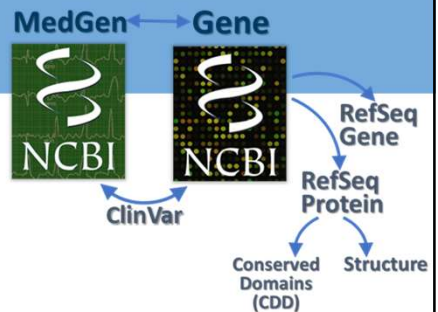


Putting it all together!

USING NCBI RESOURCES TO ASSIST IN UNDERSTANDING, EXPLAINING, DIAGNOSING AND TREATING HUMAN DISEASE

- TRANSPARENT, SUSTAINABLE, RELIABLE, TRUSTED - INFORMATION FOR CLINICAL DECISION SUPPORT

 U.S. National Library of Medicine
National Center for Biotechnology Information



Here's where your cases begin:
A Referral & a Genetic Test Result!

Here's a case guide sheet
to fill out as you go along.

ClinLab Clinical Testing Lab of California
3300 Zanker Rd., Suite 200
San Jose, CA 95128 Phone: 408.261.1212

MyClinicalService **Physician Referral Form**

ALEXIS & NOAH
3300 Zanker Rd., Suite 200
San Jose, CA 95128
Phone: 408.261.1212

Requesting Provider
Name: [Redacted]
Address: [Redacted]
Phone: [Redacted]

Consulting Provider
Name: [Redacted]
Address: [Redacted]
Phone: [Redacted]


Referral Information
Reason for Referral: Evaluation of Segregata Reductase Deficiency
History: [Redacted]

Clinical test results for Dystonia Comprehensive Panel

GENE	RESULTS	EXPLANATION
SPR1 (2q37.2)	Pathogenic Homozygous	This result supports the diagnosis of Segregata reductase deficiency. This result should be interpreted in the context of clinical presentation and results of other laboratory tests (e.g., IRCA, SFVA, BSA, Norgest, etc.). A sequence study with PCR analysis has identified one copy of this recurrent pathogenic mutation. Agg150 (SPR1:487134 in Cytoscape) mutation. ClinVar: NC_000234.11 The Agg150 mutation is an A to G change at nucleotide position 6073 in the SPR1 gene. This results in a change from a stop codon (UAG) to a stop codon (UAG) at position 6073. This mutation is associated with a mild, onset of life.
SPR2 (2q37.2)	Pathogenic Homozygous	This result supports the diagnosis of Segregata reductase deficiency. This result should be interpreted in the context of clinical presentation and results of other laboratory tests (e.g., IRCA, SFVA, BSA, Norgest, etc.). A sequence study with PCR analysis has identified one copy of this recurrent pathogenic mutation. Lys215 (SPR2:487134 in Cytoscape) mutation. ClinVar: NC_000234.11 The Lys215 mutation is an A to T change at nucleotide position 9120 in the SPR2 gene. This results in a change from a stop codon (UAG) to a stop codon (UAG) at position 9120. This mutation is associated with a mild, onset of life.

No genetic variants were detected in:
 ANKRD1 (14q32.31) IRCA (9q31.3) SLC6A1 (14q32.31)
 ATP1A1 (9q34.3) KCTD13 (12p12.3) SLC6A1 (14q32.31)
 C22orf42 (12) PRKD (12p12.3) SLC6A1 (14q32.31)
 HNRD (14q32.3) PRKRA (14q32.3) TRAP1 (9p11.2)
 OXCE1 (14q32.3) PRKRI (14q32.3) TRAP2 (9p11.2)
 OXCE2 (14q32.3) PRKRI (14q32.3) TRAP3 (9p11.2)
 OXCE3 (14q32.3) PRKRI (14q32.3) TRAP4 (9p11.2)

Patient's Name Introduce your patients!



What was the preliminary diagnosis & the rationale?

What did the genetic test find and how does this relate to the preliminary diagnosis?

What is the implicated/affected gene and what is its normal function?

Where in the gene and gene product(s) is the patient's genetic variant located?

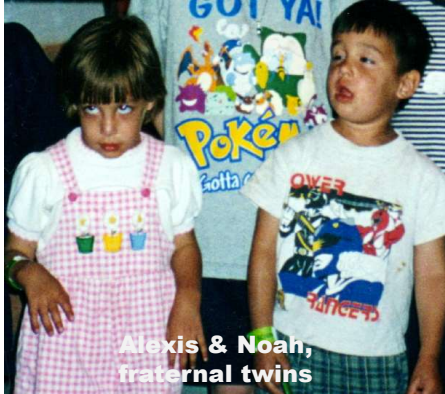
What is the molecular impact of the genetic variant on the gene product?

What do you think might be the functional impact of the variant on the gene product?

 U.S. National Library of Medicine
National Center for Biotechnology Information

NIH CLINICAL CENTER

Twins' diagnosis of Cerebral Palsy, then Segawa Dystonia, then.....



Alexis & Noan, fraternal twins

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3314311/>
<http://dystonia.thebeerys.com/Home.aspx>
<http://dystonia.thebeerys.com/Video.aspx>

PRESENTING SYMPTOMS:

developmental delay, dystonic movements, tremors, muscle hypotonia, unsteady gait, vomiting, drooling, sleep disturbances

STRANGE FINDINGS

conditions deteriorated and were temporal (significantly worse after 11am daily)

CONTINUED ISSUES AFTER

“SUCCESSFUL TREATMENT”

tremors, drooling, sleep disturbances, and eventually unexplained respiratory issues in Alexis



Researching the Referral Wait! What is Sepiapterin Reductase Deficiency?

MyClinicalService		Physician Referral Form	
Patient Information		Patient Information	
ALEXIS & NOAH		[Barcode]	
Requesting Provider		Referral Information	
Jesse Farniss, MD, MCh, Molecular		Authorization No.	
900 2000 0000		Authorization Type:	
900 2000 0000		Reason for Referral: Evaluation of Sepiapterin Reductase Deficiency	
900 2000 0000		Diagnosis: G24.1 – Sepiapterin Reductase Deficiency	
900 2000 0000		Clinical Notes: 12 year old twin boy and girl, initially diagnosed at 24 months with Cerebral Palsy due to an imaging study on the male, then diagnosed at 5 years old with Dopa-responsive Dystonia (Sagawa Disease) and treated fairly successfully with L-Dopa. However, symptoms were still present and at 14 years old, Alexis developed serious respiratory complications. A preliminary diagnosis of Sepiapterin Reductase Deficiency Syndrome was made based on normal levels of Neopterin and very low levels of BH4 and both Serotonin (5HTAA) and Dopamine (HVA) metabolites.	
900 2000 0000		Whole genome sequencing was performed at the request of the family and will be analyzed for pathogenic variants that exist in both twins. The final report will be faxed to the Molecular Science/M1 Training program for evaluation.	
900 2000 0000		Please consult with the family and send a copy of the final report back to this office. Thanks.	
900 2000 0000		Procedures: Variant Interpretation – Molecular Impact Characterization	

Researching the Referral

INFORMATION ABOUT THE PROPOSED DISEASE/DISORDER FROM HUMAN-CURATED SOURCES:

1. To learn more about the preliminary diagnosis, **go to the NCBI website** (<https://www.ncbi.nlm.nih.gov> or “google” NCBI to find the homepage) and search NCBI’s MedGen database with: **sepiapterin reductase deficiency**
WHAT KEY THINGS DO YOU FIND IN THE SUMMARY SECTION? (This is a place for *your* notes.)

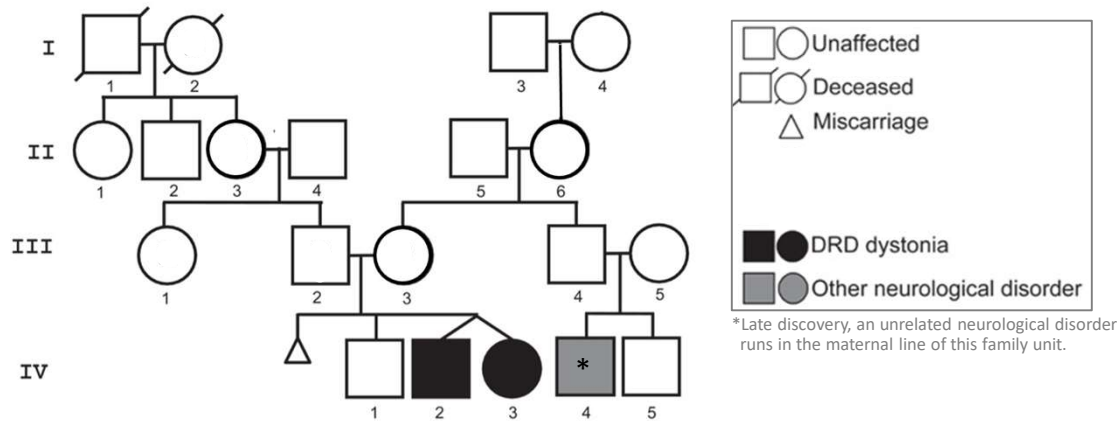
WHAT OTHER DISORDERS COULD HAVE BEEN CONSIDERED AND WHICH GENES ARE ASSOCIATED WITH EACH? (Hint: Check the **GeneReviews>Differential Diagnosis link**.)

WHAT WOULD YOU LOOK FOR IN A LABORATORY TEST AS CONFIRMATION OF THE DIAGNOSIS? (Hint: Check the **GeneReviews>Diagnosis Link** for what it says about CSF neurotransmitters and pterins.)

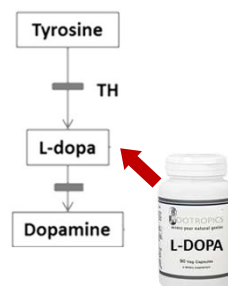
DO THE LAB RESULTS CONFIRM THE REFERRAL’S LISTED DIAGNOSES? **We’ll go over this together next!**

2. To assist you in learning more about this disorder **find links to:**
 - PubMed** – to find some helpful recent publications.
 - ClinicalTrials.gov** – to see if any are currently enrolling participants.
 - Patient Education materials** – to provide as an additional resource for the family.
 - The **NIH Genetic Testing Registry** - where you could find a genetic test to order.

MIGHT THIS BE GENETIC? HERE'S THE FAMILY PEDIGREE



INITIALLY, THEY WERE TREATED WITH L-DOPA & IT SEEMED TO WORK....ISH.
 WHAT DID THE DOCTOR THINK WAS WRONG?
 WHAT OTHER TARGETS SHOULD WE CONSIDER?



MEDGEN



AGGREGATED INFORMATION FOR GENETIC DISORDERS & HEALTH-RELATED PHENOTYPES

<https://www.ncbi.nlm.nih.gov/medgen>


What may be a possible diagnosis?



