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## KCNK9 Imprinting Syndrome

Synonym: Birk-Barel Syndrome

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## Summary

### Clinical characteristics

*KCNK9* imprinting syndrome is characterized by congenital central hypotonia (manifest as decreased movement, lethargy, and weak cry), severe feeding difficulties (resulting from facial weakness and poor suck), delayed development/intellectual disability, and dysmorphic manifestations. Poor feeding can cause failure to thrive during infancy unless managed appropriately. Significant dysphagia of solid foods typically persists until puberty. Intellectual disability can be severe. To date 19 individuals with a molecularly confirmed diagnosis have been reported.

### Diagnosis/testing

The diagnosis of the *KCNK9* imprinting syndrome is established in a proband with suggestive clinical findings and detection of the heterozygous *KCNK9* pathogenic variant p.Gly236Arg on the maternal allele.

### Management

*Treatment of manifestations:* A multidisciplinary team of specialists in clinical genetics, plastic surgery, ophthalmology, pulmonology, gastroenterology, feeding, endocrinology, and neurology is recommended (depending on the individual's needs). Standard treatment for lacrimal duct obstruction, obstructive sleep apnea, scoliosis, and seizures. Feeding problems typically require use of special nipples and/or bottles and/or nasogastric/gastrostomy tube feedings. Cleft palate and velopharyngeal insufficiency are managed as per standard practice as are developmental delay/intellectual disability. Transient neonatal hypoglycemia responds to diazoxide treatment.

*Surveillance:* Monitoring of serum glucose levels for hypoglycemia in the neonatal period. At least annual ophthalmology evaluation, monitoring for the development of scoliosis, and monitoring of nutritional status, growth, and feeding.

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## Genetic counseling

*KCNK9* imprinting syndrome is inherited in an autosomal dominant maternally imprinted manner (i.e., a heterozygous pathogenic variant on the maternally derived *KCNK9* allele results in disease; a pathogenic variant on the paternally derived *KCNK9* allele does not result in disease because normally the paternally derived *KCNK9* allele is silenced). The *KCNK9* pathogenic variant can either be inherited from the mother (80%) or arise *de novo* on the maternally derived *KCNK9* allele (20%). The risk to the sibs of the proband depends on the genetic status of their mother: if she is heterozygous for the *KCNK9* pathogenic variant, the risk to the sibs is 50%; if the *KCNK9* pathogenic variant cannot be detected in her leukocyte DNA, the risk to sibs is presumed to be slightly greater than that of the general population (though still <1%) because of the theoretic possibility of maternal germline mosaicism. To date, no individual with *KCNK9* imprinting syndrome has been known to reproduce. Once the *KCNK9* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk for *KCNK9* imprinting syndrome (i.e., one in which the mother is heterozygous for a *KCNK9* pathogenic variant) and preimplantation genetic testing are possible.

## Diagnosis

Consensus clinical diagnostic criteria for the *KCNK9* imprinting syndrome have not been established.

## Suggestive Findings

*KCNK9* imprinting syndrome **should be suspected** in individuals with normal brain imaging and the following clinical findings:

- Congenital central hypotonia and persistent generalized weakness
- Severe feeding difficulties, often requiring placement of gastrostomy tube.
- Delayed development / intellectual disability

## Establishing the Diagnosis

The diagnosis of the *KCNK9* imprinting syndrome **is established** in a proband with suggestive clinical findings and the heterozygous *KCNK9* p.Gly236Arg pathogenic variant on the maternal allele detected by molecular genetic testing (see Table 1). To date, it is unknown if other *KCNK9* pathogenic variants can cause the same phenotype.

Because the phenotype of the *KCNK9* imprinting syndrome is indistinguishable from many other inherited disorders with hypotonia, feeding difficulties, and developmental delay/intellectual disability, molecular genetic testing approaches can include **genomic testing** (comprehensive genome sequencing) OR **gene-targeted testing** (multigene panel). Note that gene-targeted testing requires the clinician to determine which gene(s) are likely involved, whereas genomic testing may not.

- **Comprehensive genome sequencing** (when available) including exome sequencing and genome sequencing can be considered. For an introduction to comprehensive genomic testing click [here](#). More detailed information for clinicians ordering genomic testing can be found [here](#).
- **A multigene panel** that includes *KCNK9* and other genes of interest (see Differential Diagnosis) can be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes

that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click [here](#). More detailed information for clinicians ordering genetic tests can be found [here](#).

