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Thiamine-Responsive Megaloblastic Anemia Syndrome

Synonyms: Rogers Syndrome, TRMA

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Summary

Clinical characteristics

Thiamine-responsive megaloblastic anemia syndrome (TRMA) is characterized by megaloblastic anemia, progressive sensorineural hearing loss, and diabetes mellitus. Onset of megaloblastic anemia occurs between infancy and adolescence. The anemia is corrected with thiamine treatment, but the red cells remain macrocytic and anemia can recur if treatment is withdrawn. Progressive sensorineural hearing loss often occurs early and can be detected in toddlers; hearing loss is irreversible and may not be prevented by thiamine treatment. The diabetes mellitus is non-type I in nature, with age of onset from infancy to adolescence. Thiamine treatment may reduce insulin requirement and delay onset of diabetes in some individuals.

Diagnosis/testing

The diagnosis of TRMA is established in a proband with: megaloblastic anemia with normal vitamin B_{12} / folic acid levels, with or without diabetes or hearing loss, in whom there is a response to oral thiamine; and/or biallelic pathogenic variants in *SLC19A2* identified by molecular genetic testing.

Management

Treatment of manifestations: Lifelong use of pharmacologic doses (50-100 mg/day) of oral thiamine (vitamin B_1) in affected individuals regardless of age. Red blood cell transfusion for severe anemia. Standard treatment for sensorineural hearing loss, diabetes mellitus, and ophthalmologic, cardiovascular, and neurologic manifestations.

Surveillance: At least annual monitoring of the efficacy of the oral thiamine therapy and of disease progression, including: hematologic tests (CBC, reticulocyte count); assessment for glucose intolerance (fasting serum glucose concentration, oral glucose tolerance test, urinalysis); and hearing, ophthalmologic, cardiac, and neurologic evaluations.

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Pregnancy management: Good diabetic control prior to and during pregnancy is recommended.

Genetic counseling

TRMA is inherited in an autosomal recessive manner. At conception, each sib of an 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. Carrier testing for at-risk relatives and prenatal testing for a pregnancy at increased risk are possible for families in which the *SLC19A2* pathogenic variants have been identified in the affected family member.

Diagnosis

Suggestive Findings

Thiamine-responsive megaloblastic anemia syndrome (TRMA) **should be suspected in** individuals with the following triad of clinical features:

- **Megaloblastic anemia** occurring between infancy and adolescence:
  - Examination of the bone marrow reveals megaloblastic changes with erythroblasts often containing iron-filled mitochondria (ringed sideroblasts).
  - Vitamin B_{12} / folic acid levels are normal.
  - The anemia is corrected with pharmacologic doses of thiamine (vitamin B_1) (50-100 mg/day).
  - Even without thiamine supplementation, serum thiamine concentrations are normal; there is no evidence of acidosis or aciduria.
- **Progressive sensorineural deafness.** Hearing loss generally occurs early and has been detected in toddlers. Whether hearing loss is congenital (prelingual) is unknown. Some affected individuals have signs of megaloblastic anemia and diabetes at an early age, but no hearing loss.
- **Diabetes mellitus** that is non-type I in nature, with age of onset from infancy to adolescence. Insulin secretion is present but defective [Valerio et al 1998].

Establishing the Diagnosis

The diagnosis of TRMA **is established** in a proband with: megaloblastic anemia with normal vitamin B_{12} / folic acid levels, with or without diabetes or hearing loss, in whom there is a response to oral thiamine; and/or biallelic pathogenic (or likely pathogenic) variants in *SLC19A2* identified by molecular genetic testing (see Table 1).

Note: Per ACMG variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of TRMA has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *SLC19A2* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

A multigene panel that includes *SLC19A2* and other genes of interest (see Differential Diagnosis) may be considered to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. 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*. (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.

