



UTSW Medical Center

March 28, 2018

NCBI RESOURCES FOR GENETIC DISEASE DISCOVERY AND CLINICAL SUPPORT

My Workshop
Workbook

File Directories for the Event
& This Workshop

<http://bit.ly/UTSW2018>

http://bit.ly/UTSW2018_ClinicalGeneticsWorkshop

Workshop Description

The use of genetic testing in patient care is becoming more common in clinical practice. NCBI has long had resources for biologists to explore what is known about genetic variation, but has recently developed clinically-focused resources. This module is designed for those involved in clinical practice and/or translational research.

Based on a real-world case study, you will learn how to:

- Find a MedGen record with links to various literature resources to assist in clinical decision support and patient education.
- Identify a relevant diagnostic genetic test and examine sample test results.
- Based on an identified genetic variant, explore the affected gene and gene product with regard to structure and function.
- Explain the patient's disease etiology and effectiveness of therapeutic interventions.

This module ends with a session where you will be given your own case study to solve.

Instructor

Rana Morris, Ph.D. is an NCBI Customer Experience team member and Team Lead for Educational Programs (Courses/Workshops, Webinars, Educational Materials). Since 2002, she has provided user support and training, as well as working with supervisors and development teams to improve NCBI resources based on user-centered design principles. Her doctoral, post-doctoral and research fellowship work integrated disciplines of computational and experimental biochemistry, molecular and cellular biology and genetics, and has included diagnostic development, drug design and coordination of genetics/genomics components of clinical trials.

NCBI RESOURCES FOR GENETIC DISEASE DISCOVERY AND CLINICAL SUPPORT:

Using Free, Online Resources to Assist in Understanding, Explaining, Diagnosing and Treating Human Disease

Rana C. Morris, Ph.D.

http://bit.ly/UTSW2018_ClinicalGeneticsWorkshop



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WORKSHOP DESCRIPTION AND GOALS

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Based on a real-world case study, you will learn how to:

- Find a MedGen record with links to various literature resources to assist in clinical decision support and patient education.
- Identify a relevant diagnostic genetic test in GTR and examine sample test results.
- Based on an identified genetic variant, explore the affected gene and gene product with regard to structure and function in Gene, CDD and Structure.
- Use the gathered information to explain the patient's disease etiology and effectiveness of therapeutic interventions.

This module ends with a session where you will be given your own case study to solve.



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WORKSHOP Agenda

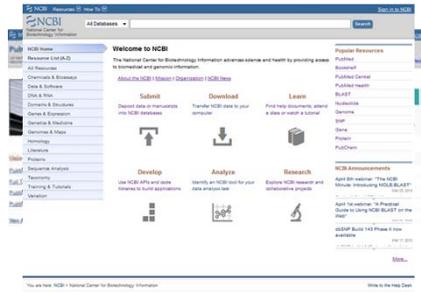
- Who am I?
- I will introduce NCBI and it's resources.
- I'll quickly discuss the evolution of clinical practice with examples of how genetics can impact patient care and outcomes.
- I'll work with you on a real-world case study!
 - We'll find clinical support and patient education materials.
 - We'll figure out which lab and genetic tests to "order" and interpret the results.
 - We'll discover the potential impact of a genetic variant on biology.
 - We'll elucidate how the variant might relate to symptoms and impact the therapy.
- You will get to practice with your own real-world case study!



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“WHAT” IS NCBI?



WHAT IS “NCBI”?

We are a “center” within the NLM responsible for creation, curation and maintenance of medical and scientific databases *and other things...*



We receive, create, archive & make available biomedical information, as well as perform computational biology & IT systems research....

but we really aspire to help make sense of the information!

WHAT DO WE DO?