NCBI
MedGen

MyClinicalService		Physician Referral Form	
Patient Information			
ALEXIS & NOAH			
Requesting Provider			
Jose Ferrera, MD, MyClinicalService		Molecular Sciences/NIH Training	
Consultant Provider			
To be assigned		Molecular Sciences/NIH Training	
Referral Information			
Reason for Referral: Evaluation of Sepiapterin Reductase Deficiency			
Diagnosis: G241 - Sepiapterin Reductase Deficiency			
<p>Clinical Note: 12 year old twin boy and girl, initially diagnosed at 24 months with Cerebral Palsy due to an imaging study on the spine, then diagnosed at 5 years old with Dopa-responsive Dystonia (DRD). Diagnosed and treated fairly successfully with L-Dopa. However, symptoms were still present and at 14 years old, Alexis developed severe respiratory complications. A preliminary diagnosis of Sepiapterin Reductase Deficiency Syndrome was made based on normal levels of Dopamine and very low levels of BH4 and both Serotonin (5HTA) and Dopamine (5HT) metabolites.</p> <p>Whole genome sequencing was performed at the request of the family and will be analyzed for pathogenic variants that exist in both twins. The final report will be sent to the Molecular Sciences/NIH Training program for evaluation.</p> <p>Please consult with the family and send a copy of the final report back to this office. Thanks.</p>			
<p>Procedure: Variant Interpretation - Molecular Inquest Characterization</p> <p>Test Name: 3</p> <p>Test Code: V (VADP)</p> <p>Reference Interval: 00/00/2018</p> <p>Note: Patient must arrive 30 minutes early, with a picture ID, insurance card and have a copy of this referral. If the referred patient is a minor and expense other than the child's parent is covering the bill for the appointment, a letter of consent by the parent is needed. Please bring a list of medications the patient is taking with you to this appointment (include over the counter).</p> <p>Please send the final report by Fax to: (202) 555-1232</p>			
<p>Signature: </p> <p>Ferrera, Jose, MD on 08/20/2018 at 8:26 AM EDT</p>			

What is the affected gene?



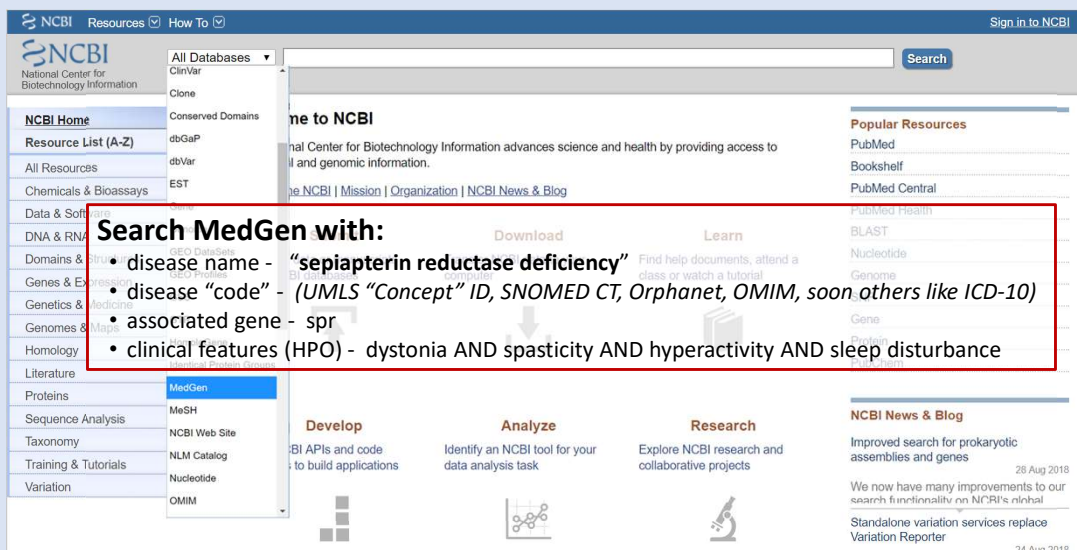
NCBI
Gene

validate
Genetic Test Result

ACTGATGGTATGGGCCAAGAGATATATCT
CAGGTACGGCTGTCACTACTGACCTCAC
CAGGGTGGTAAAGGTTGGGGAGAGC
CCATGTCGATGAAAGAGAGAGT
GCAGGTTGGTAAAGGTTAAACAGGTT
GGCACTGACTCTCTGGCTATTGGTCAT

clinvar

Let's look it up! <https://www.ncbi.nlm.nih.gov>



Search MedGen with:

- disease name - "sepiapterin reductase deficiency"
- disease "code" - (UMLS "Concept" ID, SNOMED CT, Orphanet, OMIM, soon others like ICD-10)
- associated gene - spr
- clinical features (HPO) - dystonia AND spasticity AND hyperactivity AND sleep disturbance

Okay, let's get into this!

Consumer resources

- Genetic Alliance
- Genetics Home Reference
- Genetics Home Reference
- MalaCards
- MedlinePlus
- NCATS Office of Rare Diseases Research (GARD)

Materials for your patients!

Find a genetic test to order

Best source of detailed information with direct links for help!

Is there a clinical trial available?

A tool to help you find PubMed articles.

Direct links to PubMed!

NIH U.S. National Library of Medicine
National Center for Biotechnology Information

NCBI WORKSHOP

MedGen (Medical Genetics Disorders): Sepiapterin Reductase Deficiency

GeneReviews

NIH U.S. National Library of Medicine
National Center for Biotechnology Information

NCBI WORKSHOP

MedGen (Medical Genetics Disorders): Sepsiapterin Reductase Deficiency

NCBI Resources How To Sign In to NCBI

MedGen MedGen Dystonia AND Spasticity AND Sleep disturbance AND Hyperactivity Search

Full Report + Send to +

Sepsiapterin reductase deficiency
MedGen ID: 120642 • Concept ID: C0269489 • Disease or Syndrome

Synonyms: Dopa-Responsive Dystonia Due to Sepsiapterin Reductase Deficiency; SPR deficiency
Modes of inheritance: Autosomal recessive inheritance (HPO, OMIM, Orphanet)
Autosomal dominant inheritance (HPO)
SNOMED CT: Sepsiapterin reductase deficiency (45116002); 7,8-Dihydrobiopterin synthetase deficiency (45116002); Biopterin deficiency (45116002)

Gene (location): SPR (p13.2)
OMIM#: 612716
Orphanet: ORPHA10594

Disease characteristics

Excerpted from the **GeneReviews**: Sepsiapterin Reductase Deficiency
The phenotypic spectrum of sepsiapterin reductase deficiency (SPRD), which ranges from significant motor and cognitive deficits to only minimal findings, has not been completely elucidated. Clinical features in the majority of affected individuals include motor and speech delay, axial hypotonia, dystonia, weakness, and oculogyric crises, symptoms show diurnal fluctuation and sleep benefit. Other common features include parkinsonian signs (tremor, bradykinesia, masked facies, rigidity), limb hypertonia, hyperreflexia, intellectual disability, psychiatric and/or behavioral abnormalities, autistic features, and sleep disturbances in infancy.

Characteristic CSF abnormalities of neurotransmitters and pterins include:

- Decreased levels of homovanillic acid (HVA) and 5-hydroxyindolacetic acid (5-HIAA);
- Normal to slightly increased levels of neopterin;
- Increased levels of total biopterin, dihydrobiopterin (BH2), and sepsiapterin [Bonafé et al 2001b, Friedman et al 2012, Bonafé 2006].

Note: (1) CSF should be collected using standardized protocols and analyzed by a laboratory with appropriate age-related reference ranges [Hyland et al 1993, Bräutigam et al 2002]. (2) Normal values vary by lab and by age.

From OMIM
SPRD deficiency results in neurologic deterioration due to severe dopamine and serotonin deficiencies in the central nervous system caused by a

Table of contents

- Disease characteristics
- Additional descriptions
- Clinical features
- The following clinical feature is unrelated to Sepsiapterin reductase deficiency
- Term Hierarchy
- Recent clinical studies

Genetic Testing Registry

- Analyte (1)
- Delete/duplication analysis (9)
- Linkage analysis (1)
- Sequence analysis of the entire coding region (31)
- Targeted variant analysis (1)
- See all (32)

Clinical resources

- OMIM
- Orphanet
- ClinicalTrials.gov

Molecular resources

- OMIM
- View SPR variations in ClinVar
- RefSeqGene
- Cornell Institute for Medical Research

DIAGNOSTIC LABORATORY TESTS

WHAT WOULD YOU LOOK FOR IN A LABORATORY TEST AS CONFIRMATION OF THE DIAGNOSIS?
(Hint: Check the **GeneReviews**>**Diagnosis** section for what it says about CSF neurotransmitters and pterins.)



“.....Misdiagnoses of cerebral palsy (CP) are common. Cerebrospinal fluid findings are distinctive. Diagnosis is confirmed by mutation analysis”

Friedman, et al, “Sepsiapterin reductase deficiency: a treatable mimic of cerebral palsy.”
Ann Neurol. 2012 Apr;71(4):520-30. PMID: 22522443

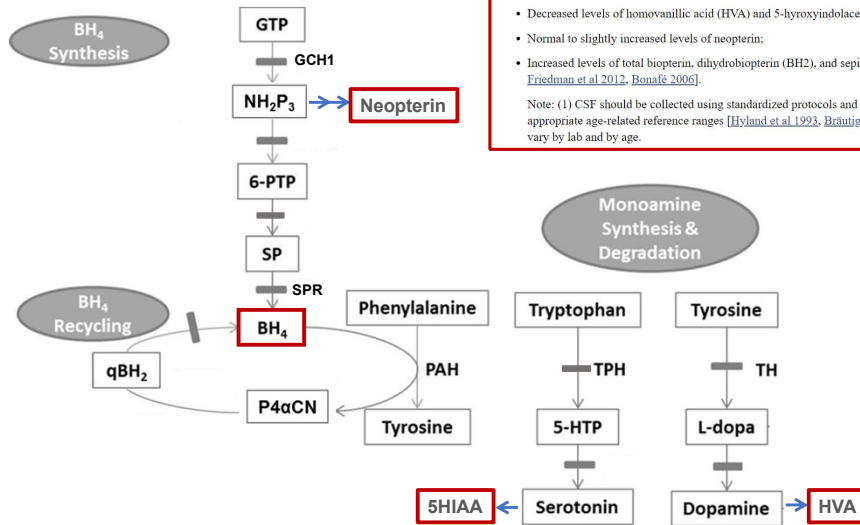
Characteristic CSF abnormalities of neurotransmitters and pterins include:

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- Increased levels of total biopterin, dihydrobiopterin (BH2), and sepsiapterin [Bonafé et al 2001b, Friedman et al 2012, Bonafé 2006].

Note: (1) CSF should be collected using standardized protocols and analyzed by a laboratory with appropriate age-related reference ranges [Hyland et al 1993, Bräutigam et al 2002]. (2) Normal values vary by lab and by age.

How do these recommendations relate to a biological pathway related to the L-Dopa (which seemed to work for a while)?

BASED ON BIOLOGY, WHAT ANALYTES COULD HAVE BEEN MEASURED?



Characteristic CSF abnormalities of neurotransmitters and pterins include:

- Decreased levels of homovanillic acid (HVA) and 5-hydroxyindolacetic acid (5-HIAA);
- Normal to slightly increased levels of neopterin;
- Increased levels of total biopterin, dihydrobiopterin (BH2), and sepiapterin [Bonafé et al 2001b, Friedman et al 2012, Bonafé 2006].