**Table 1.** Molecular Genetic Testing Used in *KCNK9* Imprinting Syndrome

Gene <sup>1</sup>	Method	Proportion of Probands with a Pathogenic Variant <sup>2</sup> Detectable by Method
<i>KCNK9</i>	Sequence analysis <sup>3, 4</sup>	9/9
	Gene-targeted deletion/duplication analysis <sup>5</sup>	0/9

1. See Table A. Genes and Databases for chromosome locus and protein.

2. See Molecular Genetics for information on allelic variants detected in this gene.

3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or 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](#).

4. Since *KCNK9* is a maternally expressed imprinted gene, determining whether a variant is maternally or paternally inherited is critical for variant classification.

5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

## Clinical Characteristics

### Clinical Description

*KCNK9* imprinting syndrome is characterized by congenital central hypotonia, severe feeding difficulties, delayed development/intellectual disability, and dysmorphic features. To date 19 individuals with a molecularly confirmed diagnosis have been reported: 15 from an Arab-Israeli family [Barel et al 2008] and four representing simplex cases (i.e., a single occurrence in a family) [Graham et al 2016]. Note that 15 individuals from the original family were reexamined for the report by Graham et al [2016].

The phenotype has been severe and consistent in all individuals examined to date.

**Congenital central hypotonia**, evident in neonates, is associated with decreased movement, lethargy, weak cry, weak facial muscles, poor suck, and feeding difficulties. Prenatally, hypotonia can manifest as decreased fetal movement and breech presentation necessitating cesarean section.

While the hypotonia may improve over time, it is present during childhood and into adulthood. Occasionally weakness of proximal muscles and the supra- and infrascapular and trapezius muscles is observed later in life. Generalized hypotonia at an early age followed by weakness of proximal muscles can lead to contractures and scoliosis.

**Poor feeding** can cause failure to thrive during infancy unless managed appropriately (see Management). Significant dysphagia of solid foods due to hypotonia and poorly coordinated swallowing typically persists until puberty [Barel et al 2008].

Cleft palate (including full cleft, submucous cleft or velopharyngeal insufficiency) is present in 42% of affected individuals.

**Delayed motor and speech milestones / intellectual disability** are observed in all individuals with the *KCNK9* imprinting syndrome. Intellectual disability is usually moderately severe with limited speech. Wide-based gait can also be observed.

### Other

Occasional neurologic findings include clonus and rarely seizures.

Subtle dysmorphic features that can evolve over time include dolichocephaly with a narrow forehead; mild atrophy of the temporalis and masseter muscles; myopathic elongated facies with a tented vermilion of the upper lip and short broad philtrum; reduced facial movement; mild micro/retrognathia with relatively prominent maxillary and premaxillary regions; medially flared, arched eyebrows; and ptosis [Graham et al 2016].

Body habitus is asthenic; a long neck and tapered chest are evident in later childhood. Fingers are tapered; fetal fingertip pads are prominent [Barel et al 2008].

A pilonidal dimple or sinus is evident in most individuals. Rarely, it is associated with a filar cyst (cystic structure in the proximal filum terminale) and lipoma in the sacral region.

Some affected individuals have transient neonatal hypoglycemia associated with hyperinsulinism that resolves with diazoxide treatment [Graham et al 2016].

Decreased lacrimation and increased risk for corneal dryness can be observed.

Sleep disturbance can be due to both central and obstructive sleep apnea, and usually responds to BiPAP.

Normal findings typically include: hearing, ophthalmologic evaluation (including vision), neuroimaging, and muscle biopsy (which may show nonspecific findings such as fiber-size disproportion). X-rays of long bones are normal [Barel et al 2008].

### Penetrance

Penetrance for maternally inherited pathogenic variants in *KCNK9* appears to be complete; however, the number of affected individuals with a molecularly confirmed diagnosis is so limited that no conclusions can be made at present.

### Prevalence

*KCNK9* imprinting syndrome has been identified in approximately 19 individuals, with most individuals from the original Arab-Israeli family reported by Barel et al [2008] having the same *KCNK9* pathogenic variant. Since 2008 an additional four simplex cases (i.e., a single occurrence in a family) have been reported [Graham et al 2016].

### Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *KCNK9*.

### Differential Diagnosis

A number of disorders can mimic some aspects of the *KCNK9* phenotype. See Table 2.

