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NLM Citation: van Karnebeek C, Häberle J. Carbonic Anhydrase VA Deficiency. 2015 Apr 2 [Updated 2021 Aug 26]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Carbonic Anhydrase VA Deficiency

Synonym: CA-VA Deficiency

Clara van Karnebeek, MD, PhD[1] and Johannes Häberle, MD[2]

Created: April 2, 2015; Updated: August 26, 2021.

Summary

Clinical characteristics

Most children with carbonic anhydrase VA (CA-VA) deficiency reported to date have presented between day 2 of life and early childhood (up to age 20 months) with hyperammonemic encephalopathy (i.e., lethargy, feeding intolerance, weight loss, tachypnea, seizures, and coma). Given that fewer than 20 affected individuals have been reported to date, the ranges of initial presentations and long-term prognoses are not completely understood. As of 2021 the oldest known affected individual is an adolescent. Almost all affected individuals reported to date have shown normal psychomotor development and no further episodes of metabolic crisis; however, a few have shown mild learning difficulties or delayed motor skills.

Diagnosis/testing

The diagnosis of CA-VA deficiency is established in children with suggestive clinical findings (metabolic hyperammonemic encephalopathy), laboratory findings (complex acid-base status including respiratory alkalosis and metabolic acidosis; elevated plasma glutamine and alanine and low-to-normal citrulline; and urine organic acid analysis showing elevations of carboxylase substrates and related metabolites suggestive of multiple carboxylase deficiency), and biallelic pathogenic variants in *CA5A* identified by molecular genetic testing.

Management

Treatment of manifestations: Acute care: Hospital admission for children with insufficient oral intake and/or signs of metabolic decompensation such as encephalopathy in order to provide IV fluids (maintenance glucose plus extra calories via IV lipids) and to monitor plasma ammonia, serum lactate, serum glucose, blood gases, electrolytes, and liver parameters. If ammonia-lowering medication is needed, consider use of carglumic acid, which (while not yet approved for this indication) has anecdotally shortened the period of hyperammonemia. Although other ammonia-lowering medications such as sodium benzoate could also be reasonable, no conclusive information has been published to date.

Author Affiliations: 1 Department of Pediatrics Emma Children's Hospital Amsterdam University Medical Center Amsterdam, the Netherlands; Email: c.d.vankarnebeek@amsterdamumc.nl. 2 Division of Metabolism Department of Pediatrics University Children's Hospital Zurich Zurich, Switzerland; Email: johannes.haeberle@kispi.uzh.ch.

To prevent metabolic decompensation during any catabolic state (viral illness or fasting conditions): Use a sick day formula (i.e., with extra calories and lipids, with but limited proteins) and monitor parameters per acute care protocols.

Surveillance: Follow up during infancy and early childhood with a metabolic disease specialist every three to six months for physical and neurologic examinations. If asymptomatic and no further episodes, monitoring can be relaxed during childhood but a sick day regime/emergency plan should be provided and followed.

Agents/circumstances to avoid: Acetazolamide as it inhibits carbonic anhydrase activity. If anti-seizure medications are necessary, avoid topiramate based on its action as carbonic anhydrase inhibitor.

Evaluation of relatives at risk: Neonatal care for:

- An affected infant diagnosed prenatally: Delivery in hospital with monitoring for ~3 days (including physical examination and monitoring especially of plasma ammonia, serum lactate, serum glucose, and blood gases)
- An infant at risk because of a previous affected sib: Close clinical monitoring for the first week of life by a healthcare professional and immediate action if symptoms (of hyperammonemia or hypoglycemia) occur

Genetic counseling

CA-VA deficiency is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *CA5A* pathogenic variant, each sib of an affected individual has at conception a 25% chance of inheriting two *CA5A* pathogenic variants and usually being affected, a 50% chance of inheriting one pathogenic variant and being an asymptomatic carrier, and a 25% chance of inheriting neither pathogenic variant being unaffected and not a carrier. Once the *CA5A* pathogenic variants in a family are known, carrier testing for at-risk relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible. Note: The results of prenatal testing cannot be used to predict with certainty whether or not an individual will be affected, as asymptomatic individuals with biallelic *CA5A* pathogenic variants have been identified.