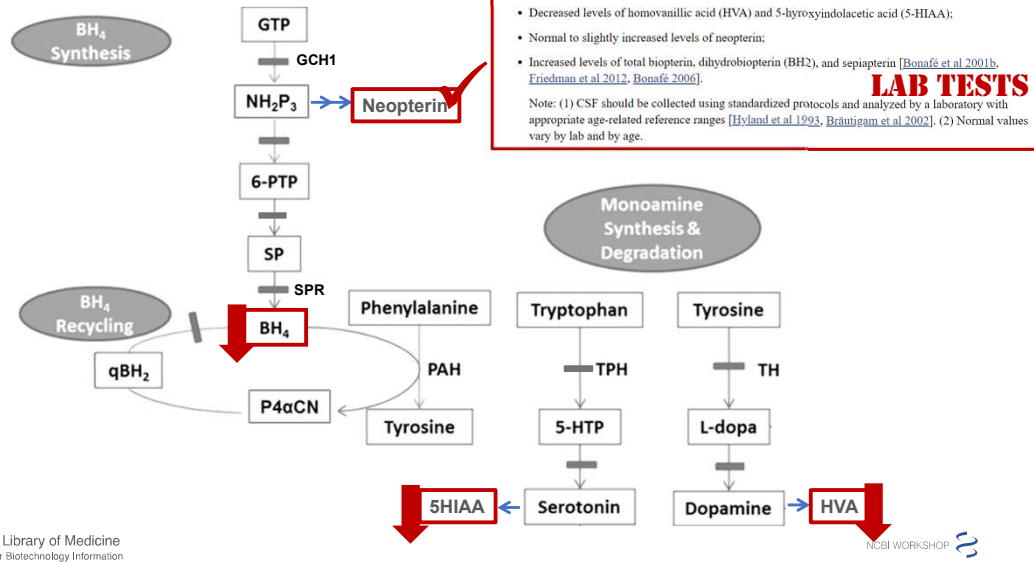
LAB TESTS

Note: (1) CSF should be collected using standardized protocols and analyzed by a laboratory with appropriate age-related reference ranges [Hyland et al 1993, Brittigam et al 2002]. (2) Normal values vary by lab and by age.

Peripheral Blood TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL	RESULT	FLAG	UNITS	REFERENCE INTERVAL	LAB
Alexis - 6 y.o. Female					Noah - 6 m.o. Male				
CBC, Platelet Ct, and Diff									
Hematocrit	30.6			30.9 - 37.0	34.8		%	30.9 - 37.0	07
Hemoglobin	10.1			10.3 - 12.4	11.7		g/dL	10.3 - 12.4	07
Red Blood Cell Count	4.70			4.10 - 5.00	4.85		x10E6/uL	4.10 - 5.00	07
White Blood Cell Count	14.3			6.2 - 14.5	12.2		x10E3/uL	6.2 - 14.5	07
RDW	nd			N/A	nd		%	N/A	07
MCV	71.2			70.5 - 81.2	73.7		fL	70.5 - 81.2	07
MCH	14.5			23.2 - 27.5	26.2		pg	23.2 - 27.5	07
MCHC	32.2			31.9 - 35.0	34.1		g/dL	31.9 - 35.0	07
Imm. Granulocytes (Absolute)	4.9			1.6 - 8.3	7.2		x10E3/uL	1.6 - 8.3	07
Granulocytes (Percent)	29.4			21.3 - 66.7	45.3		%	21.3 - 66.7	07
Eosinophils (Absolute)	nd			NA	nd		x10E3/uL	NA	07
Eosinophils (Percent)	nd			0.0 - 3.3	nd		%	0.0 - 3.3	07
Basophil (Absolute)	nd			NA	nd		x10E3/uL	NA	07
Basophil (Percent)	nd			0 - 2	nd		%	0 - 2	07
Monocytes (Absolute)	nd			N/A	nd		x10E3/uL	N/A	07
Monocytes (Percent)	nd			5 - 11	nd		%	5 - 11	07
Lymphocytes (Absolute)	5.8			1.9 - 6.8	4.7		x10E3/uL	1.9 - 6.8	07
Lymphocytes (Percent)	61			20 - 64	52		%	20 - 64	07
Platelets (Absolute)	276			219 - 452	308		x10E3/uL	219 - 452	07

CSF TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL	RESULT	FLAG	UNITS	REFERENCE INTERVAL	LAB
Alexis - 6 y.o. Female					Noah - 6 m.o. Male				
Selected Pterin/Neuro Basic									
Neopterin	13		nmol/L	7-40	38		nmol/L	7-40	07
Tetrahydrobiopterin (BH4)	0.8	Very low	nmol/L	9-40	1.2	Very low	nmol/L	9-40	07
5HIAA (Serotonin metabolite)	6	Very low	nmol/L	88-278	8	Very low	nmol/L	88-278	07
HVA (Dopamine metabolite)	28	Very low	nmol/L	200-800	31	Very low	nmol/L	200-800	07

MAPPING THE LAB TEST RESULTS TO THE BIOLOGY



MedGen (Medical Genetics Disorders): Sepiapterin Reductase Deficiency

MedGen: Dystonia AND Spasticity AND Sleep disturbance AND Hyperactivity

Sepiapterin reductase deficiency
MedGen UID: 120642 • Concept ID: C0268468 • Disease or Syndrome

Synonyms: Dopa-Responsive Dystonia Due to Sepiapterin Reductase Deficiency; SPR deficiency

Modes of inheritance: Autosomal recessive inheritance (HPO, OMIM, Orphanet)
Autosomal dominant inheritance (HPO)

SNOMED CT: Sepiapterin reductase deficiency (45116002); 7,8-Dihydrobiopterin synthetase deficiency (45116002); Biopterin deficiency (45116002)

Gene (location): SPR (9p13.2)
OMIM: 612716
Orphanet: ORP#

Establishing the Diagnosis
The diagnosis of sepiapterin reductase deficiency is established in a **probable** by detection of **pathogenic variants in SPR on molecular genetic testing** (see Table 1) or characteristic abnormalities of CSF neurotransmitters and pterins.

Disease characteristics
The phenotypic spectrum of sepiapterin reductase deficiency is highly variable. The clinical features include dystonia, weakness, and ocular tremor, bradykinesia, masked facies, and abnormal postural reflexes in infancy. These episodes involve abnormal postural reflexes in infancy, especially of the head and neck, motor skills such as sitting and time. People with sepiapterin reductase deficiency may also have intellectual disability, seizures, and sleep disturbance.

Additional description
From NCI Thesaurus: Sepiapterin reductase deficiency is a rare genetic disorder characterized by dystonia (ataxia), and involuntary jerking of the head and neck. These episodes involve abnormal postural reflexes in infancy, especially of the head and neck, motor skills such as sitting and time. People with sepiapterin reductase deficiency may also have intellectual disability, seizures, and sleep disturbance.

From OMIM: SPR deficiency results in neurodegeneration and pterinuria.

Molecular genetic testing approaches may include single-gene testing and use of a multigene panel.

- Single-gene testing:** Sequence analysis is performed first, followed by consideration of gene-targeted deletion/duplication analysis if only one or no pathogenic variants is found in an individual with characteristic clinical findings and/or abnormalities of CSF metabolites. Note: In rare cases SPR deletions or duplications requiring gene-targeted deletion/duplication analysis have been reported.
- A multigene panel:** A multigene panel that includes SPR and other genes of interest (see Differential Diagnosis) may also be considered. Note: (1) The genes included in the panel and the diagnostic accuracy 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.

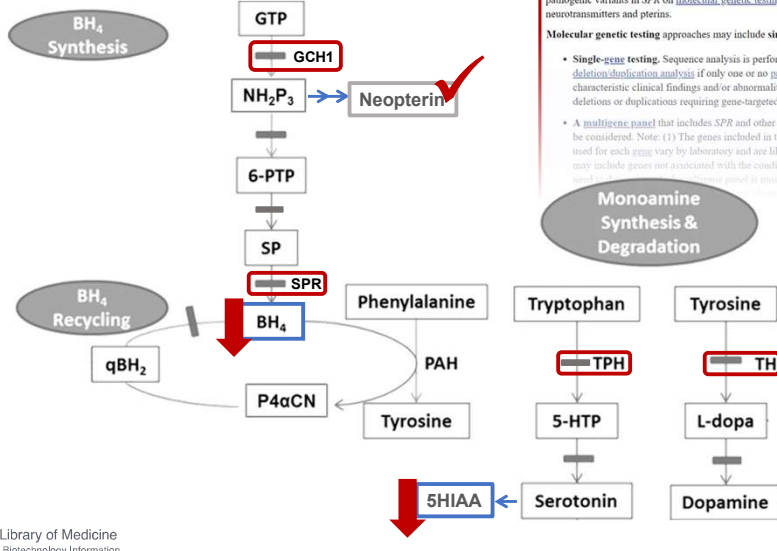
For an introduction to multigene panels click [here](#). More detailed information for clinicians ordering genetic tests can be found [here](#).

Genetic Testing Registry
Analyze (1)
Deletion/duplication analysis (9)
Linkage analysis (1)
Sequence analysis of the entire coding region (31)
Targeted variant analysis (1)

Clinical resources
Orphanet
ClinicalTrials.gov

Molecular resources
OMIM
View SPR variations in ClinVar
RefSeqGene
Coriell Institute for Medical Research

BASED ON BIOLOGY, WHICH GENES COULD BE ASSESSED?



Establishing the Diagnosis
 The diagnosis of sepiapterin reductase deficiency is established in a proband by detection of homozygous pathogenic variants in SPR on molecular genetic testing (see Table 1) or characteristic abnormalities of CSF neurotransmitters and pterins.

GENETIC TEST

Molecular genetic testing approaches may include single-gene testing and use of a multigene panel.

- Single-gene testing. Sequence analysis is performed first, followed by consideration of gene-targeted deletion/duplication analysis if only one or no pathogenic variant is found in an individual with characteristic clinical findings and/or abnormalities of CSF metabolites. Note: To date no SPR deletions or duplications requiring gene-targeted deletion/duplication analysis have been reported.
- A multigene panel that includes SPR and other genes of interest (see Differential Diagnosis) may also 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 GeneReviews; thus, clinicians may discuss options to more likely to identify the genetic cause of the condition.

MedGen (Medical Genetics Disorders): Sepiapterin Reductase Deficiency

The screenshot shows the MedGen entry for "Dopa-responsive dystonia due to sepiapterin reductase deficiency (DRD)". Key information includes:

- Synonyms:** DYT-SPR, Sepiapterin reductase deficiency, SPR deficiency
- SNOMED CT:** Sepiapterin reductase deficiency (45116002); 7,8-Dihydrobiopterin synthetase deficiency (45116002); Sepiapterin deficiency (45116002)
- Genes (location):** SPR (2p13.2)
- OMIM:** 612716
- Orphanet:** CRPHA70294
- Genetic Testing Registry:** A red box highlights the "Genetic Testing Registry" link, with a red arrow pointing to "See all (63)".