Create and maintain resources to support Biomedical Scientists & Clinicians:

- Gather, generate and archive scientific & medical data
- Manage >40 high volume online databases
- Create and maintain various search mechanisms:
 - Entrez (text-based)
 - BLAST (sequence-based)
 - VAST (3D structure-based)
 - Chemical Structure Search (chemical structure-based)
- Link related data for discovery

NCBI's INFORMATION HUBS & SOME DBS

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CLINICALLY-RELATED BIOINFORMATICS PROJECTS @NCBI

- MORE AND MORE DATA -

- **Clinical Studies** (dbGaP)
 - Framingham, AREDS, Addiction treatment, etc.
- **Genomics/Genetics Resources**
 - ClinVar, Genetic Testing Registry (GTR)
 - 1000 Genomes, ExAc, HapMap, etc.
 - Microbiomes in SRA, Pathogen Detection Project, etc.
 - Gene Expression & Genotype Studies in GEO
- **Drug Design/Discovery Assays** (PubChem BioAssay)
- **Clinical Literature Resources** (PubMed/PMC, MedGen, PubMed Health, Books, etc.)
 - ClinicalTrials.gov

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THE COMING OF AGE - MOLECULAR MEDICINE

- The Art of Medicine
- The Science of Medicine
- Evidence-based Clinical Practice

"Evidence-based medicine is the integration of best research evidence with clinical expertise and patient values."
- "Personalized" Medicine

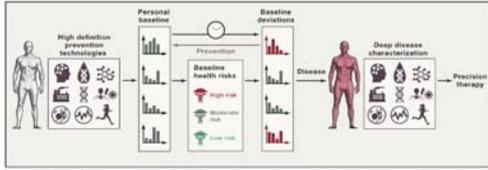
[AMA – all patient-care should be "personalized"]
- Precision (including Genomic) Medicine

"Precision medicine is an emerging approach for disease diagnosis treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person."
- and now?

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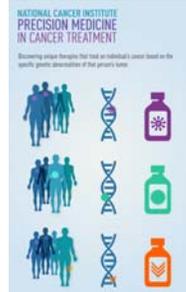
YET ANOTHER NEW TERM: HIGH-DEFINITION MEDICINE

Establish an Individual's **Baseline** of Health
 Create a Personalized "**Prevention**" Strategy
 Perform **High-Definition Diagnosis** & Select **High-Precision Treatment**



"High-Definition Medicine." Torkamani A, Andersen KG, Steinhubl SR, and EJ Topol. Cell. 24 August 2017 170(5), 828-843.

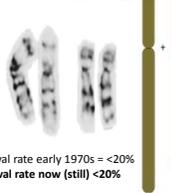
"PRECISION" MEDICINE - DISEASE CHARACTERIZATION, DIAGNOSIS & THERAPEUTIC SELECTION



COMPANION DIAGNOSTICS & TARGETED THERAPIES

Acute Myeloid Leukemia (AML) - M2 subtype
 $t(6;9)(p23;q34)$

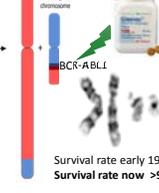
DEK-NUP214



Survival rate early 1970s = <20%
 Survival rate now (still) <20%

Chronic Myelogenous Leukemia (CML)
 $t(9;22)(q34;q11.2)$

Philadelphia chromosome



Survival rate early 1970s = <15%
 Survival rate now >94%!

PHARMACOGENOMICS EXAMPLE: DOSAGE PREDICTION

Dosing for Warfarin/Coumadin can be complicated....

Example:

Young, african american, thin, smoking male

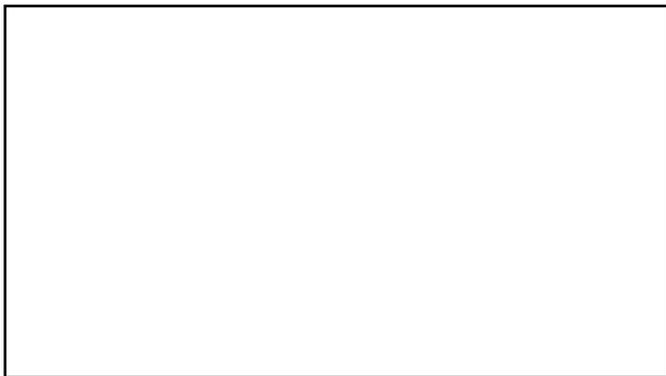
➤ high dose....120 mg

Older, caucasian, slightly heavy female

➤ low dose....2 mg



The screenshot shows the 'WARFARINDOSING' website interface. It includes a patient profile section with fields for Name, Race, Sex, Age, Weight, Height, and Ethnicity. Below this is a section for 'Genotypes' with a list of CYP2C9 and VKORC1 variants. At the bottom, there is a red button labeled 'ESTIMATE WARFARIN DOSE'.