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Thiamine-Responsive Megaloblastic Anemia Syndrome

Gene [1]	Method	Proportion Pathogenic Variants [2] Detectable by Method
SLC19A2	Sequence analysis [3]	>99% [4]
	Gene-targeted deletion/duplication analysis [5]	2 families reported [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on 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. Diaz et al [1999], Raz et al [2000], Scharfe et al [2000], Gritli et al [2001], Neufeld et al [2001], Ozdemir et al [2002], Lagarde et al [2004], Ricketts et al [2006], Bergmann et al [2009], Onal et al [2009], Pichler et al [2012], Shaw-Smith et al [2012], Yilmaz Agladioglu et al [2012], and data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Beshlawi et al [2014], Zhang et al [2021]

Clinical Characteristics

Clinical Description

Thiamine-responsive megaloblastic anemia syndrome (TRMA) is characterized by the triad of megaloblastic anemia, progressive sensorineural hearing loss, and diabetes mellitus. To date, more than 183 individuals from more than 138 families have been identified [Ortigoza-Escobar et al 2016, Habeb et al 2018, Zhang et al 2021].

Table 2. Thiamine-Responsive Megaloblastic Anemia Syndrome: Frequency of Select Features

Feature	% of Persons w/Feature	Comment
Megaloblastic anemia	60%-70%	Anemia is present in >90% of persons.
Progressive sensorineural deafness	>90%	
Non-type I diabetes mellitus	>90%	
Ophthalmologic manifestations	20%-30%	Incl optic atrophy
Cardiovascular abnormalities	20%-30%	
Neurologic manifestations	20%-40%	
Thrombocytopenia	10%-30%	

Megaloblastic anemia. The earliest findings of significant bone marrow problems have been in the first year of life and the latest in the teenage years. Peripheral blood count shows a pattern of macrocytic anemia with low hemoglobin and high mean corpuscular volume (MCV) in the absence of deficiencies of folate or vitamin B_{12}. Bone marrow shows dysplastic hematopoiesis with numerous megaloblasts. The anemia is corrected with pharmacologic doses of thiamine (vitamin B_1) (50-100 mg/day). However, the red cells remain macrocytic, suggesting a persistent erythropoietic abnormality [Haworth et al 1982, Neufeld et al 1997, Setoodeh et al 2013]; anemia can recur if thiamine therapy is discontinued.

Additional hematologic abnormalities such as thrombocytopenia and neutropenia may be present together with anemia. They can be corrected with pharmacologic doses of thiamine (vitamin B_1) (50-100 mg/day).

Progressive sensorineural deafness. Hearing defects may be present at an early age and in some families may be present at birth [Setoodeh et al 2013]. Progressive sensorineural hearing loss is irreversible and may not be prevented by thiamine treatment. The basis of the sensorineural deafness is obscure; it is not known if the deafness is caused by abnormalities of the cochlea or of the auditory nerve. However, animal studies suggest that selective inner hair cell loss in the cochlea could be the cause of hearing defects in TRMA [Liberman et al 2006].

Non-type I diabetes mellitus has appeared before school age in many (though not all) individuals with glycosuria and hyperglycemia. Diabetic ketoacidosis has been reported in 15% of individuals [Zhang et al 2021]. Initially, affected individuals respond to oral hypoglycemic agents, but most eventually become insulin dependent.

Ophthalmologic manifestations including optic atrophy, when commented on in case reports, appears common. Abnormal appearance of the retina and functional retinal dystrophy have been reported [Meire et al 2000, Kipioti et al 2003, Lagarde et al 2004]. The kindred reported as having DIDMOAD (*d*iabetes *i*nsipidus, *d*iabetes *m*ellitus, *o*ptic *a*trophy, and *d*eafness) by Borgna-Pignatti et al [1989] has in retrospect been shown by genetic analysis to have TRMA. Also, Wu et al [2022] reported an individual with Leber congenital amaurosis who was later found to have molecularly confirmed TRMA.

Cardiovascular abnormalities including sudden death, stroke, high-output heart failure, arrhythmias, atrial standstill, and congenital heart defects such as atrial septal defect or ventricular septal defect have been reported in 20%-30% of individuals with TRMA [Habeb et al 2018, Zhang et al 2021].

Significant neurologic deficits such as stroke, epilepsy, mood disorder, developmental delay, and intellectual disability have been reported during early childhood in 20%-40% of individuals with TRMA [Habeb et al 2018, Zhang et al 2021].

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Nomenclature

The synonym "Rogers syndrome" derives from the first report of the disease in a child with diabetes mellitus, sensorineural deafness, and megaloblastic anemia who responded to thiamine (vitamin B_1) treatment.