Genetic Testing Registry (GTR): Tests with SPR Deficiency listed as Condition

The screenshot shows the GTR search results for "SPR Deficiency". The table lists various tests and their details:

Test name and lab	Conditions	Genes, analytes, and microbes	Methods
Invitae Cerebral Palsy Spectrum Disorders Panel	413	255	Deletion/duplication analysis Sequence analysis of the entire coding region
Invitae Mendelian Disorders with Psychiatric Symptoms Panel	85	88	Deletion/duplication analysis Sequence analysis of the entire coding region
Dopamine Metabolism Deficiency NGS Panel	19	15	Deletion/duplication analysis Sequence analysis of the entire coding region
Early-Onset Ataxia NGS Panel	507	133	Deletion/duplication analysis Sequence analysis of the entire coding region
Dopa-Responsive Dystonia NGS Panel	4	3	Deletion/duplication analysis Sequence analysis of the entire coding region
Hyperphenylalaninemia NGS Panel	13	8	Deletion/duplication analysis Sequence analysis of the entire coding region
Sepiapterin Reductase Deficiency (SPR Single Gene Test)	1	1	Deletion/duplication analysis Sequence analysis of the entire coding region
Neurotransmitter Metabolism Deficiency NGS Panel	85	101	Deletion/duplication analysis Sequence analysis of the entire coding region
Ataxia NGS Panel	535	150	Deletion/duplication analysis Sequence analysis of the entire coding region

Red boxes and arrows highlight the "Genetic Testing Registry" link in the MedGen screenshot and the "See all (63)" link in the GTR screenshot.

Understanding and Validating the Genetic Test Results

INFORMATION ABOUT THESE VARIANTS FROM HUMAN-CURATED SOURCES:

3. **WHAT ARE THE SPECIFIC GENE AND VARIATIONS IDENTIFIED IN THE TWINS?**
(Read the test results, sometimes it is really helpful!)

WHAT DOES THE GENETIC TEST RESULT SAY ABOUT THEIR DIAGNOSES?

4. To validate what is asserted by this clinical testing laboratory, **search NCBI's ClinVar database with:**
SPR Arg150Gly OR SPR Lys251Ter

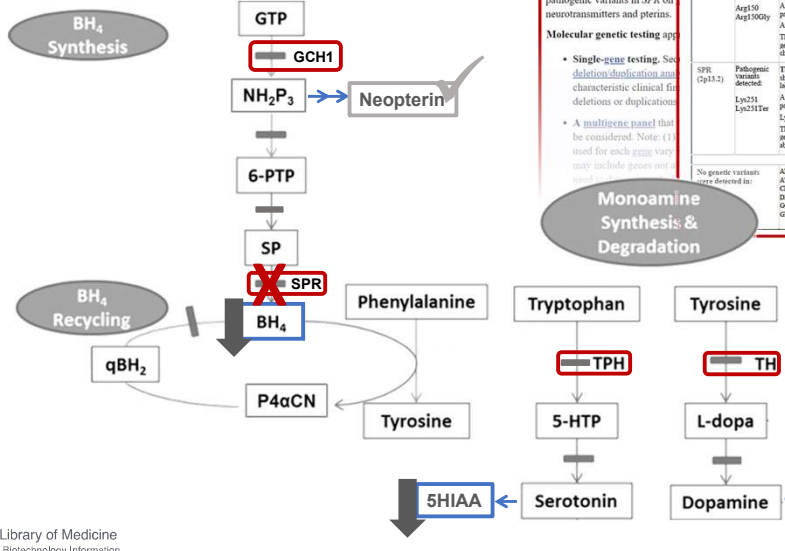
WHAT DOES CLINVAR SAY IN THE "INTERPRETATION" FIELD ABOUT EACH GENE VARIATION?

Scroll down to the "Submitted interpretations and evidence" section and look at what the various laboratories assert about the pathogenicity of each variation.

WHAT DO YOU CONCLUDE ABOUT THE VALIDITY OF THE GENETIC TEST RESULTS' CALLS WITH REGARD TO PATHOGENICITY FOR EACH VARIANT?

5. In preparation for the next step, **find and write down the HGVS formatted information for each variant.** This will help to find the location of each of the variants in the gene (NG_ g.) & protein (NP_ p.).

WHICH GENE WAS IMPLICATED IN THIS CASE?



Establishing the Diagnosis
The diagnosis of sepiapterin reductase deficiency is based on the detection of pathogenic variants in *SPR* on neurotransmitters and pterins.

Molecular genetic testing approach

- **Single-gene testing.** See **deletion/duplication and characteristic clinical findings or deletions or duplications.**
- **A multigene panel that is considered.** Note: (1) used for each gene vary may include genes not used for each gene.

GENE	RESULTS	EXPLANATION
<i>SPR</i> (q21.2)	Pathogenic variant detected: Arg150 Arg150Gly	This result supports the diagnosis of Sepiapterin reductase deficiency. This result should be interpreted in the context of clinical presentation and results of other laboratory tests (e.g., SH2AA, SHVA, BH4, Neopterin, etc.). A sequencing study with PCR validation has identified one copy of this reported pathogenic variant: Arg150Gly (c.607A>G or p.Arg150Gly) variation. ClinVar: NC_008234.1 The Arg150Gly variation is an A to G change at nucleotide position 607 in the <i>SPR</i> gene. This encodes an alternate residue at position 150 from a leucine, positively-charged polar amino acid to one with a small, neutral side chain.
<i>SPR</i> (q21.2)	Pathogenic variant detected: Lys211 Lys211Ter	This result supports the diagnosis of Sepiapterin reductase deficiency. This result should be interpreted in the context of clinical presentation and results of other laboratory tests (e.g., SH2AA, SHVA, BH4, Neopterin, etc.). A sequencing study with PCR validation has identified one copy of this reported pathogenic variant: Lys211Ter (c.932A>T or p.Lys211Ter) variation. ClinVar: NC_008234.1 The Lys211Ter variation is an A to T change at nucleotide position 932 in the <i>SPR</i> gene. This forms a premature stop codon at amino acid position 251 resulting in an abnormally short or truncated protein.

Monoamine Synthesis & Degradation

CLINVAR REGISTRY OF HEALTH-RELATED ASSERTIONS FOR HUMAN GENETIC VARIATIONS <https://www.ncbi.nlm.nih.gov/clinvar>

What may be a possible diagnosis?

NCBI MedGen

Accession	Variant	Gene	Phenotype	Frequency	Source	Review Status	Approved	Approved Date	Approved By
SCV000000000

What is the affected gene?

NCBI Gene

Validate Genetic Test Result

ClinVar


ACTGATGGTATGGGGCCAAGAGATATCT
CAGGTACGGCTGTCATCACT CACCTCAC
CAGGGTCCCAAAA GT AGGCCAGAGC
CCATGTCGAGAGAGAGT
GCAGGTTGTTAAGAGG TAAACACAGGT
GGCACTGACTCTCTGCCTATTGGCTCAT

CLINVAR

REGISTRY OF HEALTH-RELATED ASSERTIONS FOR HUMAN GENETIC VARIATIONS

<https://www.ncbi.nlm.nih.gov/clinvar>

What may be a possible "HGVS"?



TEST RESULTS (nomenclature)

SPR p.Arg150
p.Arg150Gly
p.Lys251Ter
OR
SPR g.6075A
g.6075A>G

HGVS (Human Genome Variation Syntax)
Where is the detected variation?

Gene Symbol
DNA: NC_ or NG_ g. position letter>variant letter
RNA: NM_ c. position letter>variant letter
Protein: NP_ p. position letter>variant letter

Official HGVS (if you follow all the rules):
NC_000002.12:g.72888457A>G
NG_008234.1(SPR):g.6075A>G
NM_003124.5(SPR):c.448A>G
NP_003115.1(SPR):p.Arg150Gly

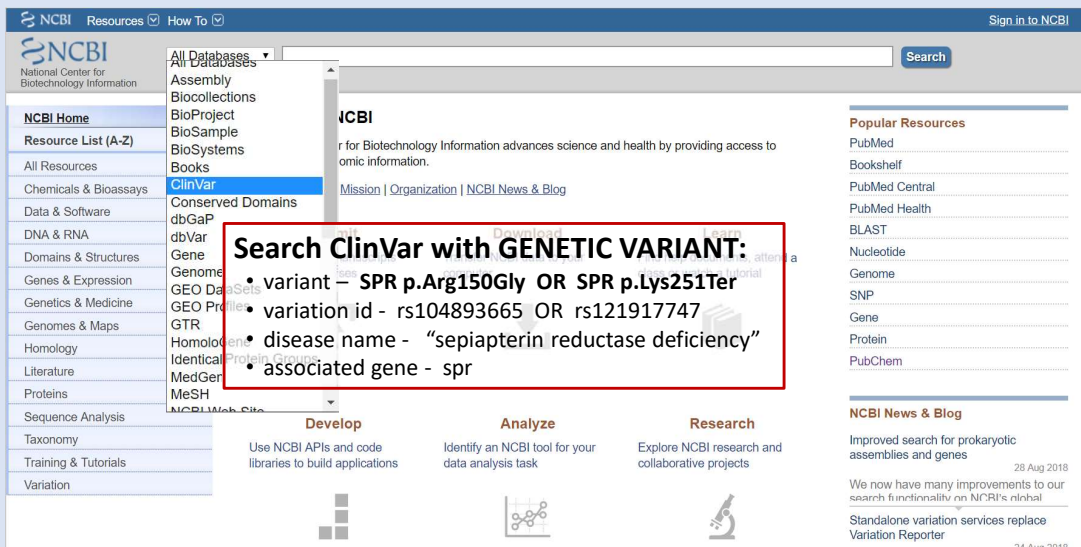
Validate Genetic Test Result

ACTGATGGTATGGGGCCAGAGATATATCT
CAGGTACGGCTGTCACTACTGACCTCAC
CAGGGTCTCTTAAAGTGGGGCAGAGC
CCATGTCCTTAAAGTGGGGCAGAGT
GCAGGTTCTTAAAGTAAACACAGGT
GGCACTGACTCTCTGCTATTGGTCTAT

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NCBI WORKSHOP

Let's look it up! <https://www.ncbi.nlm.nih.gov>



Search ClinVar with GENETIC VARIANT:

- variant - SPR p.Arg150Gly OR SPR p.Lys251Ter
- variation id - rs104893665 OR rs121917747
- disease name - "sepiapterin reductase deficiency"
- associated gene - spr

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ClinVar Genomic variation as it relates to human health

Advanced search Search ClinVar

About Access Submit Stats FTP Help Was this helpful?