Diagnosis

No consensus clinical diagnostic criteria for carbonic anhydrase VA (CA-VA) deficiency have been published.

Suggestive Findings

Carbonic anhydrase VA (CA-VA) deficiency should be suspected in children with the following clinical and laboratory findings and family history.

Clinical findings include neonatal, infantile, or early childhood-onset of metabolic hyperammonemic encephalopathy (like that observed in the urea cycle disorders) with lethargy, feeding intolerance, weight loss, tachypnea, seizures, and coma.

Laboratory findings

- **During acute decompensation,** the laboratory findings include (but may not be present in all affected individuals):
  - Significant elevation of plasma ammonia, lactate, and ketones (with concomitant increased urinary ketones). Hypoglycemia can also be seen.
  - Complex acid-base status that includes respiratory alkalosis and metabolic acidosis (with decreased bicarbonate and base excess), reflecting the respiratory consequence of hyperammonemia and accumulation of titratable organic acids, respectively

- Plasma amino acid analysis showing elevation of glutamine and alanine and low-to-normal citrulline
- Urine organic acid analysis showing elevations of carboxylase substrates and related metabolites suggestive of multiple carboxylase deficiency: 3-OH propionate, propionylglycine, methylcitrate and lactate, beta-hydroxybutyrate, and acetoacetate

- **Outside of acute events,** clinical and biochemical parameters often remain normal in affected children except for mildly elevated blood lactate and/or the presence of ketonuria [van Karnebeek et al 2014, Diez-Fernandez et al 2016, Marwaha et al 2020].
- **Normal laboratory findings**
  - While newborn screening using tandem mass spectrometry can theoretically detect carboxylase substrates (specifically C3 and C5OH levels as seen in multiple carboxylase deficiency), they were unremarkable in some of the affected individuals reported to date [van Karnebeek et al 2014]. This is likely due to the relatively mild biochemical profile for the carboxylase-related metabolites along with the low sensitivity of acylcarnitine analyses compared to urine organic acids. Note that because of this theoretic finding, individuals with elevated C3 and C5OH should be considered for this disorder in addition to multiple carboxylase deficiency.
  - Liver transaminases, albumin, and clotting factors have been normal in the affected individuals reported to date.

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of carbonic anhydrase VA (CA-VA) deficiency **is established** in a proband with the metabolic findings described in Suggestive Findings and biallelic pathogenic variants in *CA5A* identified by molecular genetic testing (see Table 1).

Note: Identification of biallelic *CA5A* variants of uncertain significance (or identification of one known *CA5A* pathogenic variant and one *CA5A* variant of uncertain significance) does not establish or rule out a diagnosis of this disorder.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing or 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 CA-VA deficiency has not been considered may be more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *CA5A* 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, such as a hyperammonemia panel, a metabolic panel, or a neonatal encephalopathy panel that includes *CA5A* and other genes of interest (see Differential Diagnosis) is most likely 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 Carbonic Anhydrase VA Deficiency

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method [3]
CA5A	Sequence analysis [4]	~50%
	Deletion/duplication analysis [5]	~50%

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants.
3. Data derived from Marwaha et al [2020], Olgac et al [2020], and the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2017]
4. 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.
5. Testing that identifies exon or whole-gene deletions/duplications not detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA) that includes this gene/chromosome segment.

Clinical Characteristics

Clinical Description

Most children with carbonic anhydrase VA (CA-VA) deficiency reported to date have presented during the newborn period (day 2 of life) or in early childhood (up to age 20 months) with hyperammonemic encephalopathy (i.e., lethargy, feeding intolerance, weight loss, tachypnea, seizures, and coma) [van Karnebeek et al 2014, Diez-Fernandez et al 2016, Marwaha et al 2020, Olgac et al 2020]. However, the range of severity on presentation is probably not yet completely understood given the small number of reported individuals to date.

Data on long-term follow up are limited as the oldest known affected individual is only an adolescent (as of 2021). Almost all of the other affected individuals reported (total number still <20) show normal psychomotor development and no further episodes of metabolic crisis. Only four individuals have shown mild learning difficulties and/or delayed gross and fine motor skills.