Prevalence

Approximately 130 pedigrees are known. TRMA is exceedingly rare outside of consanguineous families or isolated populations. Affected individuals have been observed in various ethnicities including Israeli Arab and Lebanese populations, an Alaskan kindred of native and ethnic Russian descent, and kindreds from Brazil, Japan, Oman, Tunisia, Italy (Venetian and other), Iran, India, and Pakistan, as well as Kashmiri families in Great Britain, ethnic Kurds, persons of northern European heritage, and African Americans [Ortigoza-Escobar et al 2016, Habeb et al 2018, Zhang et al 2021].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *SLC19A2*.

Differential Diagnosis

Anemia. The combination of megaloblastic red cell changes and ringed sideroblasts in individuals with thiamine-responsive megaloblastic anemia syndrome (TRMA) is unique among anemias influenced by inborn errors of metabolism or nutritional causes. Among acquired anemias, this combination is most suggestive of myelodysplastic syndromes in which megaloblastosis and sideroblasts are often noted. TRMA should not be confused with myelodysplastic disorders of premalignant potential.

Progressive sensorineural hearing loss and diabetes mellitus. See Table 3.

Table 3. Genetic Disorders with Hearing Loss and Diabetes Mellitus in the Differential Diagnosis of Thiamine-Responsive Megaloblastic Anemia Syndrome

Gene / Genetic Mechanism	Disorder	MOI	Overlapping Features	Distinguishing Features / Comment
WFS1	*WFS1* Wolfram syndrome spectrum disorder (incl DIDMOAD)	AR AD [1]	Variable combinations of DM, optic atrophy, & deafness	Notably missing megaloblastic anemia & thiamine responsiveness

Table 3. continued from previous page.

Gene / Genetic Mechanism	Disorder	MOI	Overlapping Features	Distinguishing Features / Comment
CISD2	Wolfram syndrome type 2 (OMIM 604928)	AR	Variable combinations of DM, optic atrophy, & deafness	Notably missing megaloblastic anemia & thiamine responsiveness; deafness only at higher frequencies; sometimes presents w/GI ulcers
>1,000 genes	Primary mitochondrial disorders	Mat AR AD XL	Combination of DM & deafness	Macrocytic anemia, megaloblastic bone marrow, & thiamine responsiveness distinguish TRMA from mitochondrial disorders.

AD = autosomal dominant; AR = autosomal recessive; DIDMOAD = diabetes insipidus, diabetes mellitus, optic atrophy, and deafness; DM = diabetes mellitus; GI = gastrointestinal; Mat = maternal; MOI = mode of inheritance; TRMA = thiamine-responsive megaloblastic anemia syndrome; XL = X-linked

1. Non-classic (autosomal dominant) *WFS1* Wolfram syndrome spectrum disorder (*WFS1*-SD) has a variable phenotype, with usually milder neurologic features. Individuals with non-classic *WFS1*-SD may have later onset and slower progressive optic atrophy and/or diabetes mellitus. The deafness, which is usually low-frequency sensorineural hearing loss, may present as profound hearing loss in infancy (see *WFS1* Wolfram Syndrome Spectrum Disorder).

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with thiamine-responsive megaloblastic anemia syndrome (TRMA), the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with Thiamine-Responsive Megaloblastic Anemia Syndrome

System/Concern	Evaluation	Comment
Hematologic	• Peripheral blood count • Bone marrow analysis for evidence of megaloblastic anemia	
Hearing	Audiologic eval	
Endocrine	Fasting serum glucose concentration, OGTT, & urinalysis to diagnose DM	
Eyes	Ophthalmologic eval	
Cardiac	• Cardiac eval, incl echocardiography • EKG	
Neurologic	• Neuroimaging, incl brain MRI if clinically indicated • Assess for seizures.	
Genetic counseling	By genetics professionals [1]	To inform affected persons & families re nature, MOI, & implications of TRMA to facilitate medical & personal decision making

DM = diabetes mellitus; MOI = mode of inheritance; OGTT = oral glucose tolerance test

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 5. Treatment of Manifestations in Individuals with Thiamine-Responsive Megaloblastic Anemia Syndrome