NM_003124.5(SPR):c.448A>G (p.Arg150Gly) Quick view of assertion

Follow Print Download Cite this record

Interpretation: Pathogenic

Review status: 17 criteria provided, multiple submitters, no conflicts

Submitters: 6 (Most recent: Jul 6, 2020)

Last evaluated: Nov 15, 2019

Accession: VCV000012941.7

Variation ID: 12941

Description: single nucleotide variant

Variant details Variant info

Allele ID: 27980

Variant type: single nucleotide variant

Variant length: 1 bp

Cytogenetic location: 2p13.2

Genomic location: 2:72888457 (GRCh38) GRCh37 GRCh38 UCSC

HGVs: Official HGVS terms

Nucleotide	Protein	Molecular consequence
NC_000002.11:g.73115586A>G		
NC_000002.12:g.72888457A>G		
NM_003124.5:c.448A>G	NP_003115.1:p.Arg150Gly	missense

Aggregate interpretations per condition

Interpreted condition	Interpretation	Number of submissions	Review status	Last evaluated	Variation/condition record
Dopa-responsive dystonia due to sepiapterin reductase deficiency	Pathogenic	3	criteria provided, multiple submitters, no conflicts	Nov 15, 2019	RCV000013804.20
not provided	Pathogenic	2	criteria provided, multiple submitters, no conflicts	Apr 1, 2019	RCV000498846.2
Dystonia	Pathogenic	1	criteria provided, single submitter	May 31, 2019	RCV000803472.2

Submitted interpretations and evidence Assertions from each lab

Interpretation (Last evaluated)	Review status (Assertion criteria)	Condition (Inheritance)	Submitter	Supporting information (See all)
Pathogenic (Oct 31, 2018)	criteria provided, single submitter (ACMG Guidelines, 2015) Method: clinical testing	Dopa-responsive dystonia due to sepiapterin reductase deficiency Allele origin: unknown	Fulgent Genetics Fulgent Genetics	Evidence details Publications PubMed ID: 30103332 DOI: 10.1038/gm-2018-30
Pathogenic (Jun 19, 2017)	criteria provided, single submitter (BioClini Variant Classification 00020183) Method: clinical testing	Not Provided Allele origin: germline	GeneDx	Evidence details Publications PubMed ID: 292058954.2 Submitted: (Mar 28, 2018)
Pathogenic (Apr 01, 2018)	criteria provided, single submitter (BioClini Variant Classification 00020183) Method: clinical testing	not provided Allele origin: germline	CeGaT Praxis fuer Humangenetik, Tuebingen	Evidence details Publications PubMed ID: 301004745.3 Submitted: (Jul 16, 2018)
Pathogenic (May 31, 2018)	criteria provided, single submitter (BioClini Variant Classification 00020183) Method: clinical testing	Dystonia Allele origin: unknown	Invitae	Evidence details Publications PubMed ID: 3042382.2 Submitted: (Feb 06, 2020)

Citations for this variant Helpful PubMed References

Title	Journal	Year	Link
Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology;	Genetics in medicine: official journal of the American College of Medical Genetics	2015	PMID: 25741868
Very early pattern of movement disorders in sepiapterin reductase deficiency;	Neurology	2019	PMID: 24212389
Levodopa response reveals sepiapterin reductase deficiency in a female heterozygote with adrenoleukodystrophy;	JIMD reports	2012	PMID: 23490877
Sepiapterin reductase deficiency: a treatable mimic of cerebral palsy;	Annals of neurology	2012	PMID: 22520449
Whole-genome sequencing for optimized patient management;	Science translational medicine	2011	PMID: 21677200
Genotype-phenotype correlations in sepiapterin reductase	Neurogenetics	2011	PMID: 21491397

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NCBI WORKSHOP

REVIEW OF CLINICAL INFORMATION

What we've found so far:

- Searched **MedGen** with Alexis & Noah's symptoms: *We've identified a preliminary diagnosis for the twins of **Sepiapterin Reductase Deficiency***, as well as specific information about what *clinical lab (GeneReviews)* and *genetic tests (GTR)* can be ordered to validate the proposed diagnosis.
 - **Found sources for Clinical Decision Support Materials:** GeneReviews reports, PubMed articles & Clinical Trials
- The results of the *lab and genetic tests support the diagnosis and provide clues to finding an effective therapy*.
 - **Identified sources for Patient Education Materials:** Links to Medline Plus, Genetics Home Reference, GeneReviews, & more...

Discovered two *specific heritable pathogenic SPR genetic variants (RefSeqGene NG_002234.1)*:

SPR:g.6075A>G = p.R150G (a.k.a. p.Arg150Gly) & SPR:g.9120T>A = p.K251X (a.k.a. p.Lys251Ter)

GENE

AGGREGATED INFORMATION OF EVERYTHING WE KNOW ABOUT AN ORGANISM'S GENE

<https://www.ncbi.nlm.nih.gov/gene>

What may be a possible diagnosis?

What is the affected gene?



TEST RESULTS & Clinical Features

Sepiapterin Reductase (SPR)

The Twins' clinical features:

- developmental delay
- sleep disturbances
- dystonic movements, tremors, unsteady gait
- muscle hypotonia
- drooling, vomiting, digestive issues
- anger management issues



Validate Genetic Test Result

ACTGATGGTATGGGGCCAGAGATATATCT
CAGGTACGGCTGTCTACTCTGACCTCAC
CAGGGTTCCTTTAAAAGTACGGCAGAGC
CCATGTCCTTTAAAAGTACGGCAGAGC
GCAGGTCCTTTAAAAGTACGGCAGAGC
GGACTGACTCTCTCTGGCTATTGGTCTAT

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NCBI WORKSHOP

MedGen or ClinVar → Gene

MedGen

Full Report

Dopa-responsive dystonia due to sepiapterin reductase deficiency (SRD)
MedGen UID: 120642 • Concept ID: C0206498 • Disease or Syndrome

Synonyms: DYT-SPR; Sepiapterin reductase deficiency; SPR deficiency

SNOMED CT: Sepiapterin reductase deficiency (45116002); 7,8-Dihydrobiopterin synthase deficiency (45116002); Biopterin deficiency (45116002)

Modes of inheritance: Autosomal recessive inheritance (HPO, OMIM)
Autosomal dominant inheritance (HPO, OMIM)

Gene (location): SPR (2p13.2)

Monarch Initiative: MONDO:0012994

OMIM®: 612716

Excerpted from the **GeneReview**: **Sepiapterin Reductase Deficiency**
The phenotypic spectrum of sepiapterin reductase deficiency (SRD), which findings, has not been completely elucidated. Clinical features in the major *Alstonia* weakness and excitotoxic crises, symptoms show flumazenil

SPR sepiapterin reductase (7,8-dihydrobiopterin:NADP+ oxidoreductase) [Homo sapiens (human)]
Gene ID: 6697, updated on 4-Sep-2016

Summary

Official Symbol: SPR (provided by HUGO)

Official Full Name: sepiapterin reductase (7,8-dihydrobiopterin:NADP+ oxidoreductase) (provided by HUGO)

Primary source: HGNC:HGNC:11257

See related: Ensembl:ENSG00000116096; HPRD:01632; MIM:192125; Vega:OTTHUM000000129777

Gene type: protein coding

RefSeq status: REVIEWED

Organism: *Homo sapiens*

Lineage: Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorhina; Catarrhini; Hominoidea; Homo

Also known as: SDR35C1

Summary: This gene encodes an aldo-keto reductase that catalyzes the NADPH-dependent reduction of pteridine derivatives and is important in the biosynthesis of tetrahydrobiopterin (BH4). Mutations in this gene result in DOPA-responsive dystonia due to sepiapterin reductase deficiency. A pseudogene has been identified on chromosome 1. (provided by RefSeq, Jul 2008)

Orthologs: mouse [alt](#)

ClinVar Genomic variation as it relates to human health

Advanced search

Search ClinVar

Was this helpful? [Feedback](#)

Follow [Print](#) [Download](#)

NM_003124.5(SPR):c.448A>G (p.Arg150Gly) [Cite this record](#)

Interpretation: Pathogenic

Review status: ★★☆☆ criteria provided, multiple submitters, no conflicts

Submissions: 6 (Most recent: Jul 6, 2020)

Last evaluated: Nov 15, 2019

Accession: VCV00012941.7

Variation ID: 12941

Description: single nucleotide variant

Variant details

Conditions	OMIM		ClinGen Gene Dosage Sensitivity Curation		Variation viewer	Related variants	
	HI score	TS score	HI score	TS score		Within gene	All
Gene(s)	SPR		-	-	GRCh38 GRCh37	89	100

Gene

Search

Full Report

Hide sidebar >>

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- Summary
- Genomic context
- Genomic regions, transcripts, and products
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- Phenotypes
- Variation
- Pathways from BioSystems
- Interactions
- General gene information
- Markers, Repeat pseudogenes, Homology, Gene Ontology
- General protein information
- NCBI Reference Sequences (RefSeq)
- Related sequences

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NCBI WORKSHOP

Molecular Biology Research – Normal gene function and expression

INFORMATION ABOUT THIS GENE FROM HUMAN-CURATED SOURCES:

6. On the MedGen or ClinVar record, **click the link for the gene** identified as having variants in the twins.
WHAT DOES THIS GENE NORMALLY DO? *(summary from NCBI's RefSeq Group Curators)*
7. From the Gene record, **scroll down to the “General gene information”>“Gene Ontology” section** to learn more about the protein produced from this gene. This section displays terms for where this gene product is likely to be found within a cell (Component), what processes it is often involved in (Process), and what it does (Function). *(terms assigned by the Gene Ontology Consortium's Curators)*

WHAT TYPE(S) OF PROCESS(ES) IS/ARE THIS PROTEIN NORMALLY INVOLVED WITH?
DOES THIS MAKE SENSE BASED ON THE SUMMARY OF THE GENE THAT YOU JUST FOUND?

WHAT SPECIFIC FUNCTION(S) DOES THIS PROTEIN HAVE?
(Binding to ligands, substrates and/or cofactors; General and/or specific functional activities.)
DOES THIS MAKE SENSE BASED ON THE SUMMARY OF THE GENE THAT YOU JUST FOUND?

IN WHICH COMPONENT(S) (SUB-CELLULAR LOCATION) IS THIS PROTEIN NORMALLY FOUND?

8. **Scroll down to the “Expression” section** to see in which tissues this gene is expressed and, since the protein is maintained within the cell, where it functions.

IN WHICH TISSUES HAS THIS GENE BEEN FOUND TO BE EXPRESSED?

DO ANY OF THESE CORRELATE WITH SOME OF THE TWINS' SYMPTOMS?

Based on your understanding of the complexity of gene expression, how might you **EXPLAIN SOME OF THE DIFFERENCES IN SYMPTOMS OBSERVED IN THE TWINS?**

Or look it up! <https://www.ncbi.nlm.nih.gov>

Search Gene with: human[organism] AND AND spr[preferred symbol]
or with: human spr
OR **CLICK on the relevant GENE SYMBOL link on the MedGen or ClinVar record!**

Okay, let's get into this!

