKS with a simplified gyral pattern)
- Group 2. Severe congenital microcephaly, simplified gyral pattern, and pontocerebellar hypoplasia with thin pons. Cognitive development is usually similar to that seen in MCPH; however, some have more severe developmental and neurologic abnormalities. MCPH-associated genes appear not to be involved in this form, as cerebellar hypoplasia is not common in MCPH.
- Group 3. Microcephaly with simplified gyri and enlarged extra-axial spaces
- Group 4. Microcephaly with simplified gyri, enlarged extra-axial spaces, and cerebellar hypoplasia

Note: In this classification, groups 3 and 4 (in contrast to groups 1 and 2) have microcephaly of perinatal onset and severe neurologic involvement (severe to profound intellectual disability, spastic quadriparesis that prevents ambulation, and in some cases choreiform movements).

In the following section, a distinction is made between lissencephaly/pachygyria and polymicrogyria. It is important to note that mutation of the same genes may result in either phenotype or a combination of the two phenotypes; for example, pachygyria and polymicrogyria may be present in the same individual with biallelic pathogenic variants in *DYNC1H1* or *WDR62*.

Lissencephaly-pachygyria spectrum of cortical malformation is characterized by smooth cortex with simplified gyration appearance. Lissencephaly describes a brain without sulci. Pachygyria (focal or diffuse) is a mild expression of lissencephaly in which sulci are shallow and reduced in number. Lissencephaly-pachygyria spectrum is distinguished from the simplified gyral observed in MCPH-SCKS spectrum disorders by the presence of an abnormally thick cortex with abnormal cortical layering. Microcephaly is usually not present at birth in classic lissencephaly, but may appear with time.

Classic lissencephaly is caused by mutation of one of several genes involved in neuronal migration. See Table 4.

Table 4. Types of Classic Lissencephaly and Associated Genes

Lissencephaly Type (OMIM#)	Gene (OMIM#)	Mode of Inheritance
LIS1 (607432)	*PAFAH1B1* (601545)	Autosomal recessive
LIS2 (257320)	*RELN* (600514)	Autosomal recessive
LIS3 (611603)	*TUBA1A* (602529)	Autosomal recessive
LIS4 (614019)	*NDE1* (609949)	Autosomal recessive
LISX1 (300067)	*DCX* (300121)	X linked
LISX2 (300215)	*ARX* (300382)	X linked

Microcephaly (≤-5.5 SD) with agyria/pachygyria (more severe posteriorly) and/or subcortical band heterotopias has been reported in children heterozygous for a pathogenic variant in *KIF2A* (OMIM 602591) or *TUBG1*

(OMIM 191135) [Poirier et al 2013], and in one individual with a heterozygous *TUBB2B* pathogenic variant [Cushion et al 2013].

Heterozygous pathogenic variants have been reported in *DYNC1H1* (OMIM 600112) in 11 individuals with predominantly posterior agyria/pachygyria and severe developmental delay. *DYNC1H1* was also associated with isolated polymicrogyria, nodular heterotopia, hypoplasia of the corpus callosum, and abnormally shaped basal ganglia, and, in some, evidence of peripheral neuropathy [Poirier et al 2013].

Eight of 30 individuals with lissencephaly/pachygyria spectrum born to consanguineous parents from Turkey had biallelic *WDR62* pathogenic variants (which are typically associated with MCPH2) [Bilguvar et al 2010].

Microlissencephaly (MLIS, Norman-Roberts syndrome; OMIM 257320) is characterized by microcephaly associated with lissencephaly, defined as reduction of cortical gyration and increased thickness of the cortical layer. Affected individuals have severe intellectual disability and seizures. MLIS is caused by biallelic pathogenic variants in *NDE1* (OMIM 609449). Inheritance is autosomal recessive.

Note: The term "microlissencephaly" was used in the literature prior to 2000 to designate both MLIS (with thick, disorganized cortex) and microcephaly with simplified gyral pattern (MSG).

Polymicrogyria is defined by an excessive number of small and infolded gyri separated by shallow sulci that give the cortical surface a lumpy appearance. It is usually not associated with primary microcephaly (see Polymicrogyria Overview). Cortical lamination is abnormal (unlayered or four-layered). Although polymicrogyria is often secondary to abnormal post-migrational development attributable to environmental causes, genetic causes are recognized.

- Biallelic pathogenic variants in *ADGRG1* (*GPR56*) (OMIM 604110) have been reported in persons with bilateral fronto-parietal polymicrogyria usually without microcephaly [Piao et al 2005]; however, three of 29 individuals with *ADGRG1* pathogenic variants had an OFC below the 3rd centile.
- Pathogenic variants in genes encoding tubulins are often associated with abnormalities of the corpus callosum, abnormal basal ganglia and internal capsule, and cerebellar hypoplasia. Heterozygous pathogenic variants in *TUBA1A* (OMIM 602529) [Poirier et al 2007, Cushion et al 2013], *TUBB2B* (OMIM 612850) [Jaglin et al 2009, Cushion et al 2013], *TUBB3* (OMIM 602661) [Poirier et al 2010], and *TUBB4A* (or *TUBB5*; OMIM 602662) [Breuss et al 2012] lead to variable patterns of focal or extensive polymicrogyria with gyral disorganization and simplification; dysmorphic and hypertrophic basal ganglia with fusion of the putamen with the caudate nucleus or radially oriented white matter streaks in the lenticular nucleus; vermis dysplasia; hypoplastic brain stem; and hypoplastic corpus callosum.
- Congenital microcephaly (-2.5 to -4 SD) is inconstant and does not always worsen after birth. Developmental delay ranges from mild to severe.
- Heterozygous mutation of *KIF5C* (OMIM 604593) causes frontal and perisylvian polymicrogyria and microcephaly [Poirier et al 2013].
- Biallelic loss-of-function pathogenic variants in *EOMES* (formerly known as *TBR2*) (OMIM 604615) lead to primary microcephaly with corpus callosum agenesis, extensive bilateral polymicrogyria, dilatation of the cerebral ventricles, and a small cerebellum. It has been reported in a family with a homozygous apparently balanced translocation between chromosomes 3p and 10q in which the breakpoint on chromosome 3 silences expression of *EOMES* by a position effect [Baala et al 2007].

Periventricular nodular heterotopia (PNH) is the presence of confluent nodules of gray matter located along the lateral ventricles. Affected children have microcephaly, severe developmental delay, and early-onset seizures.

- Biallelic pathogenic variants in *ARFGEF2* (OMIM 605371) have been reported in families with autosomal recessive inheritance [Sheen et al 2004].

- Pathogenic variants that appear to be male lethal in the X-linked gene *FLNA* have been reported. See X-Linked Periventricular Heterotopia.

Microcephaly with Brain Stem and/or Cerebellar Malformation (Hypoplasia, Agenesis, or Segmentation Abnormalities)

Some form of microcephalies may show major involvement of the infratentorial structures (pons, brain stem, and cerebellum):

- **MCPH10** (OMIM 615095), a form of severe primary autosomal recessive microcephaly with prenatal growth retardation that is clinically and pathologically unrelated to the other forms of MCPH observed in the MCPH-SCKS spectrum disorders, is caused by biallelic pathogenic variants in *ZNF335* (OMIM 610827) which encodes a protein that interacts with a chromatin-remodeling complex. Some affected children show low sloping forehead, micrognathia, prominent helices and nasal bridge, choanal atresia, and cataracts. Arthrogryposis (multiple joint contractures at birth) and spasticity appear to be common. Death occurs by age one year in almost all children.