Manifestation/Concern	Treatment	Considerations/Other
Megaloblastic anemia	• **Oral thiamine (vitamin B_1)** lifelong pharmacologic doses (50-100 mg/day) • Red blood cell transfusion for severe anemia	• High-dose thiamine supplementation invariably improves hematologic picture. • There is no addl clinical benefit w/thiamine dose >150mg/day. [1]
Sensorineural hearing loss	See Hereditary Hearing Loss and Deafness Overview for treatment strategies for hearing loss. Treatment has incl cochlear implant. [2]	The efficacy of high-dose thiamine in improving hearing or delaying hearing loss remains unclear. High-dose thiamine supplementation did not prevent hearing loss in some studies. [3]
Diabetes mellitus	Standard treatment of DM per endocrinologist in addition to thiamine therapy	High-dose thiamine supplementation may delay onset of DM & may ameliorate DM in short term & perhaps for decades. Insulin requirements are ↓ w/thiamine therapy in some persons. [1]
Thrombocytopenia	Oral thiamine (vitamin B_1) lifelong pharmacologic doses (50-100 mg/day)	High-dose thiamine supplementation invariably improves hematologic picture.
Ophthalmologic manifestations	Standard treatment of ophthalmologic manifestations	High-dose thiamine supplementation has not been evaluated as treatment for optic atrophy, cardiovascular abnormalities, or neurologic abnormalities assoc w/ TRMA.
Cardiovascular manifestations	Standard treatment of cardiovascular manifestations	
Neurologic manifestations (incl stroke & seizures)	Standard treatment per neurologist	

DM = diabetes mellitus; TRMA = thiamine-responsive megaloblastic anemia syndrome
1. Habeb et al [2018]
2. Hagr [2014]
3. Borgna-Pignatti et al [2009], Akın et al [2011]

Surveillance

Table 6. Recommended Surveillance for Individuals with Thiamine-Responsive Megaloblastic Anemia Syndrome

System/Concern	Evaluation	Frequency
Hematologic	Hematologic tests (CBC, reticulocyte count)	At least annually
Hearing	Hearing test	
Endocrine	• Assess for glucose intolerance (fasting serum glucose concentration, OGTT, urinalysis). • Assess for clinical manifestations of poor glycemic control.	
Eyes	Ophthalmologic eval	
Cardiac	Cardiac eval; EKG	
Neurologic	Neurologic eval	

CBC = complete blood count; OGTT = oral glucose tolerance test

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of sibs of an affected individual by molecular genetic testing for the *SLC19A2* pathogenic variants in the family in order to identify those who would benefit from prompt initiation of treatment and preventive measures.

Supplementation with pharmacologic doses of thiamine (vitamin B_1) (25-100 mg/day compared to US RDA of 1.5 mg/day) is recommended as early as possible for at-risk sibs until their genetic status can be determined.

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

Pregnancy Management

While there are no published studies evaluating pregnancy outcome in affected women, good diabetic control prior to and during pregnancy is recommended.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register 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

Thiamine-responsive megaloblastic anemia syndrome (TRMA) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are presumed to be heterozygous for an *SLC19A2* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *SLC19A2* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband [Kang et al 2021].
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for an *SLC19A2* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of inheriting neither of the familial pathogenic variants.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with TRMA are obligate heterozygotes (carriers) for a pathogenic variant in *SLC19A2*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *SLC19A2* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *SLC19A2* pathogenic variants in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

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 adults who are affected, are carriers, or are at risk of being carriers.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown).

Prenatal Testing and Preimplantation Genetic Testing

Once the *SLC19A2* pathogenic variants have been identified in an affected family member, prenatal testing 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.