Genotype-Phenotype Correlations

Genotype-phenotype correlations remain to be determined. Of note, because of the high rate of parental consanguinity most affected individuals are homozygous for a pathogenic variant.

Interestingly, for family 3 reported by van Karnebeek et al [2014] with a homozygous *CA5A* 4-kb deletion of exon 6 in whom carbonic anhydrase VA was absent in liver, the phenotype was not more severe than in the other two families with splice site and missense variants and residual (albeit reduced) carbonic anhydrase VA enzymatic activity.

Prevalence

Prevalence is currently unknown. Fewer than 20 affected individuals have been described to date; however, some underdiagnosis must be assumed based on available published data [Diez-Fernandez et al 2016].

Of note, a high proportion of affected individuals have been born to consanguineous parents from the Indian subcontinent (India, Pakistan, and Sri Lanka) due to the recurrent variant, p.Glu241Lys, in this population.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *CA5A*.

Differential Diagnosis

Clinical Findings

Disorders to consider in the differential diagnosis of carbonic anhydrase VA (CA-VA) deficiency are summarized in Table 2.

Table 2. Disorders of Interest in the Differential Diagnosis of CA-VA Deficiency

Gene	Disorder	MOI	Clinical Characteristics
BTD *HLCS*	Multiple carboxylase deficiency (biotinidase deficiency & holocarboxylase synthetase deficiency) (OMIM 253270)	AR	If untreated, children w/profound defic usually exhibit neurologic abnormalities (seizures, lethargy, & muscular hypotonia), cutaneous abnormalities, ataxia, DD, vision problems, & hearing loss.
CPS1 *NAGS*	CPS1 deficiency, NAGS deficiency, & other urea cycle defects	AR	Infants w/severe defic are nl at birth but rapidly develop cerebral edema w/lethargy, poor feeding, hyper- or hypoventilation, hypothermia, seizures, neurologic posturing, & coma. In milder (or partial) defic the elevations of plasma ammonia concentration & symptoms are often subtle (1st recognized clinical episode may not occur for months or decades).
PC	Pyruvate carboxylase deficiency	AR	Failure to thrive, DD, recurrent seizures, & metabolic acidosis [1]
UQCRC2	Ubiquinol-cytochrome *c* oxidoreductase core 2 subunit deficiency (OMIM 615160)	AR	Neonatal-onset severe metabolic acidosis, hyperammonemia & hypoglycemia w/poor sucking & tachypnea but normal development or only mild DD despite recurrent metabolic crises; hepatocellular dysfunction also reported in 1 person

AR = autosomal recessive; CPS1 = carbamoylphosphate synthetase I; DD = developmental delay; MOI = mode of inheritance; NAGS = N-acetyl glutamate synthase; nl = normal

1. Three clinical types are recognized: Type A (infantile form), in which most affected children die in infancy or early childhood; Type B (severe neonatal form), in which affected infants have hepatomegaly, pyramidal tract signs, and abnormal movement and die within the first three months of life; and Type C (intermittent/benign form), in which affected individuals have normal or mildly delayed neurologic development and episodic metabolic acidosis.

Laboratory Findings

The biochemical profiles of the disorders to consider in the differential diagnosis of CA-VA deficiency are summarized in Table 3.

Table 3. Comparison of Biochemical Findings in CA-VA Deficiency and Other Inborn Errors of Metabolism in the Differential Diagnosis

Analyte	CA-VA Deficiency	Differential Diagnosis			
		PC deficiency	Multiple carboxylase deficiency	CPS1 or NAGS deficiency	UQCRC2 deficiency
Plasma ammonia	↑	↑	Nl	↑	↑
Serum lactate	↑	↑	↑	Nl	↑
Serum glucose	Nl to ↓	↓	Nl	Nl	↓
Plasma citrulline	Nl to ↓	↑	Nl	↓	Nl
Plasma glutamine	↑	↓	Nl	↑	Nl
Plasma lysine	Nl	↑	Nl	Nl	Nl
HCO3, base excess	↓	Nl to ↓ [1]	↓	Nl	↓
Urine 3-OH butyrate	↑	↑	↑	Nl	↑[3]
Urine alpha-ketoglutarate	↑	↓	↑	Nl	Nl
Urine 3-OH propionic acid, propionylglycine, methylcitrate	↑	Nl	↑	Nl	Nl
Urine 3-methyl-crotonylglycine, 3-OH isovaleric acid	↑	Nl	↑	Nl	Nl
Fatty acids, total & free carnitine, acylcarnitine profiles	Nl	Nl	Abnormal [2]	Nl	↑ C2 & 3-OH-acylcarnitines