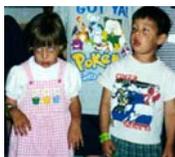


USING NCBI RESOURCES TO ASSIST IN UNDERSTANDING, EXPLAINING, DIAGNOSING AND TREATING HUMAN DISEASE

- A Case Study -

Putting it all together!

TWINS' DIAGNOSIS OF CEREBRAL PALSY, THEN SEGAWA DYSTONIA, THEN.....



Alexis & Noah, fraternal twins

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

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



TWINS' DIAGNOSIS OF CEREBRAL PALSY, THEN SEGAWA DYSTONIA, THEN.....



Alexis & Noah, fraternal twins

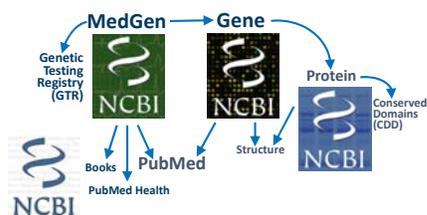
QUESTIONS TO ANSWER:

- What was wrong with them?
- What diagnostics could have been used to confirm and even further identify what was wrong with the twins?
- What therapies would be most effective at combating all the symptoms?
- Where is there more information for health care professionals and for patients/families?
- What is specifically wrong with them at the molecular level?
- How can this case be managed better now?

Mother's Story: <https://www.youtube.com/watch?v=q0jfvTPt4>
 Father's Story: <https://www.youtube.com/watch?v=vGKYudE60s>
 Discovery Health: https://www.youtube.com/watch?v=8YvGrN_evVI
 NIH Story Corps: <https://www.youtube.com/watch?v=OdiJ2z80xk>

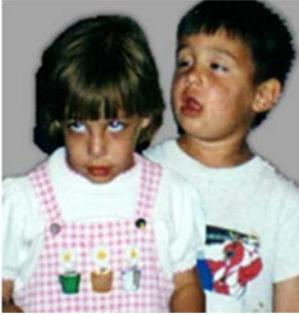


WORKFLOW



Welcome to your Patients!

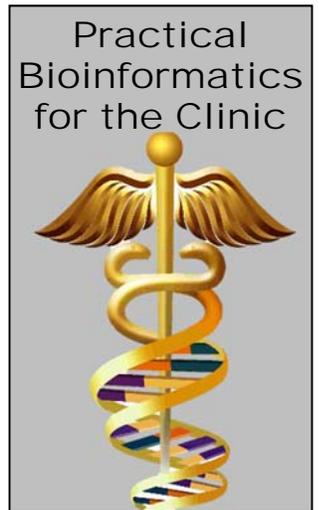
Alexis & Noah, 13 year old twins have been brought to you for a second (well, third) opinion...



Diagnosis: Originally Cerebral Palsy, then Sagawa Dystonia...

Key Symptoms: Dystonia with muscle spasticity, also severe sleep disturbance and hyperactivity.

Family history: “Unremarkable”, with several members of the family diagnosed with Major Depressive Disorder and mother diagnosed with Fibromyalgia.



The fraternal twins exhibited seemingly classic cerebral palsy symptoms from shortly after birth. An MRI of Noah’s brain provided supporting evidence. After five years, the twins seemed to be getting worse – particularly later in the day. After the mother read a 1991 LA Times article about a “treatable cerebral palsy-like syndrome” (Sagawa Dystonia), they met with the treating physician and were given a test dosage of L-Dopa with immediate, positive results. However, sleep disturbances and hyperactivity levels continued and at 13 years of age, Alexis’s severe untreatable respiratory problems prompted a reassessment of their diagnosis.