  Brain MRI shows extreme microcephaly including hypoplastic cerebellum and brain stem, increased extra-axial space, enlarged ventricles, a simplified gyral pattern, absence of the corpus callosum, delayed myelinization, and probable progressive brain atrophy. Neuropathologic examination of one child showed thin cortex, reduced density of neurons with little apparent neuronal polarity or dendritic maturation, and disorganization of cortical layering. The cerebellum was also hypoplastic [Yang et al 2012].

- Biallelic pathogenic variants in *SLC25A19* result in extreme microcephaly, simplified gyral pattern, a moderate degree of cerebellar vermis hypoplasia, and 2-ketoglutaric aciduria [Rosenberg et al 2002]. The disorder, reported exclusively to date in the Old Order Amish, is inherited in an autosomal recessive manner. See Amish Lethal Microcephaly.

- Pontocerebellar hypoplasia (PCH) describes a heterogeneous group of neurodegenerative disorders characterized by hypoplasia of the cerebellum and pons, severe delay in cognitive and motor development, and seizures. Primary microcephaly with simplified gyral pattern is present in some forms of PCH. Progressive cerebral atrophy (which does not occur in MCPH) is associated with worsening microcephaly, dyskinesia, seizures, and death in early childhood. Pathogenic variants are found in a dozen genes, many of them encoding subunits of the tRNA splicing endonuclease complex:
  - PCH type 1 is characterized by central and peripheral motor dysfunction associated with anterior horn cell degeneration and early death. Biallelic pathogenic variants in *VRK1* (OMIM 602168) cause PCH 1A; pathogenic variants in *EXOSC3* (OMIM 606489) cause PCH 1B.
  - PCH type 2 is characterized by progressive microcephaly from birth combined with extrapyramidal dyskinesias. PCH 2A is caused by biallelic pathogenic variants in *TSEN54* (see TSEN54-Related Pontocerebellar Hypoplasia), PCH 2B by biallelic pathogenic variants in *TSEN2* (OMIM 608753), PCH 2C by biallelic pathogenic variants in *TSEN34* (OMIM 608754), and PCH 2D by biallelic pathogenic variants in *SEPSECS* (OMIM 613009).
  - PCH type 4 is characterized by hypertonia, joint contractures, olivopontocerebellar hypoplasia, and early death. It is caused by biallelic pathogenic variants in *TSEN54*. See TSEN54-Related Pontocerebellar Hypoplasia.
  - PCH type 3 is characterized by hypotonia, hyperreflexia, microcephaly, optic atrophy, and seizures. The associated gene is unknown.
  - PCH type 5 shows cerebellar hypoplasia of prenatal onset and seizures. It is caused by biallelic pathogenic variants in *TSEN54*. See TSEN54-Related Pontocerebellar Hypoplasia.
  - PCH type 6 is caused by biallelic pathogenic variants in *RARS2* (OMIM 611524).
  - PCH type 8 caused by biallelic pathogenic variants in *CHMP1A* (OMIM 164010).

- Mutation of the X-linked gene *CASK* results in male lethality [Najm et al 2008]. Females have severe-to-profound intellectual disability and structural brain anomalies including mild primary microcephaly and severe secondary microcephaly, simplified gyral pattern, thin brain stem with flattening of the pons, and pontocerebellar hypoplasia. See *CASK*-Related Disorders.

Syndromic Microcephaly

Feingold syndrome type 1 and **type 2** (OMIM 614326) are characterized by congenital, mild microcephaly, mild syndactyly, and a high frequency of tracheo-esophageal fistula and duodenal or intestinal atresias (≤1/3 of cases). Brachymesophalangy of the fifth fingers, thumb hypoplasia, 4-5 syndactyly of the toes (and occasionally 2-3 syndactyly), small jaw, and short palpebral fissures are distinctive features. Intelligence is subnormal in many individuals.

Heterozygous mutation of *MYCN* (Feingold type 1) [van Bokhoven et al 2005] or deletion of *MIR17HG* (OMIM 609415) (Feingold type 2) [de Pontual et al 2011] is causative. Inheritance is autosomal dominant.

Mandibulofacial dysostosis with microcephaly comprises microcephaly, developmental delay, and a recognizable dysmorphic appearance reminiscent of Treacher Collins syndrome. Choanal atresia, sensorineural hearing loss, and cleft palate occur in some individuals. It is caused by heterozygous mutation or deletion of *EFTUD2* (OMIM 603892). Inheritance is autosomal dominant.

Syndromes with Severe Short Stature (previously termed Dwarfism)

Microcephalic osteodysplastic dwarfism, type II (MOPD2; OMIM 605925) is characterized by extreme pre- and postnatal growth retardation, relative shortness of the limbs (relative micromelia), facial features resembling those of Seckel syndrome, dental abnormalities, and severe microcephaly which is usually comparable in young children to the short stature (expressed in SDs), but worsens over time [Majewski et al 1982a]. MOPD2 is caused by biallelic pathogenic variants in *PCNT,* which encodes pericentrin (OMIM 210720).

Meier-Gorlin ear-patella-short stature syndrome (MGORS; OMIM 224690) is characterized by intrauterine and postnatal growth retardation (< -2 SD) in 90% of affected individuals, difficulty feeding, and severe proportionate dwarfism with a markedly delayed bone age. Small ears, hypoplastic patellae, and absence of breast development are common. MGORS may be clinically confused with SCKS, particularly SCKL1 (caused by biallelic pathogenic variants in *ATR*) in which small ears and small patellae are observed [Ogi et al 2012].

MGS is caused by heterozygous mutation of *ORC1* (OMIM 601902), *ORC4* (OMIM 603056), *ORC6* (OMIM 607213), *CDT1* (OMIM 605525), or *CDC6* (OMIM 602627) [de Munnik et al 2012].

Taybi-Linder syndrome (OMIM 210710) is characterized by the following:

- Extreme microcephaly with structural brain malformations (abnormal gyration, pachygyria, heterotopias; agenesis of the cerebellar vermis and corpus callosum; and sometimes complex brain dysgenesis, sometimes associated with intractable seizures) [Sigaudy et al 1998, Klinge et al 2002, Pierce & Morse 2012]
- Profound developmental delay
- Distinctive facial findings (a prominent nose, bulging eyes, and a large, pointed nose)
- Severe intrauterine growth retardation (IUGR)
- Severe dwarfism (short neck; short limbs with relatively large hands but short fingers; platyspondyly with abnormal vertebral bodies; short, bowed and undermodeled long bones)
- Distinctive skeletal findings (dislocation of the elbows and hips; long clavicles; wide metaphyses; delayed bone age; and hypoplastic pelvis with horizontal acetabulum)
- Sparse scalp hair and dry skin

Taybi-Linder syndrome was described independently as three apparently distinct disorders: Taybi and Linder described the first cases in 1967 and Majewski in 1982 delineated two apparently "new" phenotypes, referred to as microcephalic osteodysplastic dwarfism, type I (MOPD1) [Majewski & Goecke 1982]) and microcephalic osteodysplastic dwarfism, type III (MOPD3) [Majewski et al 1982b]). These three entities were subsequently shown to be identical [Winter et al 1985, Vichi et al 2000]. Fewer than 40 affected individuals have been reported.

Biallelic pathogenic variants in *RNU4ATAC* (OMIM 601428), which encodes a small non-coding RNA involved in the splicing machinery of several messenger RNAs, are causative [Edery et al 2011, He et al 2011].

IGF1R (insulin-like growth factor 1 receptor) deficiency (OMIM 270450) includes intrauterine growth retardation (birth length -1 to -6 SD) or postnatal growth retardation, variably present (but sometimes marked) microcephaly (OFC between -4 and -5 SD) without structural brain defects, and variable intellectual disability. IGF1R deficiency has been observed in at least five families with biallelic *IGF1R* (OMIM 147370) pathogenic variants. IGF and its receptor play an important role in prenatal brain development independent of their role in growth hormone signaling. Inheritance is autosomal recessive.