- **Alexander Graham Bell Association for the Deaf and Hard of Hearing**

  Phone: 866-337-5220 (toll-free); 202-337-5221 (TTY)

  Fax: 202-337-8314

  Email: info@agbell.org

  Listening and Spoken Language Knowledge Center

- **American Diabetes Association**

  Phone: 800-DIABETES (800-342-2383)

  Email: AskADA@diabetes.org

  diabetes.org

- **American Society for Deaf Children**

  Phone: 800-942-2732 (ASDC)

  Email: info@deafchildren.org

  deafchildren.org

- **BabyHearing.org**

  This site, developed with support from the National Institute on Deafness and Other Communication Disorders, provides information about newborn hearing screening and hearing loss.

  www.babyhearing.org

- **National Association of the Deaf**

  Phone: 301-587-1788 (Purple/ZVRS); 301-328-1443 (Sorenson); 301-338-6380 (Convo)

  Fax: 301-587-1791

  Email: nad.info@nad.org

  nad.org

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. Thiamine-Responsive Megaloblastic Anemia Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
SLC19A2	1q24.2	Thiamine transporter 1	SLC19A2 database	SLC19A2	SLC19A2

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 Thiamine-Responsive Megaloblastic Anemia Syndrome (View All in OMIM)

249270	THIAMINE-RESPONSIVE MEGALOBLASTIC ANEMIA SYNDROME; TRMA
603941	SOLUTE CARRIER FAMILY 19 (THIAMINE TRANSPORTER), MEMBER 2; SLC19A2

Molecular Pathogenesis

Defect of a high-affinity thiamine transporter, SLC19A2, causes thiamine-responsive megaloblastic anemia syndrome (TRMA); however, it is still unclear how the absence of *SLC19A2* expression results in the seemingly divergent disorders of megaloblastic anemia, diabetes mellitus, and deafness. Biochemical studies on fibroblasts or erythrocytes from individuals with TRMA showed that absence of the high-affinity component of thiamine transport results in low intracellular thiamine concentrations [Rindi et al 1992, Stagg et al 1999]. Defective RNA ribose synthesis caused by intracellular thiamine deficiency is thought to be the cause of megaloblastic changes in TRMA [Boros et al 2003]. *Slc19a2* knockout mouse models have been developed [Oishi et al 2002, Fleming et al 2003]; the animal models manifest megaloblastic changes, diabetes mellitus, and sensorineural deafness (the main features of TRMA) when dietary thiamine levels are decreased [Oishi et al 2002]. While the mechanism of megaloblastic changes is still to be elucidated, these models showed defects in insulin secretion and selective loss of inner hair cells in cochlea [Oishi et al 2002, Liberman et al 2006]. It was demonstrated in cultured human islet cells that SLC19A2 deficiency causes impaired insulin secretion with mitochondrial dysfunction [Jungtrakoon et al 2019].

Studies to demonstrate *SLC19A2* variant pathogenicity have all identified severe dysfunction of thiamine transport. These studies described three pathophysiologic mechanisms [Marcé-Grau et al 2019]:

- Reduction of protein expression caused by impaired RNA translation;
- Protein retained within an intracellular segment such as the endoplasmic reticulum;
- Proteins that are able to reach the cell membrane but are functionally impaired.

Questions regarding TRMA disease pathogenesis that still require explanation include why individuals with TRMA do not have manifestations seen in dietary thiamine deficiency [Mandel et al 1984, Poggi et al 1984, Abboud et al 1985] and why the findings in TRMA are organ specific.

Studies have shown that a second high-affinity thiamine transporter, encoded by *SLC19A3*, has major roles in intestinal thiamine uptake in mice, accounting for the absence of overt thiamine deficiency in persons with TRMA [Reidling et al 2010]. In support of this, two Japanese brothers with a Wernicke-like encephalopathy were reported to have compound heterozygous pathogenic variants in *SLC19A3* [Kono et al 2009]. In addition, the difference in distribution of expression of the two thiamine transporters is critical in TRMA: in pancreatic endocrine cells, the expression of *SLC19A2* is much higher than that of *SLC19A3*, and TRMA-associated *SLC19A2* mutated alleles disrupt thiamine uptake significantly [Mee et al 2009]. Similarly, it is hypothesized that in TRMA, the other affected tissues (namely, bone marrow and cochlea) do not express or minimally express *SLC19A3* [Eudy et al 2000, Rajgopal et al 2001].

Mechanism of disease causation. Loss of function resulting in impaired thiamine uptake. Pathogenic variants result in either a truncated protein from a premature stop codon or aberrantly folded protein caused by missense variants in transmembrane domains.

Chapter Notes

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