SPR sepiapterin reductase (7,8-dihydrobiopterin:NADP+ oxidoreductase) [Homo sapiens (human)]
 Gene ID: 6697, updated on 4-Sep-2016

Summary
 Official Symbol: SPR provided by HUGO
 Official Full Name: sepiapterin reductase (7,8-dihydrobiopterin:NADP+ oxidoreductase) provided by HUGO
 Primary source: HGNC:HGNC:11257
 See related: Ensembl:ENSG00000116096 HPRD:01632; MIM:182125; Vega:OTTHUMG00000129777
 Gene type: protein coding
 RefSeq status: REVIEWED
 Organism: Homo sapiens
 Lineage: Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Haplorhini; Catarrhini; Hominoidea; Homo; Hominidae; Homo sapiens

Also known as
 SPR38*1

Summary
 This gene encodes an aldo-keto reductase that catalyzes the NADPH-dependent reduction of pteridine derivatives and is important in the biosynthesis of tetrahydrobiopterin (BH4). Mutations in this gene result in DOPA-responsive dystonia due to sepiapterin reductase deficiency. A pseudogene has been identified on chromosome 1. [provided by RefSeq, Jul 2008]

Orthologs
 mouse all

Genomic context
 Location: 2p14-p12 See SPR in Genome Data Viewer Map Viewer
 Exon count: 3

Annotation release	Status	Assembly	Chr	Location
108	current	GRCh38.p7 (SCF_000001405.33)	2	NC_000002.12 (72887383..72892160)
105	previous assembly	GRCh37.p13 (SCF_000001405.25)	2	NC_000002.11 (73114512..73119289)

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 Interactions **Link to gene product function info**
 General gene information
 Markers, Related pseudogene(s), Homology, Gene Ontology
 General protein information
 NCBI Reference Sequences (RefSeq)
 Related sequences
 Additional links
 Locus-specific Databases

Gene (Gene Summary Hub): Human Sepiapterin Reductase

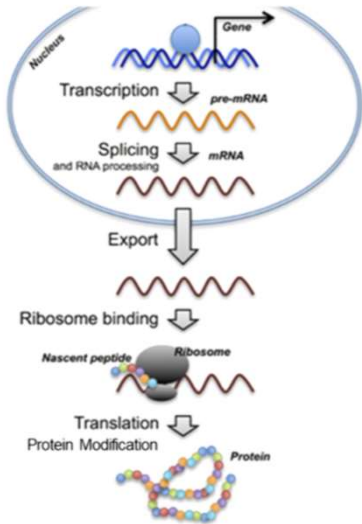
SPR **sepiapterin reductase (7,8-dihydrobiopterin:NADP+ oxidoreductase) [Homo sapiens (human)]**
Gene ID: 6697, updated on 4-Sep-2016

Function	Evidence Code	Pubmed
NADP binding	TAS	PubMed
aldo-keto reductase (NADP) activity	TAS	PubMed
sepiapterin reductase activity	IBA	PubMed
sepiapterin reductase activity	ISS	

Process	Evidence Code	Pubmed
colloidal metabolic process	TAS	
nitric oxide biosynthetic process	IDA	PubMed
oxidation-reduction process	TAS	PubMed
regulation of nitric oxide synthase activity	TAS	
tetrahydrobiopterin biosynthetic process	IBA	PubMed
tetrahydrobiopterin biosynthetic process	TAS	PubMed

Component	Evidence Code	Pubmed
cytosol	IDA	
cytosol	TAS	
extracellular exosome	HDA	PubMed
nucleolus	IDA	

A Review of Molecular Biology & UNDERSTANDING VARIANT IMPACT



Genome, assembly level → GRCh38

Chromosome/DNA → NC_ (RefSeq)

HGVS Variant Example: NC_000002.12:g.72888457A>G
might impact chromatin structure or function

Gene/DNA, gene region level → NG_* (RefSeqGene)

HGVS Variant Example: NG_008234.1(SPR):g.6075A>G
might impact expression for or splicing of a gene transcript

Transcript/RNA → NM_ , NR_ ("RefSeq RNA" | RefSeq Select)

HGVS Variant Example: NM_003124.5(SPR):c.448A>G
might impact transcript processing and/or translation

Protein, mRNA-encoded sequence → NP_* ("RefSeq Protein")

HGVS Variant Example: NP_003115.1(SPR):p.Arg150Gly
might impact protein folding, processing or function

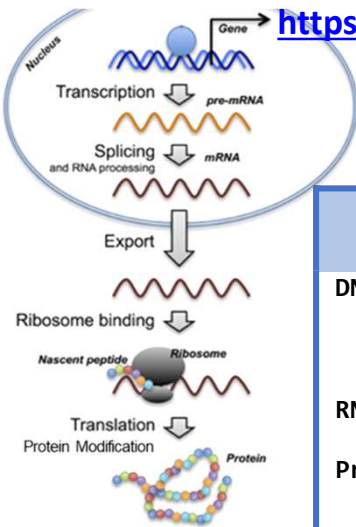
Structure

For more information about our RefSeq curation project:
<https://www.ncbi.nlm.nih.gov/refseq/>

GENE

AGGREGATED INFORMATION OF EVERYTHING WE KNOW ABOUT AN ORGANISM'S GENE

<https://www.ncbi.nlm.nih.gov/gene>



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What is the affected gene?

TEST RESULTS in HGVS Format (& why this is helpful)

DNA: NC_000002.12:g.72888457A>G
might impact chromatin structure or function

NG: NG_008234.1(SPR):g.6075A>G
might impact gene expression for a particular gene

RNA: NM_003124.5(SPR):c.448A>G
might impact splicing and/or translation

Protein: NP_003115.1(SPR):p.Arg150Gly
might impact protein folding, processing or function

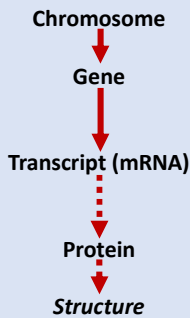


Gene

NCBI WORKSHOP



Chromosome - Gene Region shown in GDV Human Septaplerin Reductase



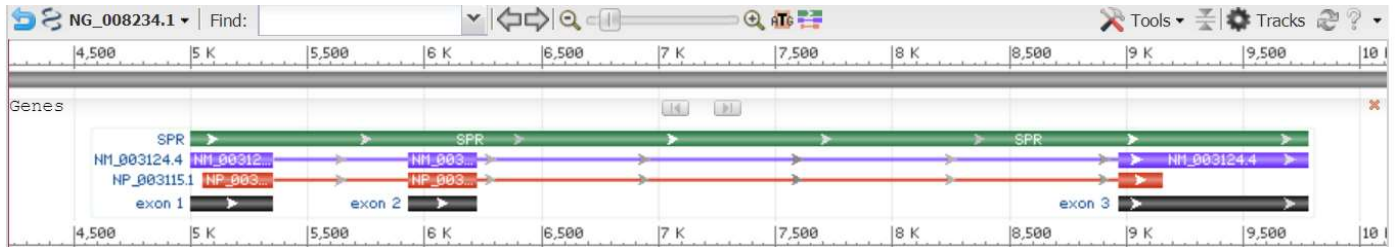
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NCBI WORKSHOP

Molecular Biology Research – Variant location and potential impact

INFORMATION ABOUT THIS GENE DETERMINED FROM SEQUENCE-BASED SOURCES:

9. On the right-hand side of the Gene record, [click the “RefSeqGene” link](#) to see the “Graphic” view of the gene structure defined on the chromosome on a RefSeqGene nucleotide page.



HOW MANY TRANSCRIPT VARIANTS AND ENCODED PROTEINS ARE KNOWN TO BE PRODUCED BY THIS GENE?

There are several different “Tracks” available in this view, with names shown on the left. (You can manipulate what is shown by the “Tracks” button in the upper-right.)

At the very top of this view, the **grey bar** shows the region corresponding to the genome with a “ruler” above showing nucleotide or base/residue.

Below this is the “**Genes**” track with the following:

A **green bar** with the gene symbol (SPR) shown is the full length of the gene region with little arrow-heads indicating the 5’ to 3’ direction of the coding. There is a single “green” gene region for each gene annotated on the genome.

Underneath the **green bar** may be shown the gene products of the gene:

The **purple bar** with the accession indicates regions that are transcribed into RNAs. For mRNAs, thicker regions are the designated “exons” and the connecting lines (with directional arrow-heads) representing the connecting “introns” (which will be removed by splicing) and the **red bar** indicates the regions on the mRNA exons that encode the protein (also called coding sequence or CDS).

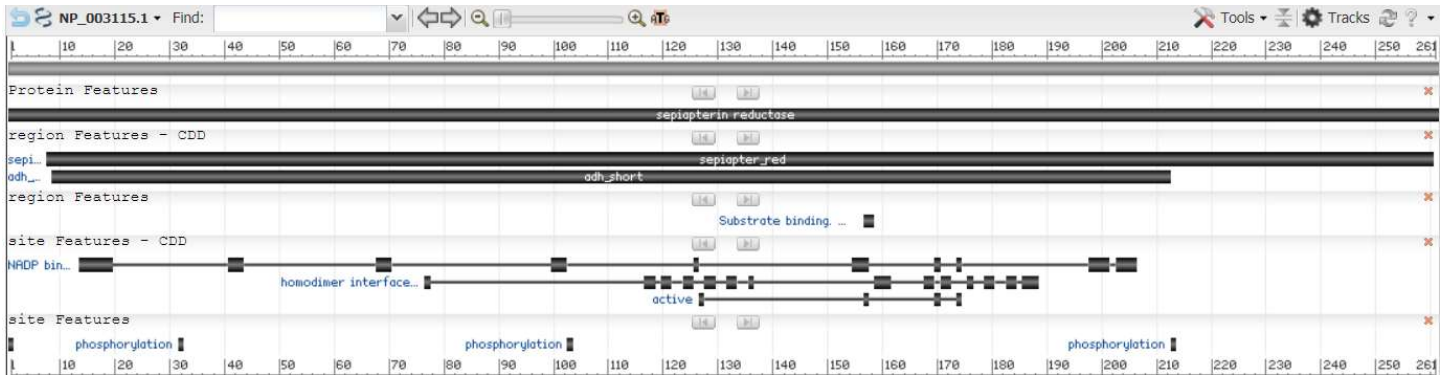
For some genes, it is known that there are multiple transcript splice-variants formed due to RNA processing (splicing), these would be shown as addition purple (and corresponding red – if protein coding) tracks. In order to help to establish a common numbering system of exons (since there may be different combinations in different transcript variants), the **black bar** below shows numbered boxes corresponding to each possible exon identified for the particular gene.

WHERE IS/ARE THE TWINS’ GENETIC VARIANTS LOCATED IN THIS GENE AND IN THE MRNA?

(on the picture above or on your screen – draw or visualize a vertical line at the position of each if the variants)

BASED ON THE POSITION(S) OF THE VARIANT(S) IN THE GENE, WHAT IS THE MOST LIKELY MECHANISM FOR IMPACTING THE FINAL GENE PRODUCT? *(alter gene expression, influence transcript processing, or change encoded protein sequence)*

10. On the right-hand side of the RefSeqGene page, **can click the “Protein” link** or go back to the Gene record and **click the “RefSeq Proteins” link. Click “Graphics”** to see a graphical view of the annotated regions curated on the protein sequence. The information shown in in these “tracks” of this view can help you to learn more about this protein.



WHERE IN THE PROTEIN SEQUENCE IS/ARE THE TWINS’ GENETIC VARIANTS LOCATED?

(on the picture above or on your screen – draw or visualize a vertical line at the position of each if the variants)

Take a look at the annotations shown in the Graphic view. **BASED ON WHERE IT THE VARIANT(S) IS/ARE LOCATED, WHICH MIGHT THE VARIANT(S) ALTER:**

- the protein’s **location**
(signal peptide)
- post-translational **processing** of the protein
(cleavage site)
- post-translational modification** of the protein
(phosphorylation or methylation site, for example)
- the **functional activity** of the protein (domain, motif, and/or specific site/“key” residue – *binding, active site, catalysis, for example*)

to learn more about the main functional regions of the protein **click “Identify Conserved Domains”**.