IGF1 deficiency (OMIM 608747) includes intrauterine growth retardation (IUGR), primary microcephaly, deafness, and severe intellectual disability [Walenkamp & Wit 2008]. The clinical findings are similar to but more severe than those associated with mutation of *IGF1R*. IGF1 deficiency has been observed in at least four individuals with homozygous *IGF1* (OMIM 147440) pathogenic variants. Inheritance is autosomal recessive.

Renpenning syndrome (OMIM 309500) (also known as Sutherland-Haan syndrome, MRXS3) is characterized in affected males by intellectual disability, microcephaly, short stature, and variably present mild spastic paraplegia. The phenotype also includes thin body habitus winged scapulae; long face with a prominent pointed jaw, malar hypoplasia, and upslanting palpebral fissures; absence of flexion of the interphalangeal joint of the thumbs; small testes; and anal stenosis. Cleft palate, hypernasal speech, iris colobomata, and tetralogy of Fallot may be present [Germanaud et al 2011]. Mutation of *PQBP1* (OMIM 300463) is causative. Inheritance is X linked.

Syndromes with Chorioretinal Dysplasia (Pseudotoxoplasmosis Syndrome)

These syndromes are characterized by either a stable retinal dysplasia or a progressive retinal degeneration. Because the chorioretinal dysplasia can be asymptomatic, fundus examination is necessary to establish this finding.

Some affected individuals have punched-out, hypopigmented retinal lesions that may resemble those caused by a TORCH syndrome agent (*t*oxoplasmosis, *o*ther agents, *r*ubella, *c*ytomegalic virus, *h*erpes simplex virus) or Aicardi syndrome. Intellectual disability is variably present. In individuals without visual impairment the syndrome may resemble MCPH [Author, personal observation]. No pathogenic variants in the MCPH-related genes have been reported to date with this phenotype.

The disorders include:

- An autosomal recessive disorder, also called chorioretinal dysplasia-microcephaly-mental retardation (CDMM) syndrome (OMIM 251270), caused by biallelic pathogenic variants in *TUBGCP6* (OMIM 610053) [Puffenberger et al 2012];
- An autosomal dominant disorder comprising microcephaly, chorioretinopathy and/or retinal folds, and/or lymphedema (OMIM 152950), caused by heterozygous mutation of *KIF11* (OMIM 148760) [Ostergaard et al 2012].

Microcephaly in Disorders of DNA Repair (including syndromes with chromosome instability, photosensitivity, and hematologic or immunologic disorders)

Microcephaly is a common feature of most DNA repair disorders [Katyal & McKinnon 2007, O'Driscoll & Jeggo 2008], most of which also have some growth impairment, and a high risk of malignancy.

- **Fanconi anemia** is clinically defined by pancytopenia in the first decade of life and complicated by leukemia, pigmentary changes in the skin, and cardiac, kidney, and limb (radius aplasia) malformations. Affected adults are also at high risk for non-hematologic malignancies. Mild microcephaly (often without intellectual disability) is observed in 10%-25% of individuals. Fanconi anemia can be caused by mutation of one of the following genes that comprise the Fanconi anemia complementation group: *FANC-A,-B,-C,-D1, -D2, -E, -F, -G, -I, -J, -L, -M,* and *-N*. Inheritance is autosomal recessive for all genes except *FANCB* (for which inheritance is X-linked).
- **Nijmegen breakage syndrome** (or ataxia-telangiectasia variant 1) is characterized by progressive microcephaly that is primary in 75% of cases; growth failure; distinctive craniofacial features reminiscent of Seckel syndrome; immunodeficiency; and high risk of malignancy (e.g., lymphoma, rhabdomyosarcoma). Mild to moderate intellectual disability is present in a minority of individuals. Cells exhibit chromosome instability and multiple rearrangements involving chromosomes 7 and 14, and hypersensitivity to ionizing radiation with the same cytogenetic features as ataxia-telangiectasia. Nijmegen breakage syndrome is caused by biallelic pathogenic variants in *NBN*. Inheritance is autosomal recessive.
- **Warsaw breakage syndrome** (OMIM 613398), reported in two families, is characterized by severe microcephaly, pre- and postnatal growth retardation, and abnormal skin pigmentation. Affected individual shows excessive drug-induced chromosome breakage and chromatid cohesion defects. Warsaw breakage syndrome is caused by biallelic pathogenic variants in *DDX11* (in the XPD helicase family member *ChlR)* [van der Lelij et al 2010, Capo-Chichi et al 2013]. Inheritance is autosomal recessive.
- **Microcephaly with severe combined immunodeficiency and short stature** is characterized by hypogammaglobulinemia, severe B-cell and T-cell lymphocytopenia, and sensitivity to ionizing radiation. Affected individuals exhibit microcephaly, unusual facial features reminiscent of Seckel syndrome, mild growth retardation, developmental delay, and skin anomalies. The disorder is caused by biallelic pathogenic variants in *NHEJ1* (Cernunnos) (OMIM 611290) [Buck et al 2006] or *LIG4* (OMIM 606593) [Chistiakov et al 2009]. Inheritance is autosomal recessive.
- **Cockayne syndrome,** characterized by abnormal slow growth and development within the first few years (dwarfism, microcephaly with severe intellectual disability), photosensitivity, skin carcinoma with hypersensitivity to UV radiation, progressive retinopathy, sensorineural deafness, and severe neurologic deterioration, is caused by biallelic pathogenic variants in either *ERCC8* or *ERCC6*. Inheritance is autosomal recessive.
- **Xeroderma pigmentosum** **(XP),** characterized by hair shaft abnormalities, photosensitivity with multiple skin cancers, short stature, and microcephaly, is caused by mutation of *ERCC2*, *ERCC3*, or *ERCC5*. Some types of XP have phenotypes that overlap with Cockayne syndrome, i.e., XP complementation group B (*ERCC3*), group D (*ERCC2*), and group G (*ERCC5*). Inheritance is autosomal recessive.

Microcephaly and Mitotic Instability

Mosaic variegated aneuploidy (MVA) syndrome (OMIM 257300) is usually characterized by severe microcephaly, growth deficiency, intellectual disability, and variably present anomalies including cataracts and Dandy-Walker malformation. MVA syndrome is associated with acquired mosaicism for several different aneuploidies involving many different chromosomes with or without premature centromere division. It is associated with a high risk for malignancy, in particular Wilms tumor. MVA is caused by biallelic pathogenic

variants in *BUB1B* (OMIM 602860), encoding a key protein in the mitotic spindle checkpoint. Inheritance is autosomal recessive.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with the primary autosomal recessive microcephalies (MCPH) and Seckel syndrome (SCKS) spectrum disorders, the following evaluations are recommended:

- Neurology consultation
- Age-adapted psychomotor or neuropsychological evaluation
- Electroencephalogram if seizures are suspected
- Review of brain MRI performed at the time of diagnosis to evaluate for malformations which can have a prognostic value in young children
- If short stature is present, skeletal survey (if not performed at the time of diagnosis)

Treatment of Manifestations

Therapy is supportive and involves the following:

- Special education programs tailored to the needs of the individual
- Speech and language therapy
- Behavioral therapy as needed
- Occupational therapy as needed
- Community services that provide support for families

Ritalin® may be helpful to treat marked hyperkinesia.

Seizures are usually responsive to monotherapy with standard antiepileptic drugs (AEDs).

Growth hormone may be considered in individuals with mild growth retardation; objective efficiency of GH therapy has not been evaluated.

Intubation may be difficult in affected individuals with small chin [Gürkan et al 2006].