**Table 2.** Disorders to Consider in the Differential Diagnosis of *KCNK9* Imprinting Syndrome

Disorder	Genetic Mechanism	MOI	Clinical Features of Differential Diagnosis Disorder	
			Overlapping w/ <i>KCNK9</i> imprinting syndrome	Distinguishing from <i>KCNK9</i> imprinting syndrome
Congenital myotonic dystrophy type 1	>1000 CTG trinucleotide repeat expansion in <i>DMPK</i> <sup>1</sup>	AD	<ul style="list-style-type: none"> <li>Hypotonia &amp; severe generalized weakness at birth</li> <li>Intellectual disability</li> </ul>	<ul style="list-style-type: none"> <li>Usually no cleft palate</li> </ul>
Prader-Willi syndrome (PWS)	Abnormal parent-specific imprinting w/in the Prader-Willi critical region	See footnote 2.	<ul style="list-style-type: none"> <li>Severe hypotonia &amp; feeding difficulties in early infancy</li> <li>Delayed motor milestones &amp; language development; some degree of cognitive impairment in all persons</li> </ul>	<ul style="list-style-type: none"> <li>Hypotonia &amp; feeding problems resolve more quickly.</li> <li>Usually no cleft palate</li> </ul>
22q11.2 deletion syndrome	Deletion of genes w/in the DiGeorge chromosome region	AD	<ul style="list-style-type: none"> <li>Palatal abnormalities</li> <li>Characteristic facial features</li> <li>Learning difficulties</li> <li>Immune deficiency</li> <li>Hypocalcemia w/significant feeding &amp; swallowing problems</li> </ul>	<ul style="list-style-type: none"> <li>Initial hypotonia less severe</li> <li>Presence of heart defects</li> </ul>

AD = autosomal dominant; MOI = mode of inheritance

1. Redman et al [1993] reported a few individuals with congenital myotonic dystrophy type 1 with repeats between 730 and 1000.

2. PWS is caused by lack of expression of the paternally derived PWS/AS region of chromosome 15q11.2-q13 by one of several genetic mechanisms.

## Management

### Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *KCNK9* imprinting syndrome, the evaluations following diagnosis summarized in Table 3 (if not performed as part of the evaluation that led to diagnosis) are recommended.

**Table 3.** Recommended Evaluations Following Initial Diagnosis of *KCNK9* Imprinting Syndrome

System/Concern	Evaluation	Comment
<b>Oropharynx</b>	Assessment by cleft/craniofacial team if cleft palate, bifid uvula, or velopharyngeal insufficiency is present	
<b>Feeding</b>	Feeding & swallowing eval	Consider gastrostomy tube placement if clinically indicated by significant microretrognathia &/or recurrent aspiration.
<b>Pulmonary</b>	Polysomnogram if obstructive apnea is suspected	
<b>Musculoskeletal</b>	Eval for skeletal manifestations (i.e., joint contractures, scoliosis)	Consider referral to orthopedist if indicated.
<b>Neurologic</b>	<ul style="list-style-type: none"> <li>Assess strength &amp; motor skills.</li> <li>EEG if seizures are suspected</li> <li>Spinal ultrasound of a pilonidal dimple or sinus to assess for filar cyst &amp; lipoma in sacral region</li> </ul>	
<b>Endocrine</b>	Assess for hypoglycemia during neonatal period & infancy.	If present, consider consultation w/ endocrinologist to discuss possible treatment w/diazoxide.

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
<b>Miscellaneous/ Other</b>	<ul style="list-style-type: none"> <li>Developmental assessment</li> <li>Consultation w/clinical geneticist &amp;/or genetic counselor</li> </ul>	

## Treatment of Manifestations

No specific management guidelines have been developed. Management is mostly supportive.

A multidisciplinary team of specialists in clinical genetics, plastic surgery, ophthalmology, pulmonology, gastroenterology, feeding, endocrinology, and neurology is recommended depending on the affected individual's manifestations.

Table 4. Treatment of Manifestations in Individuals with *KCNK9* Imprinting Syndrome