↑ = elevated; ↓ = decreased; CA-VA = carbonic anhydrase VA; CPS1 = carbamoyl phosphate synthetase 1; NAGS = N-acetyl-glutamate synthase; Nl = normal; PC = pyruvate carboxylase; UQCRC2 = ubiquinol-cytochrome *c* oxidoreductase core 2 subunit

1. HCO3 as low as 5 mmol/L and base excess as low as -21 found in some affected individuals

2. Low C0 (free carnitine) and elevated C2, C3, and C5OH

3. Elevated ketones, dicarboxylic acids, and tricarboxylic acid cycle intermediates

Pyruvate carboxylase (PC) deficiency**.** As in individuals with PC deficiency, individuals with CA-VA have hyperammonemia and hyperlactatemia (± hypoglycemia) in common. The differences, however, include the following:

- Glutamine levels are elevated in CA-VA deficiency but normal to decreased in PC deficiency.
- Citrulline levels are decreased to normal in CA-VA deficiency but often elevated in PC deficiency.
- Lysine levels are normal, and 2-ketoglutarate and other Krebs cycle intermediates are relatively mildly elevated in CA-VA deficiency. In PC deficiency, lysine is elevated and 2-ketoglutarate and other Krebs cycle metabolites are decreased.

The biochemical profiles in children with CA-VA deficiency support a predominant effect of (secondary) CPS1 deficiency vs PC deficiency.

Multiple carboxylase deficiency (holocarboxylase synthetase and biotinidase deficiency**).** Although biotinidase deficiency and holocarboxylase synthetase (HCS) deficiency share the metabolite profiles of secondary deficiencies of PC, propionyl-CoA-carboxylase (PCC), and 3-methylcrotonyl-CoA-carboxylase (3MCC), the three major differences relative to primary CA-VA deficiency are:

- The significantly higher level of PCC and 3MCC metabolites in (even well-controlled) individuals with the two former disorders compared to those with CA-VA deficiency during metabolic decompensation;
- The presence of secondary CPS1 deficiency (high plasma glutamine and low plasma citrulline) as the (likely) major cause of hyperammonemia in CA-VA deficiency;
- The presence of acetyl-CoA carboxylase deficiency in HCS deficiency and biotinidase deficiency. Individuals with CA-VA deficiency exhibited normal levels of free fatty acids and total and free carnitine, as well as normal acylcarnitine profiles (data not shown), mostly likely as a result of the activity of the cytosolic acetyl-CoA carboxylase 2 isoform that is not affected by impaired provision of mitochondrial HCO_3^-.

Urea cycle defects**.** Severe deficiency or total absence of activity of any of the first four enzymes (CPS1, OTC, ASS, ASL) in the urea cycle or the cofactor producer (NAGS) results in the accumulation of ammonia and other precursor metabolites during the first few days of life [Häberle 2013]. In particular, the proximal urea cycle defects (NAGS deficiency and CPS1 deficiency) show the following similarities with CA-VA deficiency: hyperammonemia, low plasma citrulline and high plasma glutamine, and no orotic aciduria; and good response to carglumic acid. Differences include:

- Absence of hyperlactatemia in urea cycle defects;
- Presence of multiple carboxylase deficiency metabolites in CA-VA deficiency.

Ubiquinol-cytochrome *c* oxidoreductase core 2 subunit (UQCRC2) deficiency (OMIM 615160) can present with a similar combination of lactic acidosis and episodes of hyperammonemia and hypoglycemia. The pathogenesis of the biochemical phenotype is currently unclear.