Surveillance

The following are appropriate:

- Monitoring of head circumference and stature using standard growth charts
- Neurologic follow-up from birth to adulthood to detect behavioral difficulties, hyperactivity, attention disorder, and motor problems (spasticity), and to monitor for evidence of seizures which can be late onset
- Periodic neuropsychologic evaluation in order to adapt interventions and schooling to the level of the individual's cognitive abilities

Evaluation of Relatives at Risk

See Related Genetic Counseling Issues for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and www.ClinicalTrialsRegister.eu in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

The primary autosomal recessive microcephalies (MCPH) and Seckel syndrome (SCKS) spectrum disorders discussed in this *GeneReview* are inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate carriers and therefore carry one heterozygous pathogenic variant.
- Heterozygous individuals (carriers) are asymptomatic.

Sibs of a proband

- At conception, each sib of one affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier if the parents are heterozygous.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygous individuals (carriers) are asymptomatic.

Offspring of a proband. To date, no individual with a MCPH-SCKS spectrum disorder has been known to reproduce.

Other family members of a proband. Each sib of the proband's parents is at a 50% risk of being a carrier.

Carrier (Heterozygote) Detection

Carrier testing for at-risk relatives requires prior identification of the pathogenic variants in the family.

Note: Carriers are heterozygotes for these autosomal recessive disorders and are not at risk of developing the disorder. No health problem has been associated with carrier status.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of the genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are carriers or are at risk of being carriers.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Diagnosis

For pregnancies at a priori high risk

- **Ultrasound examination**
  - **MCPH.** Ultrasound examination is not reliable in MCPH, as decreased head circumference often occurs only at the end of the pregnancy.
  - **SCKS.** Ultrasound examination can be performed to detect recurrence in SCKS. The severity of intrauterine growth retardation (IUGR) allows detection in the second trimester with high reliability.
- **Fetal brain MRI** is not reliable in MCPH, as decreased head circumference often occurs only at the end of the pregnancy. However, MRI could detect early in gestation malformations inconstantly associated with some forms of MCPH (e.g., MCPH2).
- **Molecular genetic testing.** Once the pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic diagnosis for a MCPH-SCKS spectrum disorder are possible.

For pregnancies at a priori low risk

- **Ultrasound examination alone** is unable to discriminate SCKS from other causes of intrauterine growth retardation (IUGR), particularly without a known family history of SCKS.
- **Fetal brain MRI** could help distinguish MCPH-SCKS spectrum disorders from other conditions listed in Differential Diagnosis.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

No specific resources for Primary Autosomal Recessive Microcephalies and Seckel Syndrome Spectrum Disorders have been identified by *GeneReviews* staff.

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Primary Autosomal Recessive Microcephalies and Seckel Syndrome Spectrum Disorders: Genes and Databases

Locus Name	Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
MCPH1	MCPH1	8p23.1	Microcephalin	MCPH1 @ LOVD	MCPH1	MCPH1
MCPH2	WDR62	19q13.12	WD repeat-containing protein 62		WDR62	WDR62
MCPH3	CDK5RAP2	9q33.2	CDK5 regulatory subunit-associated protein 2	CDK5RAP2 @ LOVD	CDK5RAP2	CDK5RAP2

Table A. continued from previous page.

MCPH4	*KNL1*	15q15.1	Kinetochore scaffold 1		KNL1	KNL1
MCPH6/ SCKL4	*CENPJ*	13q12.12-q12.13	Centromere protein J	CENPJ @ LOVD	CENPJ	CENPJ
MCPH7	*STIL*	1p33	SCL-interrupting locus protein	STIL database	STIL	STIL
MCPH8	*CEP135*	4q12	Centrosomal protein of 135 kDa		CEP135	CEP135
MCPH9/ SCKL5	*CEP152*	15q21.1	Centrosomal protein of 152 kDa	CEP152 database	CEP152	CEP152
MCPH11	*PHC1*	12p13.31	Polyhomeotic-like protein 1		PHC1	PHC1
MCPH12	*CDK6*	7q21.2	Cyclin-dependent kinase 6	CDK6 database	CDK6	CDK6
SCKL1	*ATR*	3q23	Serine/threonine-protein kinase ATR	ATR database	ATR	ATR
SCKL2	*RBBP8*	18q11.2	DNA endonuclease RBBP8		RBBP8	RBBP8
SCKL3	Unknown	14q22.3	Unknown			
SCKL6	*CEP63*	3q22.2	Centrosomal protein of 63 kDa		CEP63	CEP63
SCKL7	*NIN*	14q22.1	Ninein		NIN	NIN
SCKL8	*ATRIP*	3p21.31	ATR-interacting protein		ATRIP	ATRIP
	ASPM	1q31.3	Abnormal spindle-like microcephaly-associated protein	ASPM @ LOVD	ASPM	ASPM

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Primary Autosomal Recessive Microcephalies and Seckel Syndrome Spectrum Disorders (View All in OMIM)

181590	SCL/TAL1-INTERRUPTING LOCUS; STIL
210600	SECKEL SYNDROME 1; SCKL1
251200	MICROCEPHALY 1, PRIMARY, AUTOSOMAL RECESSIVE; MCPH1
601215	ATR GENE; ATR
603368	CYCLIN-DEPENDENT KINASE 6; CDK6
604124	RETINOBLASTOMA-BINDING PROTEIN 8; RBBP8
604317	MICROCEPHALY 2, PRIMARY, AUTOSOMAL RECESSIVE, WITH OR WITHOUT CORTICAL MALFORMATIONS; MCPH2
604321	MICROCEPHALY 4, PRIMARY, AUTOSOMAL RECESSIVE; MCPH4
604804	MICROCEPHALY 3, PRIMARY, AUTOSOMAL RECESSIVE; MCPH3
605481	ABNORMAL SPINDLE-LIKE, MICROCEPHALY-ASSOCIATED; ASPM
606605	ATR-INTERACTING PROTEIN; ATRIP
606744	SECKEL SYNDROME 2; SCKL2

Table B. continued from previous page.

607117	MCPH1 GENE; MCPH1
608201	CDK5 REGULATORY SUBUNIT-ASSOCIATED PROTEIN 2; CDK5RAP2
608393	MICROCEPHALY 6, PRIMARY, AUTOSOMAL RECESSIVE; MCPH6
608684	NINEIN; NIN
608716	MICROCEPHALY 5, PRIMARY, AUTOSOMAL RECESSIVE; MCPH5
609173	KINETOCHORE SCAFFOLD 1; KNL1
609279	CENTROMERIC PROTEIN J; CENPJ
611423	CENTROSOMAL PROTEIN, 135-KD; CEP135
612703	MICROCEPHALY 7, PRIMARY, AUTOSOMAL RECESSIVE; MCPH7
613529	CENTROSOMAL PROTEIN, 152-KD; CEP152
613583	WD REPEAT-CONTAINING PROTEIN 62; WDR62
613676	SECKEL SYNDROME 4; SCKL4
613823	SECKEL SYNDROME 5; SCKL5
614673	MICROCEPHALY 8, PRIMARY, AUTOSOMAL RECESSIVE; MCPH8
614724	CENTROSOMAL PROTEIN, 63-KD; CEP63
614728	SECKEL SYNDROME 6; SCKL6
614851	SECKEL SYNDROME 7; SCKL7
614852	MICROCEPHALY 9, PRIMARY, AUTOSOMAL RECESSIVE; MCPH9

Molecular Genetic Pathogenesis

The genes in which mutation causes MCPH-SCKS spectrum disorders are involved in basic, intricate cell processes. Not surprisingly, loss of function of these genes results in overlapping phenotypes. The cell processes involved can include:

- Control of DNA integrity (double-strand breaks)
- Control of initiation of mitosis at cell cycle checkpoints 1 and 2
- Control of the metaphase-anaphase checkpoint
- Regulation of centrosome duplication
- Regulation of mitotic spindle organization and kinetics

Two distinct pathogenic mechanisms give rise to MCPH-SCKS spectrum disorders.