There are several different “Tracks” available in this view, with names shown on the left. (You can manipulate what is shown by the “Tracks” button in the upper-right.)

At the very top of this view, the **grey bar** shows the length of the protein with a “ruler” above showing amino acid position/residue from N-terminus to C-terminus. The **“Protein Features”** bar mimics the grey bar, above, and displays the gene name.

Other “Features” tracks indicate important residues for the function of the protein.
- **Mouse-over the features to learn more about each -**

The **“region Features - CDD”** track shows bars corresponding to functional domains that have been annotated in this protein sequence by the NCBI Conserved Domain Curation Staff.

“region Features” indicates critical amino acid positions *involved* in the activity of the protein

“site Features – CDD” shows specific amino acid positions that are critical for various functions of this protein (including binding, catalysis, active site, interface & protein-protein interactions, etc.)

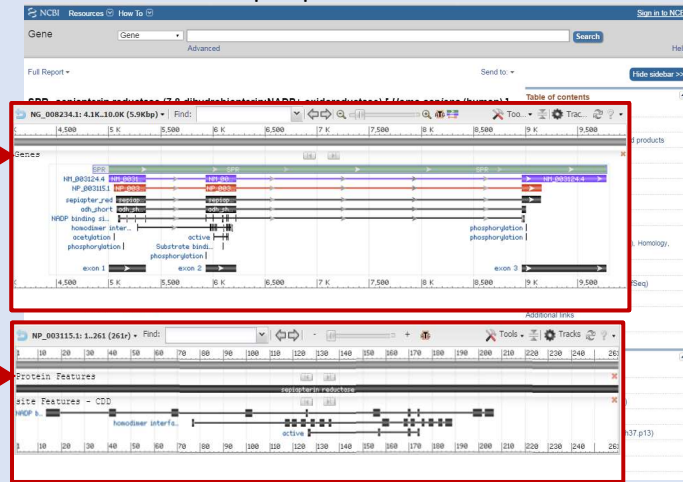
“site Features” identifies other important amino acid positions which are predicted to be targets of other cellular processes (including sites for targeting with post-translational modifications or targets for proteolytic cleavage).

When there is evidence of Other tracks that are shown here when there is information to support it, include “signal peptide” if the protein is to be targeted to a specific subcellular location other than the cytosol.

WHAT MIGHT BE THE IMPACT OF THE GENETIC VARIATIONS ON THE PROTEIN’S FUNCTION?

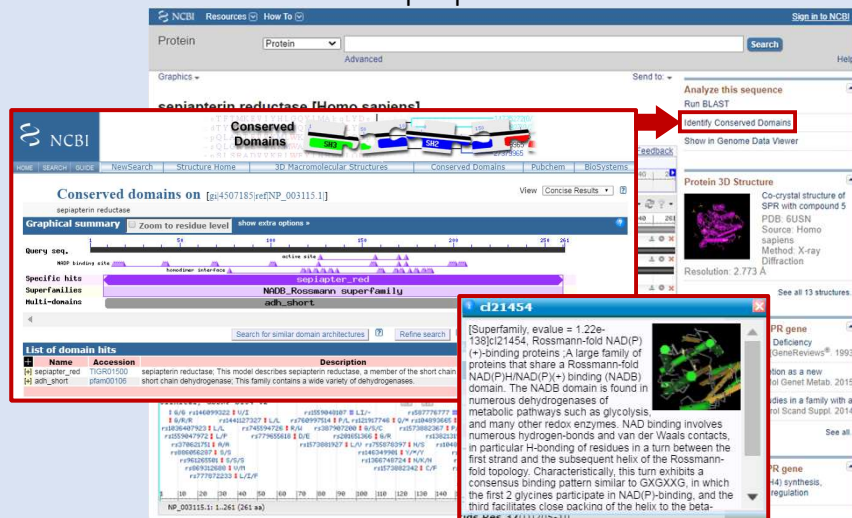
Gene (Gene Summary Hub): Human Sepiapterin Reductase

Gene
↓
Transcript (mRNA)
↓
Protein
↓
Structure



- Related information**
- 3D structures
 - Conserved Domains
 - PubMed
 - RefSeq Proteins
 - RefSeq RNAs
 - RefSeqGene
 - SNP: VarView
 - UniGene

Protein (RefSeq Protein & CDD records): Human Sepiapterin Reductase



Gene (Gene Summary Hub) Human Sepiapterin Reductase

Structure (Curated PDB Records) Human Sepiapterin Reductase

NCBI Resources | How to | Sign in to NCBI

Gene:

Full Report -

SPR sepiapterin reductase [*Homo sapiens* (human)]

Gene ID: 6597, updated on 6-May-2021

Summary

Official Symbol SPR provided by HGNC

Official Full Name sepiapterin reductase provided by HGNC

Primary source HGNC:HGNC:11237

See related [Ensembl:ENSG00000116096](#) [MIM:182128](#)

Gene type protein coding

RefSeq status REVIEWED

Organism [Homo sapiens](#)

Lineage Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorhina; Catarrhini; Hominoidea; Homo

Also known as SDR35C1

Summary This gene encodes an aldo-keto reductase that catalyzes the NADPH-dependent reduction of pteridine derivatives and is important in the biosynthesis of tetrahydrobiopterin (BH4). Mutations in this gene result in DOPA-responsive dystonia due to sepiapterin reductase deficiency. A pseudogene has been identified on chromosome 1. [provided by RefSeq, Jul 2008]

Expression Ubiquitous expression in kidney (RPKM 23.8), colon (RPKM 21.8) and 24 other tissues [View tissue](#)

Ontology

Genomic context

Location: 2p13.2

Exon count: 3

Annotation release	Status	Assembly	Chr	Location
109.20210226	current	GRCh38.p13 (GCF_000001495.20)	2	NC_000002.12 (72887408..72887408)
108.20200203	previous	GRCh37.p13.103 (GCF_000001495.16)	2	NC_000002.11 (72887408..72887408)

Related information

- Order cDNA clone
- 3D structures
- BioAssay by Target (List)
- BioAssay by Target (Summary)
- BioAssay, by Gene target
- BioAssays, RNAi Target, Active
- BioAssays, RNAi Target, Tested
- BioProjects

NIH National Library of Medicine
National Center for Biotechnology Information

NCBI Structure Summary MMDB

4Z3K: Human Sepiapterin Reductase In Complex With The Cofactor NADP+ And The Tryptophan Metabolite Xanthurenic Acid

Citation: Tetrahydrobiopterin Biosynthesis as a Potential Target of the Kynurenine Pathway Metabolite Xanthurenic Acid Hanuš M, Hovius R, Pedersen MG, Johnson K J Biol Chem (2016) 291 p.652-7

Abstract: Tryptophan metabolites in the kynurenine pathway are up-regulated by pro-inflammatory cytokines or glucocorticoids, and are linked to anti-inflammatory and immunosuppressive activities. In addition, they are up-regulated in pathologies such as cancer, autoimmune diseases, and psychiatric disorders. The molecular mechanisms of how kynurenine pathway metabolites cause these effects. [Read more](#)

PDB ID: 4Z3K

MMDB ID: 104251

PDB Deposition Date: 2015/3/31

Updated in MMDB: 2015/11

Experimental Method: X-ray diffraction

Resolution: 2.35 Å

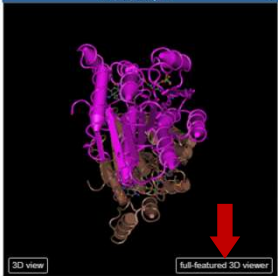
Source Organism: Homo sapiens

Similar Structures:

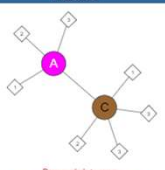
All Biological Units (2)

Biological Unit for 4Z3K: dimeric, determined by author and by software (PISA) =

Molecular Graphic



Interactions



Drag symbols to move

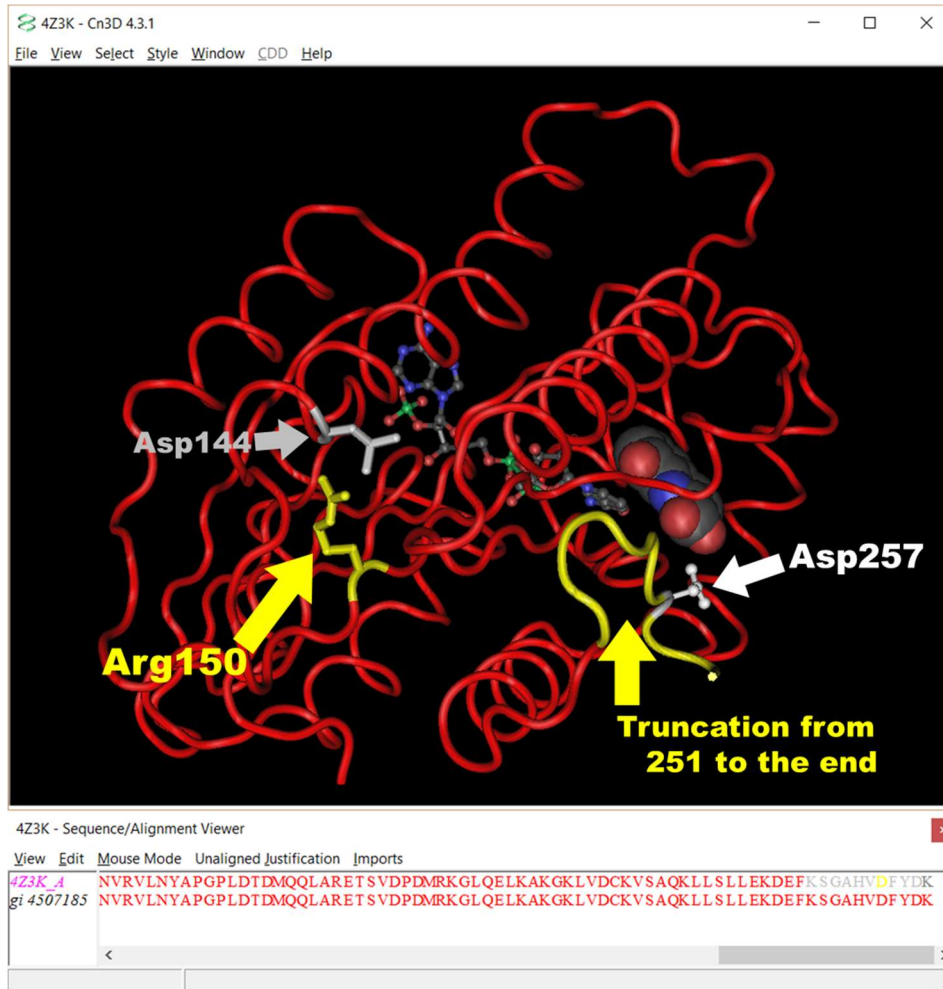
Double click symbols to explore molecules

Format:

Data Set:

Molecular Components in 4Z3K

11. From either the Gene or Protein record, **can click a link to 3D Structure** to visualize experimentally-determined molecular structures for this protein. In the 3D structure you can see precisely the locations of the amino acids affected by the genetic variations.