Management

No clinical practice guidelines for carbonic anhydrase VA (CA-VA) deficiency have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with carbonic anhydrase VA (CA-VA) deficiency, the following evaluations are recommended:

- Measurement of serum lactate, plasma ammonia, serum glucose, blood gases, plasma amino acids, blood acylcarnitines, urine ketone bodies, and urine organic acid profiles (during periods of illness; when stable for monitoring, preferably fasting)
- Liver function parameters (coagulation, albumin, AST, ALT) as acute liver failure can occur in the urea cycle disorders, which are metabolically similar
- Consideration of:
  - Brain MRI to define extent of or to exclude brain edema
  - Neurodevelopmental testing
- Consultation with a medical geneticist, certified genetic counselor, or certified advanced genetic nurse to inform affected individuals and their families about the nature, mode of inheritance, and implications of CA-VA deficiency in order to facilitate medical and personal decision making

Treatment of Manifestations

During acute episodes. Admit to the hospital children with insufficient intake or refusal to take anything orally and/or signs of metabolic decompensation such as encephalopathy. The following are recommended:

- Always provide IV fluids (with glucose at maintenance doses) and extra calories via IV lipids; restrict protein intake if plasma ammonia is elevated.

- Always monitor plasma ammonia, serum lactate, serum glucose, blood gases, electrolytes, and liver parameters.
- Consider administration of carglumic acid (which – though not approved yet for this indication – enhances CPS1 activity and thus partially compensates for reduced HCO_3^- resulting from CA-VA deficiency). In most reported individuals who were given carglumic acid during the acute phase, hyperammonemia and clinical symptoms resolved within 12 hours. Without carglumic acid, hyperammonemia persisted longer (i.e., an additional 1-2 days).
- Other ammonia-lowering medications such as sodium benzoate would also be reasonable; however, to date no conclusive information has been published.

Care to prevent metabolic decompensation during any catabolic state (viral illness or fasting conditions)

- Use a sick day formula (i.e., with extra calories and lipids, but limited proteins).
- Monitor plasma ammonia, serum glucose, blood gases, serum lactate, and plasma amino acids (frequency according to patient's clinical state and physician's expertise).
- There is no evidence to date that use of a special diet and/or cofactor (zinc) treatment during periods of wellness prevents metabolic decompensations.

Surveillance

Follow up during infancy and early childhood with a metabolic disease specialist every three to six months for physical and neurologic examinations.

- Consider neurodevelopmental testing and measurement of the following: plasma ammonia and amino acids (to check for chronic hyperammonemia and citrulline deficiency as well as general nutritional state); serum lactate and glucose; blood gases; liver parameters; and urine organic acids.
- If asymptomatic and no further episodes, monitoring can be relaxed during childhood but a sick day regime/emergency plan should be provided and followed.

Agents/Circumstances to Avoid

Acetazolamide should be avoided, as it inhibits carbonic anhydrase activity.

If anti-seizure medication is necessary, avoid topiramate based on its action as a carbonic anhydrase inhibitor.

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of all sibs of an affected individual in order to identify those who would benefit from prompt treatment when symptoms appear.

- **Neonatal care for an affected infant diagnosed prenatally.** Delivery in hospital is indicated with monitoring for about three days (including physical examination and monitoring especially of plasma ammonia, serum lactate, serum glucose, and blood gases).
- **Neonatal care for an infant at risk because of a previous affected sib.** Close clinical monitoring for the first week of life by a healthcare professional is indicated; and immediate action if symptoms (of hyperammonemia or hypoglycemia) occur.

Of note, in some families, asymptomatic (older) sibs were found to have biallelic *CA5A* pathogenic variants through family screening [van Karnebeek et al 2014]. This finding suggests a possible "susceptibility period" during childhood after which individuals with biallelic *CA5A* pathogenic variants may no longer be at risk of developing signs of CA-VA deficiency.

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

Pregnancy Management

Avoidance of severe catabolism for a pregnant woman with CA-VA deficiency seems prudent.

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

Carbonic anhydrase VA (CA-VA) deficiency is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are obligate heterozygotes (i.e., presumed to be carriers of one *CA5A* pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *CA5A* 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, the following possibilities should be considered:
  - 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].
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant resulted in homozygosity for the pathogenic variant in the proband.
- 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 a *CA5A* pathogenic variant, each sib of an affected individual has at conception:
  - A 25% chance of inheriting two *CA5A* pathogenic variants and usually being affected;

    Note: In some families, asymptomatic (older) sibs with biallelic *CA5A* pathogenic variants have been identified [Author, unpublished].
  - A 50% chance of inheriting one pathogenic variant and being an asymptomatic carrier;
  - A 25% chance of inheriting neither pathogenic variant being unaffected and not a carrier.
- Clinical status of sibs cannot be used to refine their genetic risk as asymptomatic (older) sibs with biallelic *CA5A* pathogenic variants have been identified.

- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with CA-VA deficiency are obligate heterozygotes (carriers) for a pathogenic variant in *CA5A*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *CA5A* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *CA5A* 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 have or are at risk of having one or two *CA5A* pathogenic variants.

Prenatal Testing and Preimplantation Genetic Testing

Once the *CA5A* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for CA-VA deficiency are possible. Note: The results of prenatal testing cannot be used to predict with certainty whether or not an individual will be affected, as asymptomatic individuals with biallelic *CA5A* pathogenic variants have been identified.

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.

- **Metabolic Support UK**
  United Kingdom
  Phone: 0845 241 2173
  metabolicsupportuk.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. Carbonic Anhydrase VA Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
CA5A	16q24.2	Carbonic anhydrase 5A, mitochondrial	CA5A homepage	CA5A	CA5A

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 Carbonic Anhydrase VA Deficiency (View All in OMIM)

114761	CARBONIC ANHYDRASE VA; CA5A
615751	CARBONIC ANHYDRASE VA DEFICIENCY, HYPERAMMONEMIA DUE TO; CA5AD

Molecular Pathogenesis

Carbonic anhydrase VA (CA-VA) comprises two domains: (1) the alpha carbonic anhydrase domain, which spans from amino acid position 33 to 296; (2) the carbonic anhydrase, alpha-class, conserved site (within the aforementioned domain), which spans from amino acid position 141 to 157. Both domains are important for catalyzing the reversible hydration of carbon dioxide to bicarbonate.

Acute decompensations are consistent with dysfunction of all four enzymes to which CA-VA provides bicarbonate as substrate in mitochondria:

- Carbamoyl phosphate synthetase 1 (CPS1) encoded by *CPS1* (See Urea Cycle Disorders Overview.)
- The three biotin-dependent carboxylases:
  - Propionyl-CoA carboxylase (PCC) encoded by *PCCA* and *PCCB* (See Propionic Acidemia.)
  - 3-methylcrotonyl-CoA carboxylase (3MCC) encoded by *MCCC1* and *MCCC2* (OMIM 210200, OMIM 210210)
  - Pyruvate carboxylase (PC) encoded by *PC* (See Pyruvate Carboxylase Deficiency.)

The authors propose several explanations for the relatively benign clinical course observed in children with carbonic anhydrase VA deficiency:

- The overlapping function of CA-VB may help prevent deleterious sequelae of reduced CA-VA activity [Shah et al 2013];
- Some bicarbonate is produced via the non-enzymatic reaction, even in the absence of carbonic anhydrases; thus, during stable periods, this may be sufficient for the four different bicarbonate-requiring intra-mitochondrial enzymes to function normally.

Mechanism of disease causation. Loss-of-function variants result in reduced protein stability and/or reduced enzymatic activity or absence of carbonic anhydrase VA in the liver.

***CA5A*-specific laboratory technical considerations.** A pseudogene, *CA5AP1*, has sequences homologous to exons 3-7 and introns 3-6 [Nagao et al 1995].

Table 4. Notable *CA5A* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_001739.1 NP_001730.1	c.619-3421_774+502del	p.Asp207_Gln258del	The phenotype was not more severe in persons homozygous for this deletion (resulting in absence of carbonic anhydrase VA in the liver) than the phenotype observed w/other variants [van Karnebeek et al 2014].
	c.721G>A	p.Glu241Lys	Recurrent variant found in majority of affected persons from the Indian subcontinent.

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). See Quick Reference for an explanation of nomenclature.

Chapter Notes

Author Notes

TIDE (www.tidebc.org) and Omics2TreatID (www.treatable-id.org)

Clara van Karnebeek, MD, PhD is a pediatrician and biochemical geneticist who dedicates her research to enhancing early diagnosis and treatment of inborn errors of metabolism to prevent intellectual developmental disabilities.