- **General growth failure.** This quantitative effect is related to a general slowing of the cell cycle that reduces the total number of cell divisions during development. Physiologic compensation and redundancies probably explain why growth failure is inconstant, and when present varies and is gene dependent.
- **Brain growth failure.** An additional pathogenic mechanism explains the sensitivity of brain growth to alterations of mitotic dynamics. Normal brain volume critically depends on the number of mature neurons produced during neuronogenesis (before 20 weeks' gestation). The fate of neuronal progenitor cells is determined at each cell division by the orientation of the spindle pole relative to the ventricular wall: either (1) one mother neuronal progenitor divides into two daughter neuronal progenitors or (2) one mother progenitor divides into one daughter neuronal progenitor and one neuroblast, which subsequently migrates to the cortex. Subtle alteration of the dynamics of mitosis disrupts the delicate equilibrium between the two types of division, favoring premature differentiation and, consequently, premature depletion of the pool of neuronal progenitors.

For a detailed summary of gene and protein information for the genes listed below, see Table A, **Gene**.

MCPH1 (locus name MCPH1)

Gene structure. *MCPH1 (*known previously as *BRIT1*) spans 236 kb. NCBI Gene recognizes three protein-encoding MCPH1 isoforms; isoform 1 (NM_024596.3) has 14 exons and encodes a protein of 835 amino acids (NP_078872.2).

Benign variants. Benign variants in *MCPH1* do not correlate generally with brain size [Woods et al 2006], although in Chinese Han population, a normal variant was associated with variation in cranial size [Wang et al 2008].

Pathogenic variants

- Missense and nonsense variants and small and gross deletions have been reported; see Table 5 (pdf).
- A homozygous 1-bp duplication in exon 5 of *MCPH1* (c.427dupA) was observed in a family with premature chromosome condensation syndrome (PCC; microcephaly, short stature, and premature chromosome condensation) [Neitzel et al 2002].

See Table 5 (pdf) for a list of all reported pathogenic variants.

Normal gene product. Microcephalin has three breast cancer 1 C-terminal (BRCT) domains, which are common to many DNA repair proteins (e.g., BRCA1, BRCA2, MDC1, NBN). MCPH1 binds directly to the SWI-SNF chromatin remodeling complex and interacts with a number of proteins including histone H2AFX, phosphorylated CDC27, and pericentrin (involved in microcephalic osteodysplastic dwarfism, type II [MOPD2]).

The physiology of MCPH1 is complex. It has been implicated in various cellular processes including DNA damage checkpoint (ATM-and ATR-mediated DNA-damage response), control of intra-S and G2-M mitotic checkpoints, DNA repair, repression of the human telomerase reverse transcriptase (hTERT), and transcription. Interaction of MCPH1 with condensin II may explain the premature chromatin condensation that occurs in microcephalin-deficient microcephalies.

Abnormal gene product. All but one pathogenic variant predicts the production of nonfunctional, truncated microcephalin. Considering the multiple facets of MCPH1, its deficiency causes a wide range of cellular defects in DNA-damage repair, centrosome and spindle organization, and cell-cycle progression.

Chromosome preparations of patients with MCPH1 exhibit an elevated fraction of prophase-like cells and show poor metaphase resolution. Increased frequency of spontaneous chromosome breakage, endomitosis, and hypersensitivity to clastogenic agents was reported in one case [Tommerup et al 1993, Farooq et al 2010].

WDR62 (MCPH2)

Gene structure. *WDR52* spans 51 kb. NCBI Gene recognizes two protein-encoding isoforms. The longest transcript (isoform 1 - NM_001083961.1) has 32 exons and encodes a protein of 1523 amino acids (NP_001077430.1).

Pathogenic variants. The majority of molecular details come from the three papers that simultaneously implicated WDR62 in microcephalies with or without brain malformation [Bilguvar et al 2010, Nicholas et al 2010, Yu et al 2010].

See Table 6 (pdf) for a list of all reported pathogenic variants.

Normal gene product. WDR62 contains several functional WD40 domains, a short (about 40 amino acid) motif involved in protein-protein interaction. WDR62 is a scaffold protein and is often observed in proteins known to

serve as mediators for the assembly of protein complexes. It is both a centrosomal and a nuclear protein, like ASPM and MCPH1. Its localization varies with the cell cycle phase: during mitotic entry WDR62 accumulates at the spindle pole where it persists until metaphase-anaphase transition. In interphase, WDR62 predominantly localizes in the nucleus.

Abnormal gene product. In vitro studies done on transfected cells carrying a pathogenic *WDR62* missense variant showed expression of the fusion protein in the cytoplasm but not at the spindle pole during mitosis [Nicholas et al 2010]. Impact on stress granules has not been assessed.

Experimental depletion of WDR62 by siRNA results in spindle orientation defects, decreased integrity of centrosomes which are displaced from the spindle pole, and delayed mitotic progression [Bogoyevitch et al 2012].

CDK5RAP2 (MCPH3)

Gene structure. *CDK5RAP2* (also known as *CEP215*: centrosome expressed protein 215 kd) spans 191 kb. NCBI Gene recognizes three protein-encoding isoforms. The longest transcript (isoform 1 - NM_018249.5) has 39 exons and encodes a protein of 1893 amino acids (NP_060719.4).

Pathogenic variants. Pathogenic variants were first reported in *CDK5RAP2* in four Pakistani families with primary microcephaly [Bond et al 2005]. Other patients have been reported (see Table 7).

- A pathogenic variant, originally described as p.Ser81Ter in one family [Bond et al 2005], was subsequently correctly described as p.Tyr82Ter [Park et al 2011]. The same pathogenic variant was found in two other families [Hassan et al 2007].
- In one family the c.4186-15A>G variant was originally considered to result in the insertion of a new splice acceptor site, leading to a subsequent frameshift and a premature stop codon [Bond et al 2005]; it was later reassessed as p.Arg1334SerfsTer5 [Park et al 2011].

See Table 7 (pdf) for a list of all reported pathogenic variants.

Normal gene product. CDK5RAP2 is a gamma-tubulin complex-binding protein, a centrosome component for pericentriolar matrix protein recruitment and association with CDK5 and CDK5R1. CDK5RAP2 contains a microtubule-associated domain and localizes to microtubule plus ends where it promotes microtubule polymerization. CDK5RAP2 is found in the Golgi apparatus, in the pericentriolar region (where it adheres to the surface of the centrosome) and in the region of the centrosomal appendages. It localizes to the mid-body during cytokinesis and is required for docking and stabilizing the γ-tubulin ring complex to the centrosome. CDK5RAP2 works as a negative regulator of centriole disengagement (thus enabling the spindle checkpoint) by maintaining (in cooperation with pericentrin) the cohesion between mother and daughter centrioles, which is responsible for MOPD2.

Abnormal gene product. Loss of CDK5RAP2 function causes an increased cell-cycle exit by promoting premature neuronal differentiation [Buchman et al 2010]. Inhibition of CDK5RAP2 expression causes chromosome missegregation by affecting the spindle checkpoint [Zhang et al 2009].

KNL1 (MCPH4/SCKL5)

Gene structure. *KNL1* (cancer susceptibility candidate 5, also often referred to as blinkin, *Spc105*, or *AF15Q14*) spans 70 kb. NCBI Gene recognizes two protein-encoding isoforms. The longest transcript (isoform 1 - NM_170589.4) has 27 exons and encodes a protein of 2342 amino acids (NP_733468.3).

Pathogenic variants. Three families from the same rural area of Morocco had a homozygous *KNL1* missense variant which causes amino acid substitution p.Met2041Ile and is predicted to inactivate an exon splicing

enhancer (ESE), leading to an abnormal transcript with absence of exon 18 [Jamieson et al 1999, Genin et al 2012].