Manifestation/Concern	Treatment	Considerations/Other
<b>Lacrimal duct obstruction</b>	Tear duct massage; consider lacrimal duct stent placement.	
<b>Cleft palate, bifid uvula, or velopharyngeal insufficiency</b>	Mgmt by cleft/craniofacial team; retrognathia & underdevelopment of mandible may require mandibular distraction osteogenesis.	
<b>Obstructive sleep apnea</b>	CPAP or BiPAP; ENT eval for tonsillectomy/adenoidectomy	Pulmonary consultation; consider treatment w/mefenamic or flufenamic acid (See Therapies Under Investigation.)
<b>Feeding difficulties or signs of aspiration</b>	Use of a special nipple or bottle w/cleft palate; short-term nasogastric feeding tube; consideration of gastrostomy tube	
<b>Gastroesophageal reflux disease</b>	Standard positioning & pharmacologic treatment	
<b>Musculoskeletal findings (i.e., contractures, scoliosis)</b>	Ankle-foot orthoses or other assistive devices; standard treatment for scoliosis	PT &/or OT eval; consultation w/orthopedist
<b>Seizure disorder</b>	Eval of blood sugar & electrolytes; standard treatment for seizures	Consider EEG & referral to neurologist.
<b>Unexplained hypoglycemia or suspected hyperinsulinism</b>	Consideration of diazoxide therapy	Consider referral to an endocrinologist.
<b>Developmental delay</b>	Early referral for developmental support/special education, which may incl: PT, OT, speech therapy, &/or cognitive therapy	Consider referral to neurodevelopmental specialist &/or neuropsychiatric testing.

OT = occupational therapy; PT = physical therapy

## Surveillance

Table 5. Recommended Surveillance for Individuals with *KCNK9* Imprinting Syndrome

System/Concern	Evaluation	Frequency/Comment
<b>Growth</b>	Eval of nutritional status & growth	Every 6 mos until age 2 yrs, then annually
<b>Eyes</b>	Ophthalmology assessment for ↓ lacrimation & ↑ risk for corneal dryness	At least annually
<b>ENT/Mouth</b>	Eval of feeding difficulties	Every 6 mos until age 2 yrs, then annually
<b>Respiratory</b>	Sleep study (if history of sleep disturbance)	Pulmonary eval every 6 mos until age 2 yrs, then annually



Table 5. continued from previous page.

System/Concern	Evaluation	Frequency/Comment
<b>Musculoskeletal</b>	Eval for scoliosis	At least annually
<b>Endocrine</b>	Monitor serum glucose levels for hypoglycemia secondary to poor feeding & ↑ risk for hyperinsulinemia.	Every 6 mos until age 2 yrs

## Evaluation of Relatives at Risk

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

## Therapies Under Investigation

*KCNK9*, which is imprinted and expressed from the maternal allele with paternal silencing, encodes a member of the two pore-domain potassium channel (K2p9.1 or TASK3). The only *KCNK9* pathogenic variant reported to date, p.Gly236Arg, reduces the outward current of the TASK3 channel by approximately 80% [Veale et al 2014].

Three members of the nonsteroidal anti-inflammatory fenamic acid class of drugs – flufenamic acid (FFA), niflumic acid (NFA) and mefanamic acid (MFA) – have been shown to stimulate two pore-domain potassium channels [Takahira et al 2005]. The reduced outward current through abnormal p.Arg236-containing TASK3 channels has been shown to be partially rescued by FFA, suggesting that fenamic acid compounds could be useful in treating this condition [Veale et al 2014].

Two affected individuals to date have been treated with oral MFA starting at age 14 months, with noted increased energy while on the medication and no adverse reactions. Clinical features are still present, and long-term studies are necessary to predict the outcome of individuals treated with MFA [Graham et al 2016].

Search [ClinicalTrials.gov](https://clinicaltrials.gov) in the US and [EU Clinical Trials Register](https://clinicaltrialsregister.eu) in Europe for access to information on clinical studies for a wide range of diseases and conditions.

## 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

*KCNK9* imprinting syndrome is inherited in an autosomal dominant, maternally imprinted manner (i.e., a heterozygous pathogenic variant on the maternally derived *KCNK9* allele results in disease; a pathogenic variant on the paternally derived *KCNK9* allele does not result in disease because normally the paternally derived *KCNK9* allele is silenced). In any given affected individual, a pathogenic variant (typically p.Gly236Arg) that causes *KCNK9* imprinting syndrome can either be inherited from the mother or arise *de novo* on the maternally derived *KCNK9* allele.

## Risk to Family Members

### Parents of a proband

- Approximately 80% of affected individuals reported to date inherited the p.Gly236Arg *KCNK9* pathogenic variant from a clinically unaffected mother.

- Approximately 20% of individuals diagnosed with *KCNK9* imprinting syndrome have the disorder as the result of a *de novo* pathogenic variant on the maternally derived *KCNK9* allele [Graham et al 2016].
- Recommendations for the evaluation of the mother of a proband include *KCNK9* molecular genetic testing. If the pathogenic variant found in the proband cannot be detected in maternal leukocyte DNA, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in the mother. Although no instances of germline mosaicism have been reported to date, it remains a possibility.
- The father of an affected individual will not be affected with *KCNK9* imprinting syndrome nor will he be heterozygous for a *KCNK9* pathogenic variant.