Johannes Häberle, MD is a neonatologist and metabolic pediatrician who specializes in the diagnosis and treatment of urea cycle defects and related disorders with hyperammonemia.

Acknowledgments

We gratefully acknowledge Casper Shyr, PhD student (University of British Columbia, Vancouver, Canada) for his contributions to the molecular genetics section of this paper.

Revision History

- 26 August 2021 (bp) Comprehensive update posted live
- 2 April 2015 (me) Review posted live
- 8 September 2014 (cvk) Original submission

References

Literature Cited

Diez-Fernandez C, Rüfenacht V, Santra S, Lund AM, Santer R, Lindner M, Tangeraas T, Unsinn C, de Lonlay P, Burlina A, van Karnebeek CD, Häberle J. Defective hepatic bicarbonate production due to carbonic anhydrase VA deficiency leads to early-onset life-threatening metabolic crisis. Genet Med. 2016;18:991–1000. PubMed PMID: 26913920.

Häberle J. Clinical and biochemical aspects of primary and secondary hyperammonemic disorders. Arch Biochem Biophys. 2013;536:101–8. PubMed PMID: 23628343.

Jónsson H, Sulem P, Kehr B, Kristmundsdottir S, Zink F, Hjartarson E, Hardarson MT, Hjorleifsson KE, Eggertsson HP, Gudjonsson SA, Ward LD, Arnadottir GA, Helgason EA, Helgason H, Gylfason A, Jonasdottir A, Jonasdottir A, Rafnar T, Frigge M, Stacey SN, Th Magnusson O, Thorsteinsdottir U, Masson G, Kong A, Halldorsson BV, Helgason A, Gudbjartsson DF, Stefansson K. Parental influence on human

germline de novo mutations in 1,548 trios from Iceland. Nature. 2017;549:519–22. PubMed PMID: 28959963.

Marwaha A, Ibrahim J, Rice T, Hamwi N, Rupar CA, Cresswell D, Prasad C, Schulze A. Two cases of carbonic anhydrase VA deficiency-An ultrarare metabolic decompensation syndrome presenting with hyperammonemia, lactic acidosis, ketonuria, and good clinical outcome. JIMD Rep. 2020;57:9–14. PubMed PMID: 33473334.

Nagao Y, Batanian JR, Clemente MF, Sly WS. Genomic organization of the human gene (CA5) and pseudogene for mitochondrial carbonic anhydrase V and their localization to chromosomes 16q and 16p. Genomics. 1995;28:477–84. PubMed PMID: 7490083.

Olgac A, Kasapkara CS, Kilic M, Keskin EY, Sandal G, Cram DS, Haberle J, Torun D. Carbonic anhydrase VA deficiency: a very rare case of hyperammonemic encephalopathy. J Pediatr Endocrinol Metab. 2020;33:1349–52. PubMed PMID: 32809955.

Shah GN, Rubbelke TS, Hendin J, Nguyen H, Waheed A, Shoemaker JD, Sly WS. Targeted mutagenesis of mitochondrial carbonic anhydrases VA and VB implicates both in ammonia detoxification and glucose metabolism. Proc Natl Acad Sci USA. 2013;110:7423–8. PubMed PMID: 23589845.

Stenson PD, Mort M, Ball EV, Evans K, Hayden M, Heywood S, Hussain M, Phillips AD, Cooper DN. The Human Gene Mutation Database: towards a comprehensive repository of inherited mutation data for medical research, genetic diagnosis and next-generation sequencing studies. Hum Genet. 2017;136:665–77. PubMed PMID: 28349240.

van Karnebeek CDM, Sly WS, Ross CJ, Salvarinova R, Yaplito-Lee J, Santra S, Shyr C, Horvath GA, Eydoux P, Lehman AM, Bernard V, Newlove T, Ukpeh H, Chakrapani A, Preece MA, Ball S, Pitt J, Vallance HD, Coulter-Mackie M, Nguyen H, Zhang L-H, Bhavsar AP, Sinclair G, Waheed A, Wasserman WW, Stockler-Ipsiroglu S. Mitochondrial carbonic anhydrase VA deficiency resulting from CA5A alterations presents with hyperammonemia in early childhood. Am J Hum Genet. 2014;94:453–61. PubMed PMID: 24530203.

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