See Table 8 (pdf) for a list of all reported pathogenic variants.

Normal protein product. CASC5 is a large protein containing several conserved motif repeats (S/GILK, RRVSF, and MELT).

CASC protein functions as a molecular scaffold to dock other proteins (notably BUB1 and BUB1B) to kinetochores at the equatorial plate. It has two major roles during mitosis: proper attachment of the kinetochores of chromosome centromeres to the microtubule apparatus and spindle-assembly checkpoint (SAC) signaling. It is weakly expressed in interphase nuclei. Expression increases from prophase to anaphase, and declines during the exit of mitosis.

Abnormal protein product. Although the pathogenic variant was shown in vitro to cause exon skipping, patient lymphoblasts showed no abnormalities in mitosis, no changes in growth rate, and no micronuclei. Expression was normal in patient fibroblasts, and mitotic spindles were normal [Genin et al 2012].

ASPM (MCPH5)

Gene structure. *ASPM* (abnormal spindle homolog microcephaly associated) comprises 31 exons spanning 63 kb. NCBI Gene recognizes two protein-encoding isoforms. The longest transcript (isoform 1 - NM_018136.4) has 28 exons and encodes a protein of 3477 amino acids (NP_060606.3).

Pathogenic variants. In Pakistan and India mutation of *ASPM* accounts for one third to one half of MCPH. Pathogenic variants include a translocation, large and small deletions, insertions/duplications, and base substitutions (stop variants and mRNA splice sites) [Bond et al 2002, Bond et al 2003, Kumar et al 2004, Pichon et al 2004, Shen et al 2005, Gul et al 2006b, Gul et al 2007, Desir et al 2008, Muhammad et al 2009, Nicholas et al 2009, Passemard et al 2009, Saadi et al 2009, Darvish et al 2010, Kousar et al 2010, Mahmood et al 2011, Bacino et al 2012, Hussain et al 2013].

Even in consanguineous families, compound pathogenic variants have been reported [Saadi et al 2009]. Absence of correlation between variant type and predominance of truncating variants is consistent with the notion that the lack of the C-terminal domain of ASPM, which mediates midbody localization, may be sufficient to cause microcephaly [Paramasivam et al 2007].

Even in consanguineous families, compound heterozygosity of pathogenic variants has been reported [Saadi et al 2009]. Absence of a correlation between variant type and the predominance of truncating variants are consistent with the notion that the lack of the C-terminal domain of ASPM (which mediates localization to the midbody of the centrosome) may be sufficient to cause microcephaly [Paramasivam et al 2007].

Only one missense variant has been reported in *ASPM* (p.Gln3180Pro) [Gul et al 2006b]. This pathogenic variant has not been functionally tested to confirm its deleterious impact.

A balanced familial chromosome translocation t(1;4)(q31;p15.3) was reported in an infant with primary microcephaly [Pichon et al 2004]. The translocation breakpoint was situated within intron 17 of *ASPM*.

An apparently balanced familial chromosome translocation t(1;4)(q31;p15.3) – in which the translocation breakpoint was situated within intron 17 of *ASPM* - was reported in an infant with primary microcephaly [Pichon et al 2004].

See Table 9 (pdf) for a list of all reported pathogenic variants until 2010.

Nicholas et al [2009] reported molecular findings in 99 consanguineous families with a strict diagnosis of MCPH (several patients were published previously). In this cohort 41% were homozygous at the MCPH5 locus;

pathogenic variants were identified in all but two families. Eleven of 27 non-consanguineous families of predominantly northern European origin with a strict diagnosis of MCPH had biallelic *ASPM* pathogenic variants. Among patients with microcephaly and intellectual disability, with or without other neurologic features, only three (7%) had biallelic *ASPM* pathogenic variants.

Normal gene product. ASPM contains a NH2-terminal microtubule-binding domain, two calponin homology domains (CH-domains) that are found in cytoskeletal and signal transduction proteins, and 81 IQ motifs (an extremely basic unit of ~23 amino acids, whose conserved core contains an isoleucine-glutamine [I-Q] pair). The IQ motif serves as a binding site for different proteins including the essential and regulatory myosin light chains, calmodulin, and calmodulin-like proteins. IQ motifs are protein kinase C (PKC) phosphorylation sites. Protein isoforms, derived from splice variants of *ASPM*, contain different numbers of IQ domains.

ASPM localizes to centrosomes and is recruited in a microtubule-dependent manner to the pericentriolar matrix (PCM) at the spindle poles during mitosis, where it binds to the microtubule minus end. It colocalizes with the centrosomal marker γ-tubulin. It is concentrated at the midbody ring during cytokinesis [Higgins et al 2010, Singhmar & Kumar 2011]. ASPM interacts with CIT (citron kinase) and with UBE3A (ubiquitin protein ligase E3A), the protein whose haploinsufficiency causes Angelman syndrome.

Abnormal gene product. One pathogenic missense variant has been reported in a Pakistani family with consanguinity. The remaining described pathogenic variants predict the production of a truncated protein, as at least some mutant *ASPM* transcripts escape nonsense-mediated decay [Kouprina et al 2005]. Truncated proteins are thought to be expressed in the cytosol and thus may have residual activity. However, no correlation was observed between the size of the truncated protein and OFC, IQ, or gyral pattern, even with very C-terminal variants [Bond et al 2003, Higgins et al 2010]. These results do not support the presence of residual activity for such truncated proteins, although the mechanism which prevents truncated ASPM from exerting any biologic function is unknown (e.g., early protein decay, intracellular mistargeting).

In mice, truncating *Aspm* homozygous pathogenic variants cause mild microcephaly. These mice show severe reduction in the size of testes and ovaries accompanied by reduced fertility, secondary to a massive loss of germ cells [Pulvers et al 2010]. Ovarian dysfunction has not been addressed in humans.

CENPJ (MCPH6/SCKL4)

Gene structure. *CENPJ* (centromere protein J) spans 86 kb. NCBI Gene recognizes one protein-encoding isoform. The transcript (NM_018451.4) has 18 exons and encodes a protein of 1138 amino acids (NP_060921.3).

Pathogenic variants. Loss-of-function variants were observed in several patients with the MCPH phenotype.

One homozygous transition in the last nucleotide of intron 11 (c.3302-1G>C) was reported in a consanguineous Saudi family with SCKL [Al-Dosari et al 2010]. This splice-junction variant leads to the generation of three different abnormal transcripts.

See Table 10 (pdf) for a list of all reported pathogenic variants.

Normal gene product. CENPJ (also known as CPAP) contains five CC4 coiled coil domains (a domain that binds tubulin dimers and is important for centriole elongation) and a C-terminal domain that interacts with CEP152. It forms a ternary complex with SASS6 and CEP350.

CENPJ is present in the cytoplasm of proliferating cells. During centriole biogenesis, it is concentrated within the proximal lumen of both parental centrioles and procentrioles, and in the pericentriolar matrix.

CENPJ and Polo-like kinase PLK4 are recruited to the centrosome by CEP152 [Cizmecioglu et al 2010]. CENPJ is associated with the γ-tubulin ring complex. CENPJ forms a homodimer [Zhao et al 2010]. CENPJ phosphorylation by PLK2 and PLK4 increases at the G1/S transition phase and decreases during the exit of

mitosis. Phosphorylated CENPJ is preferentially located at the procentriole [Chang et al 2010]. CENPJ is involved in microtubule disassembly at the centrosome [Basto et al 2006].

Abnormal gene product. Pathogenic variants are thought to lead to the production of nonfunctional CENPJ proteins.