To make things easier for you right now....

here's a picture of the **3D crystal structure** monomer of the Human SPR protein complex (PDB accession: 4Z3K) as displayed in NCBI's Cn3D Viewer.

The protein backbone is showed in a long **red tube**, with two bound substrates (NADPH & a sepiapterin analog) for the SPR reaction shown as ball-and-stick and spacefill rendering, respectively.

The position of where the variants would exist (Arg150 & Lys251) are highlighted in **yellow** and two additional important residues displayed in **grey** (Asp144) and **white** (Asp257).

WHAT DO YOU THINK THE CHANGE IN AMINO ACIDS MIGHT DO TO THE 3D STRUCTURE AND FUNCTION OF THE PROTEIN?

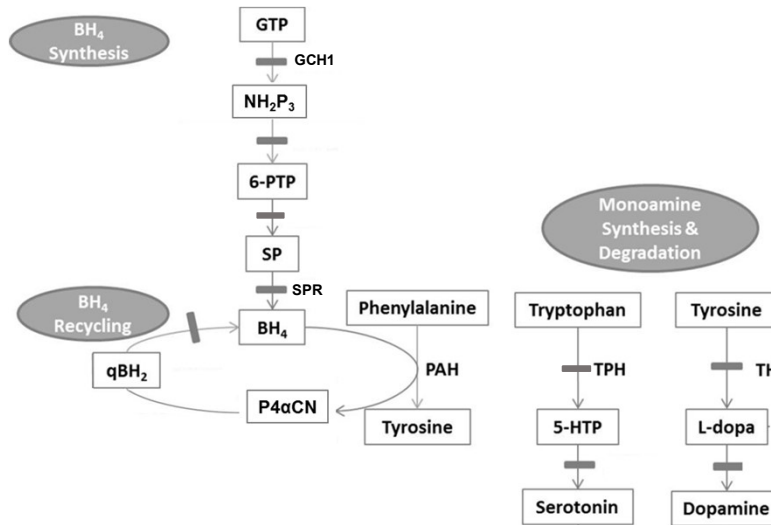
Arg150 normally forms a salt-bridge with Asp144 to stabilize the protein's 3D structure.

Loss of this salt-bridge, due to replacement of the negatively-charged arginine with a neutral glycine (Arg150Gly), causes the enzyme to unfold and lose all activity.

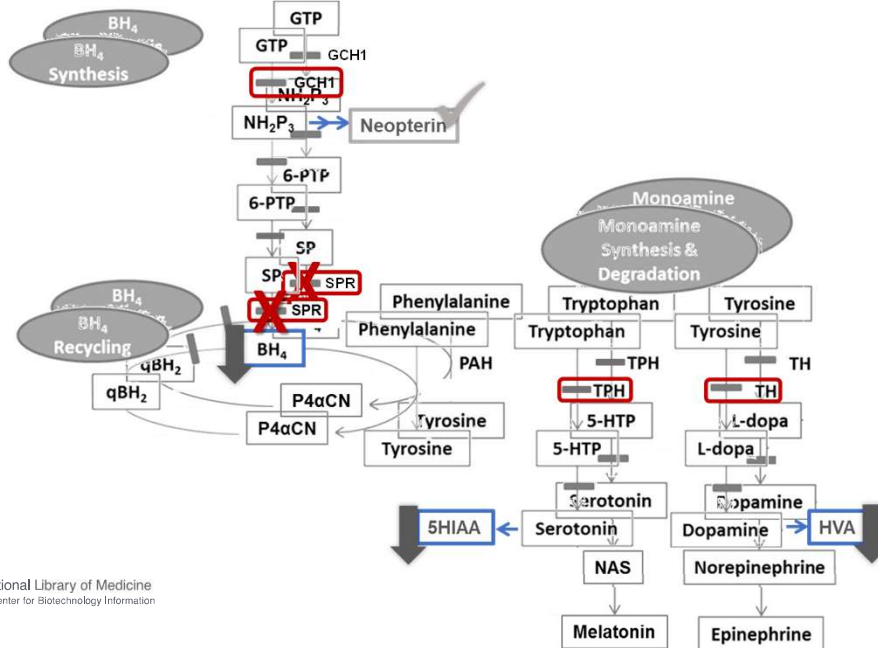
The C-terminal end of the protein and Asp257, in particular, stabilizes the binding and locks the sepiapterin substrate into the active site of the enzyme.

Loss of the C-terminal tail and this particular residue (as in the truncation variant Lys251Ter) causes loss of the ability of the enzyme to efficiently bind and lock-in its substrate – resulting in the loss of all activity.

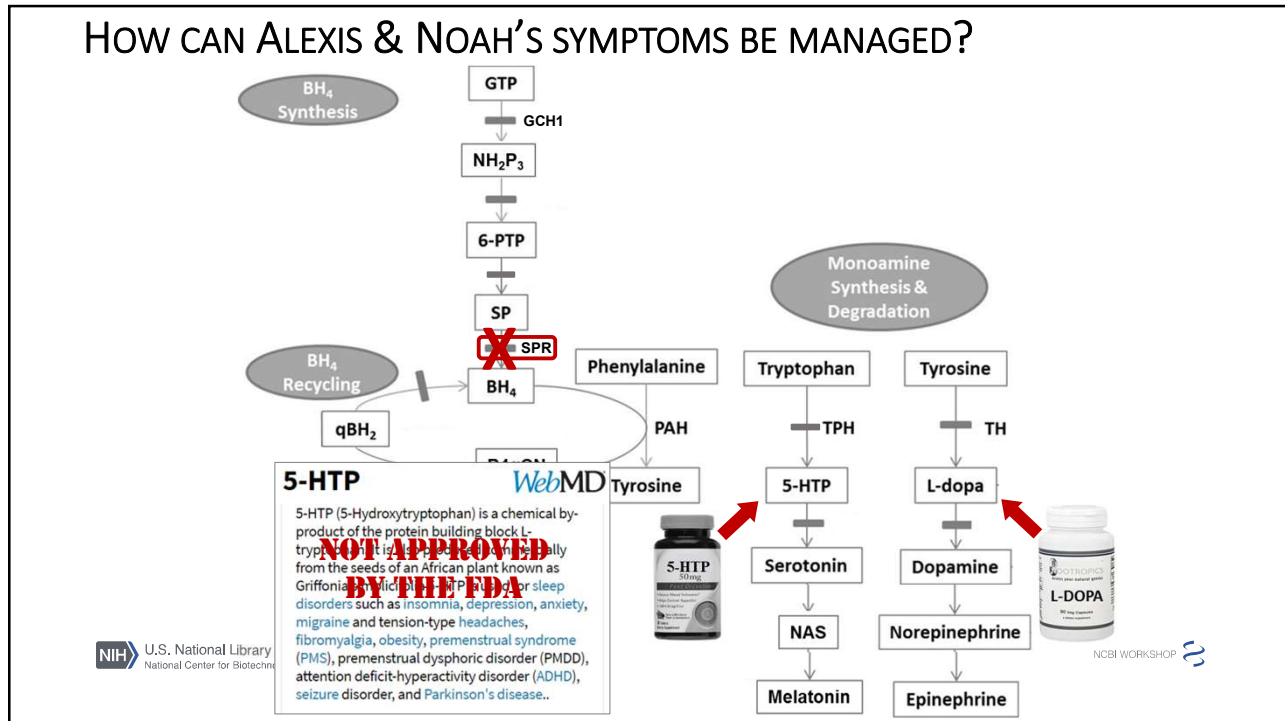
Review of the biological system: lab & genetic test info mapping



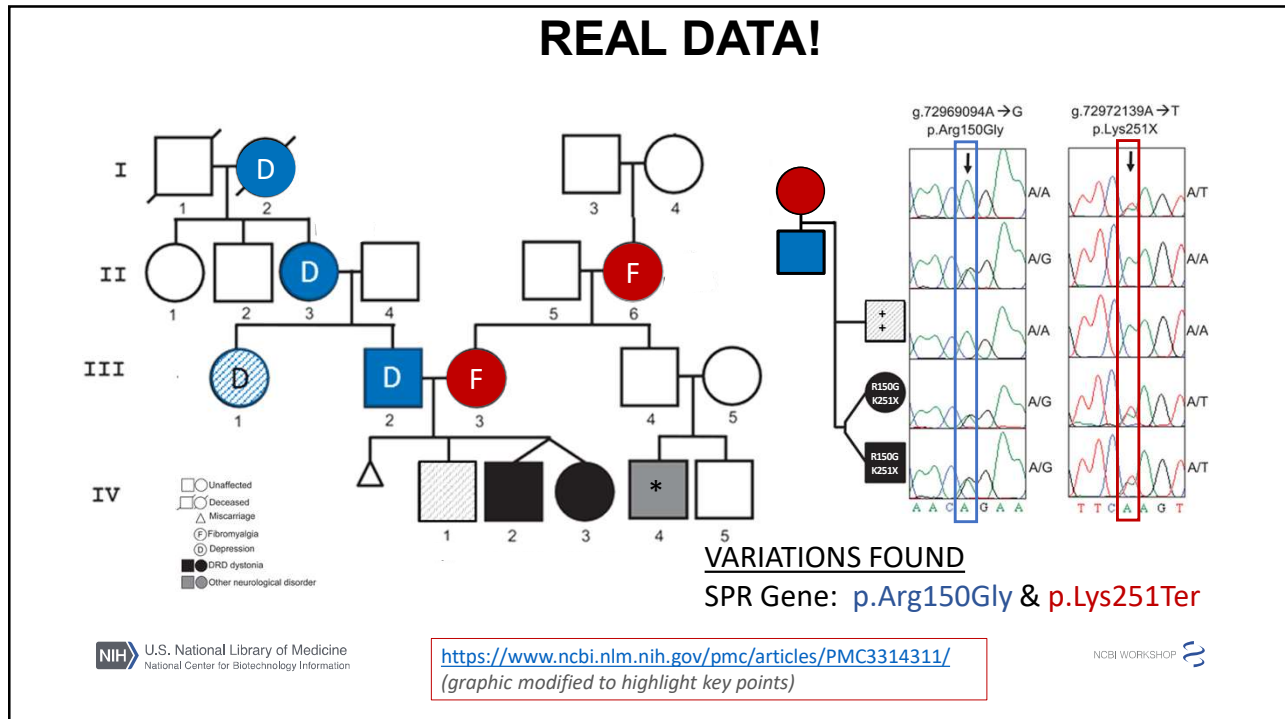
HOW CAN ALEXIS & NOAH'S SYMPTOMS BE MANAGED?



HOW CAN ALEXIS & NOAH'S SYMPTOMS BE MANAGED?




REAL DATA!



HOW ARE THE BEERYS DOING NOW?



 U.S. National Library of Medicine
National Center for Biotechnology Information



Advocacy for:

- Collaborative Patient Care
- Genetic Testing
- NIH Funding

RARE DISEASE DAY - 2/17/2022



NCBI WORKSHOP 

<https://www.lunadna.com/rare-disease-day-personal-experience-into-technology/>