### Sibs of a proband

- The risk to the sibs of the proband depends on the genetic status of the proband's mother.
- If the mother of the proband is heterozygous for the *KCNK9* pathogenic variant, the risk to the sibs is 50%.
- If the *KCNK9* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of the mother, the risk to sibs is presumed to be slightly greater than that of the general population (though still <1%) because of the theoretic possibility of maternal germline mosaicism.

**Offspring of a proband.** To date, no individual affected with *KCNK9* imprinting syndrome has been known to reproduce.

### Other family members

- The risk to other family members depends on the genetic status of the proband's mother.
- If the proband's mother is heterozygous for a *KCNK9* pathogenic variant, other male and female family members may also be heterozygous for the pathogenic variant.
  - Offspring of heterozygous females would be at risk for *KCNK9* imprinting syndrome.
  - Offspring of heterozygous males would not be at risk for *KCNK9* imprinting syndrome because the paternally inherited *KCNK9* allele is silenced. However, a heterozygous male can transmit the pathogenic variant to his daughter, who would then be at risk of having affected children.

## Related Genetic Counseling Issues

### Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young females heterozygous for a paternally inherited *KCNK9* pathogenic variant.

**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 Testing

Once the *KCNK9* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk for *KCNK9* imprinting syndrome (i.e., one in which the mother is heterozygous for a *KCNK9* pathogenic variant) and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.



## 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](#).

- **CDC - Developmental Disabilities**  
**Phone:** 800-CDC-INFO  
**Email:** [cdcinfo@cdc.gov](mailto:cdcinfo@cdc.gov)  
[Intellectual Disability](#)
- **MedlinePlus**  
[Intellectual Disability](#)

## 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.** KCNK9 Imprinting Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
<a href="#">KCNK9</a>	<a href="#">8q24.3</a>	<a href="#">Potassium channel subfamily K member 9</a>	<a href="#">KCNK9 database</a>	<a href="#">KCNK9</a>	<a href="#">KCNK9</a>

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 KCNK9 Imprinting Syndrome ([View All in OMIM](#))

<a href="#">605874</a>	<a href="#">POTASSIUM CHANNEL, SUBFAMILY K, MEMBER 9; KCNK9</a>
<a href="#">612292</a>	<a href="#">BIRK-BAREL SYNDROME; BIBARS</a>

**Gene structure.** *KCNK9* has five exons. This gene is also known in the literature as *KT3.2*, *TASK3*, and *K2p9.1*.

**Pathogenic variants.** The two maternally inherited pathogenic variants associated with the *KCNK9* imprinting syndrome, c.770G>A and c.770G>C, both predict the protein change p.Gly236Arg.

**Table 6.** *KCNK9* Pathogenic Variants Discussed in This GeneReview

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.770G>A and c.770G>C	p.Gly236Arg	<a href="#">NM_001282534.1</a> <a href="#">NP_001269463.1</a>

Variants listed in the table have been provided by the authors. GeneReviews staff have not independently verified the classification of variants.

GeneReviews follows the standard naming conventions of the Human Genome Variation Society ([varnomen.hgvs.org](http://varnomen.hgvs.org)). See [Quick Reference](#) for an explanation of nomenclature.

**Normal gene product.** *KCNK9* (also called *TASK3*) is maternally expressed and encodes a member of the two pore-domain potassium channel (K2P) subfamily and functions as a pH-dependent potassium channel, known as *TASK3* [Veale et al 2014, Graham et al 2016].

Because *KCNK9* is an imprinted gene, the paternal allele is normally silenced; thus, a pathogenic variant on the maternal copy of *KCNK9* causes disease, whereas a pathogenic variant on the paternal copy will have no effect.

TASK3 channels are found throughout the body, especially in the brain where they may play a role in the migration of cortical pyramidal neurons by regulating membrane potential and in action potential repolarization [Bando et al 2014, Graham et al 2016].

**Abnormal gene product.** The c.770G>C and c.770G>A (p.Gly236Arg) pathogenic variants reduce by 80% the functional currents of the TASK3 channels [Veale et al 2014]. Because granule neurons do not maintain sustained repetitive firing in the absence of TASK3 channels [Brickley et al 2007, Graham et al 2016], reduction in the activity of these channels alters both neuronal activity and neuronal development

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## Chapter Notes

### Author Notes

[KCNK9 Imprinting Syndrome website](#)

[Facebook: KCNK9 Imprinting Syndrome - Birk-Barel](#)

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