STIL (MCPH7)

Gene structure. *STIL* (SCL/TAL1 interrupting locus) spans 98 kb. NCBI Gene recognizes two protein-encoding isoforms. The longest transcript (isoform 1 - NM_001048166.1) has 17 exons and encodes a protein of 1288 amino acids (NP_001041631.1). The second transcript variant (NM_003035.2) uses an alternate in-frame splice site in the 3' coding region, resulting in an isoform that is one amino acid residue shorter.

Pathogenic variants. *STIL* homozygous loss-of-function variants were described in four of 24 consanguineous Indian families unlinked to known MCPH loci [Kumar et al 2009].

See Table 11 (pdf) for a list of all reported pathogenic variants.

Normal gene product. STIL is expressed in human brain as early as 16 weeks [Kumar et al 2009]. It has a 90 amino-acid-long C-terminal domain (STAN or STIL/Ana2 motif).

STIL is a cytoplasmic protein that localizes to the pericentriolar region surrounding parental centrioles. It is implicated in regulation of the mitotic spindle checkpoint by increasing phosphorylation of CDK1, a regulatory pathway that monitors chromosome segregation during cell division to ensure the proper distribution of chromosomes to daughter cells. STIL is recruited by PLK4 and is necessary for SAS6 recruitment to centrioles. It interacts with the centromere proteins CENPJ and SAS4 [Tang et al 2011]. STIL is phosphorylated in mitosis and in response to activation of the spindle checkpoint, and disappears when cells transition to the G1 phase [Arquint et al 2012].

CEP135 (MCPH8)

Gene structure. *CEP135* (centrosomal protein 135 kd) spans 107 kb. NCBI Gene recognizes one protein-encoding isoform. The transcript (NM_025009.4) has 26 exons and encodes a protein of 1140 amino acids (NP_079285.2).

Pathogenic variants. A pathogenic variant of *CEP135* was found in a single family with severe microcephaly (-12 to 14.5 SD) from northern Pakistan [Hussain et al 2012].

See Table 12 (pdf) for a list of all reported pathogenic variants.

Normal gene product. CEP135 is an α-helical protein located throughout the cell cycle in the pericentriolar matrix, around the centriolar surface, and within the proximal lumen of both parental and nascent centrioles where it is associated with CENPJ. CEP135, a scaffolding protein during early centriole biogenesis, is required for centriole-centriole cohesion during interphase. It interacts with C-NAP1 and CEP250 during interphase [Kim et al 2008], and with the 50-kd subunit of the dynactin complex (p50) which is involved in anchoring microtubules to centrosomes [Uetake et al 2004].

Abnormal gene product. In fibroblasts from an affected individual, 22% of cells had no centrosome (identified by γ-tubulin staining) and 18% of cells had three to five centrosomes, which sometimes appeared fragmented. Many nuclei were misshapen and fragmented, and the tubulin network was disorganized [Hussain et al 2012].

CEP152 (MCPH9)

Gene structure. *CEP152* (centrosome protein 152 kd) spans 98 kb. NCBI Gene recognizes two protein-encoding isoforms. The longest transcript (isoform 1 - NM_001194998.1) has 27 exons and encodes a protein of 1710 amino acids (NP_001181927.1).

Pathogenic variants. Pathogenic variants in seven families with SCKS have been reported [Kalay et al 2011]. A recurrent c.261+1G>C pathogenic variant was present in several unrelated individuals of Turkish origin. Two pathogenic variants in *cis* configuration were observed in one Pakistani family [Hussain et al 2013]. Pathogenic variants in *CEP152* wer reported in persons with MCPH from a Canadian Maritime population [Guernsey et al 2010].

See Table 13 (pdf) for a list of all reported pathogenic variants.

Normal gene product. CEP152, the human ortholoolog of the *Drosophila Asterless* gene, contains two structural maintenance of chromosomes (SMC)-like coiled-coil domains and a centrosome-localization domain. It is localized in the periphery of centrioles. CEP152 scaffolds procentriole formation by promoting centrosomal accumulation of CENPJ and PLK4. It is recruited by CEP63 to form a ring at the proximal end of parental centrioles and is required for centriole duplication.

Abnormal gene product. Interphase cells from tissues of affected individuals show a variety of morphologic abnormalities: multinucleated cells, centrosomes without astral microtubules (microtubules that only exist immediately before and during mitosis), unseparated centrosomes without asters (microtubules that radiate from a centrosome during mitosis), fragmented centrosomes, and micronuclei. At metaphase, chromosomes are incorrectly aligned on the metaphase plate; the following are observed: a monopolar and a tripolar spindle with structurally abnormal centrosomes, an excess of early anaphasic cells, and defects in cytokinesis. Mitotic segregation errors led to variable aneuploidies in 10% of cells in one affected individual [Kalay et al 2011]. Impaired CEP152 function leads to accumulation of genomic defects resulting from replicative stress through enhanced activation of ATM signaling, leading to delays in S-phase entry and to G2/M progression.

PHC1 (MCPH11)

Gene structure. *PHC1* (polyhomeotic-like protein 1) spans 28 kb. NCBI Gene recognizes one protein-encoding isoform. The transcript (NM_004426.2) has 15 exons and encodes a protein of 1004 amino acids.

Pathogenic variants. A missense variant (p.Leu992Phe) was reported in a consanguineous Saudi family [Awad et al 2013]. Head circumferences were -4.3 and -5.8 SD below the mean; heights were -3.6 SD and 2.3 SD below the mean.

See Table 14 (pdf) for a list of all reported pathogenic variants.

Normal gene product. Polycomb repressive complexes (PRC) 1 and 2 are protein complexes that function as transcriptional repressors that silence many genes throughout development via chromatin remodeling and histone modification. PHC1, a component of the PRC1 complex, acts as an E3 ubiquitin ligase and is implicated in H2A and geminin ubiquitination. PHC1 is also involved in DNA repair as it is recruited to chromatin regions in response to DNA damage [Awad et al 2013].

Abnormal gene product. The pathogenic variant observed by Awad et al [2013] led to increased proteasome-mediated degradation of the mutated PHC1 protein and a concomitant increased geminin expression. In patient cells, the authors showed defects in cellular proliferation, cell cycle, and DNA repair.

CDK6 (MCPH12)

Gene structure. NCBI Gene recognizes two protein-encoding transcript variants. The transcript NM_001259.6 has seven exons and encodes a protein of 326 amino acids (NP_001250.1)

Pathogenic variants. The p.Ala197Thr variant was observed in ten individuals from a consanguineous Punjabi family [Hussain et al 2013].

See Table 15 (pdf) for a list of all reported pathogenic variants.

Normal gene product. CDK6, a member of the cyclin-dependent protein kinase (CDK) family, is a catalytic subunit of a protein kinase complex that is important for cell cycle G1 phase progression and G1/S transition. CDK6 is present in the cytoplasm and nucleus of non-dividing cells, notably in the edges and in cytoplasmic extensions of astrocytes where it partially colocalizes with actin. During mitosis, from prophase to telophase, CDK6 accumulates at the centrosome and surrounds pericentrin [Hussain et al 2013].

Abnormal gene product. Mutant CDK6 does not accumulate at centrosomes [Hussain et al 2013].

ATR (SCKL1)

Gene structure. *ATR* (ataxia-telangiectasia and rad3 related) spans 130 kb. NCBI Gene recognizes one protein-encoding isoform. The transcript (NM_001184.3) has 47 exons and encodes a protein of 2644 amino acids (NP_001175.2).

Pathogenic variants. A single homozygous pathogenic variant was reported in two consanguineous families of Pakistani origin [O'Driscoll et al 2003]. The variant did not change an amino acid, but resulted in use of two cryptic splice-donor sites in exon 9 resulting in both exon 9 skipping followed by a premature translation termination codon in exon 10. Affected individuals had typical SCKS with severe microcephaly (head circumference -12 SD, height -5 SD) [Goodship et al 2000]. Three other patients were reported [Ogi et al 2012, Mokrani-Benhelli et al 2013].

See Table 16 (pdf) for a list of all reported pathogenic variants.

Normal protein. ATR (ATM- and Rad3-related) kinase is a member of the phosphoinositide 3-kinase (PI3K)-like serine/threonine protein kinase (PIKK) family, a family that also includes ATM (ataxia telangiectasia mutated), the DNA-PK (DNA-dependent protein kinase, an enzyme involved in NHEJ), and mTOR (mammalian target of rapamycin). ATR is a DNA damage sensor.

ATR forms a stable complex with ATRIP [Cortez et al 2001]. When DNA replication is impeded, extensive single-stranded DNA (ssDNA) is exposed through discordance between DNA polymerases and the MCM helicase, and then coated by replication protein A (RPA), which in turn recruits ATR through ATRIP binding.

Once activated, ATR phosphorylates and activates several downstream effector kinases (BRCA1, CHEK1, MCM2, RAD17, RPA2, SMC1, and TP53) which collectively inhibit DNA replication and mitosis, promote DNA repair, and phosphorylate histone H2AX at sites of DNA damage. Activated ATR and Chk1 coordinate DNA replication, DNA repair, and cell-cycle transitions. Action of ATR requires its interaction with the FANCD2 complex (one of the complexes formed by genes associated with Fanconi anemia) which it ubiquinates. ATR also forms a complex with CHD4 and HDAC2 and interacts with a number of proteins including BCR-ABL, CLSPN, CEP164, and TELO2.

Abnormal protein function. Mutation of *ATR* results in deficiency in ATR signaling and damage responses.

RBBP8 (SCKL2)

Gene structure. *RBBP8* (retinoblastoma binding protein 8; previously known as *CTIP*) spans 228 kb. NCBI Gene recognizes two protein-encoding isoforms but three transcripts (variants 1 and 2 both encode isoform a). The longest transcript (isoform a - NM_002894.2) has 20 exons and encodes a protein of 897 amino acids.

Pathogenic variants. Pathogenic variants in *RBBP8* were identified for the first time in SCKS in 2011. The two *RBBP8* pathogenic variants reported to date lead to a loss of function.

- A 2-bp deletion in exon 11 [Qvist et al 2011] was identified in affected members of a consanguineous Pakistani family previously reported to have Jawad syndrome [Hassan et al 2008].
- A homozygous T>G transversion 53 bp within intron 15 [Qvist et al 2011] was found in a consanguineous Iraqi family previously reported to have Seckel syndrome type 2 [Borglum et al 2001].

See Table 17 (pdf) for a list of all reported pathogenic variants.

Normal gene product. RBBP8 is a ubiquitously expressed nuclear endonuclease protein that cooperates with the MRE11-RAD50-NBN (MRN) complex in processing meiotic and mitotic double-strand breaks. It belongs to a complex with transcriptional co-repressor CTBP. RBBP8 has both transcription-dependent and transcription-independent roles in cell cycle progression, and plays a major role as a partner of ATR/ATRIP- functioning downstream of the MRN complex- to promote ATR activation and its recruitment to double-strand breaks in the S/G2 phase. RBBP8 forms a complex with BRCA1 that regulates CHEK1 activation and controls cell cycle G2/M checkpoints on DNA damage.

Abnormal gene product. In the absence of RBBP8, the processing of double-strand breaks (DBS) is impaired, ATR activation is reduced, and mutant cells do not respond optimally to DNA damage [Qvist et al 2011].

CEP63 (SCKL6)

Gene structure. *CEP63* (centrosomal protein 63 kd) spans 89 kb. NCBI Gene recognizes one protein-encoding isoform. The transcript (NM_025009.4) has 26 exons and encodes a protein of 1140 amino acids (NP_079285.2).

Pathogenic variants. A hypomorphic pathogenic variant was identified in three cousins from a consanguineous Pakistani family [Sir et al 2011].

See Table 18 (pdf) for a list of all reported pathogenic variants.

Normal gene product. The CEP63 protein contains six coiled-coil domains. CEP63 localizes to the centrosomes throughout the cell cycle, mediated by its N-terminus (amino acids 1 to 290). CEP63 interacts with CEP152 to form a ring at the proximal end of parental centrioles where parental centrioles and procentrioles are predicted to engage [Sir et al 2011]. CEP63 recruits CDK1, a key mitotic kinase, to the centrosome [Loffler et al 2011]. Following DNA damage, such as double-strand breaks, CEP63 is removed from centrosomes, inactivating the spindle assembly, and delaying mitotic progression.

Abnormal gene product. Lack of CEP63 delays procentriole assembly (explaining unipolar spindles) and impairs engagement of centrioles (explaining mis-segregation of duplicated centrioles in the same pole). Cells knocked out for *CEP63* show spindle defects such as monopolar and multipolar spindles, and mitotic skipping leading to endopolyploidy (a polyploid state in which the chromosomes have divided repeatedly without subsequent division of the nucleus or cell) [Loffler et al 2011, Sir et al 2011].

NIN (SCKL7)

Gene structure. *NIN* (ninein or GSK3B interacting protein) spans 111 kb. NCBI Gene recognizes four protein-encoding isoforms. The longest transcript (isoform 2 - NM_020921.3) has 32 exons and encodes a protein of

2133 amino acids (NP_065972.3). *NIN* has several isoforms which may differ largely from isoform 2. Isoform 5 has also been referred to as hNinein-Lm.

Pathogenic variants. Two native Mexican Indian sisters were reported with compound heterozygous pathogenic variants in *NIN* [Dauber et al 2012].

See Table 19 (pdf) for a list of all reported pathogenic variants.

Normal gene product. Ninein is a coiled-coil centrosomal protein important for centrosomal function. In interphase cells, ninein is localized in the centrosome. It forms oligomeric tubular structures. Ninein decreases in metaphase and anaphase and reappears in telophase. In the mother centrosome, ninein localizes at both ends of the centrosome tube, including the site of centrosome duplication, while in the daughter centrosome it is present only at the closed end. This protein is important for positioning and anchoring the microtubule minus-ends. Ninein constitutes a molecular link between microtubule nucleation and microtubule-anchoring activities at the centrosome. PCM1 is required for its centrosomal localization.

ATRIP

Gene structure. ATRIP (ATR-interacting protein) spans 21 kb. The longest transcript (isoform 1 - NM_130384.2) has 15 exons and encodes a protein of 791 amino acids.

Pathogenic variants. Ogi et al [2012] identified a pathogenic nonsense variant in compound heterozygous state in an individual with SCKS. Although the authors demonstrated a splice defect leading to severe decrease in ATRIP expression in the patient (and modest reduction in the carrier father), they failed to identify the cause of this exon skipping (despite identifying two unreported SNPs in intron 1 -92 bp and -13 bp upstream of exon 2).

See Table 20 (pdf) for a list of all reported pathogenic variants.

Normal gene product. ATRIP is a component of the DNA damage checkpoint. It forms a heterodimer with ATR. It binds to single-stranded DNA coated with replication protein A that accumulates at sites of DNA damage. ATRP interacts with CEP164 (via N-terminus) and CINP.

ATRIP mediates the accumulation of ATR on damaged chromatin via an interaction with the RPA complex (which recognizes and coats single-stranded DNA), resulting in accumulation of the ATR kinase at intranuclear foci induced by DNA damage.

Abnormal gene product. Unknown

See Table 20 for a list of all reported pathogenic variants.

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Chapter Notes

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- 10 September 2018 (ma) Chapter retired: Chapter does not reflect current use of genetic testing.
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