Clinical Research

1. Search NCBI’s MedGen database with:

dystonia AND hypotonia AND sleep disturbance

WHAT IS A POSSIBLE DIAGNOSIS FOR THE TWINS?

2. What are other disorders that you should consider? (Differential Diagnoses)
(**Hint:** Check the [GeneReviews>Differential Diagnosis](#) link.)

3. There are many **relevant publications** on the MedGen record – about **Recent clinical studies** and **Recent systematic reviews**. **WRITE DOWN PMIDS FOR THOSE OF INTEREST TO YOU.**

4. Find some helpful **Patient Education Materials** and any potential **Clinical Trials** that may be **available**. - **WRITE IN THE LINK NAMES.**

5. To establish a diagnosis, **WHAT LABORATORY TEST(S) COULD YOU ORDER?**
(Hint: Check the [GeneReviews>Diagnosis](#) Link *or* take a look at PubMed articles listed in the [Recent clinical studies>Diagnosis](#) section.)

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

➤ Lab Test results: http://bit.ly/Twins_LabTestResults

NOTES:

How do these lab test results map to a biological pathway related to the L-Dopa?

Based on your research and the results of the Lab Test, **WHAT DO YOU THINK IS WRONG WITH ALEXIS & NOAH?**



You discuss the diagnosis and hand the twins' parents, Retta & Joe, some Patient Education materials.

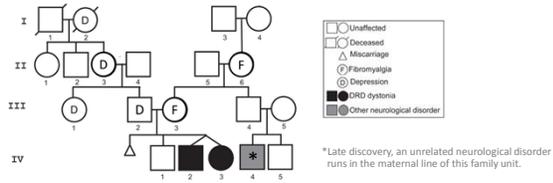
Both Retta & Joe are concerned about this diagnosis and want to understand why this is happening. Just having a "label" isn't enough for them - as the twins have been labeled twice before incorrectly. Retta also wants to know why L-Dopa seemed to work initially and understand why the treatment you are recommending should work at the molecular level.

The family had recently moved to San Diego where Joe became the CIO of a biotechnology company which supports human genome research and Retta has become a strident patient advocate. Thus, they are familiar with the latest technologies and are very interested in participating in cutting-edge research studies that may have an impact and help other patients as well.

MIGHT THIS BE GENETIC? HERE'S THE FAMILY PEDIGREE

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

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



*Late discovery, an unrelated neurological disorder runs in the maternal line of this family unit.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3314311/>

SOME THINGS WORTH CONSIDERING WHEN THINKING ABOUT ORDERING A GENETIC TEST

Genetic Testing & Results Interpretation are still developing sciences.

Is it relevant?

- Are you potentially diagnosing a *known* genetic disorder?
- Do the symptoms or related conditions seem to "run" in the family?

Is it helpful?

- What will you do with the information? (ex: actionability & potential psychosocial impact)

Is it advisable?

- What are the recommended guidelines?
- What is the standard-of-care in your hospital or Healthcare system?

Things to keep in mind:

- You may *not* get a clear answer ("variants of uncertain significance", VUS)
- Failure to detect a pathogenic variant *does not rule out* a diagnosis.
- Discordance between symptoms and conclusive genetic test results does occur and often depends upon penetrance of the trait and characteristics of the particular condition.

Genetics Research

- From the MedGen record, **find a genetic test that you could order for them.**
(For this case-study, this should be a CLIA-certified clinical lab in California.) **WRITE DOWN THE GTR TEST ID.**

➤ Genetic Test results: http://bit.ly/Twins_GeneticTestResults

NOTES:

WHAT ARE THE SPECIFIC GENE AND VARIATIONS IDENTIFIED IN THE TWINS?

To find out what various genetic testing laboratories, clinical genetic organizations, and OMIM are asserting for these genetic variations, **search the ClinVar database.**

(You can search with an HGVS expression, rsID or Gene Symbol and nucleotide or protein change, for example type *SPR p.Arg150Gly* or *SPR p.Lys251Ter.*) **WHAT IS THE KNOWN FOR THE TWINS' GENETIC VARIATIONS?**

How do these genetic test results relate to the biological pathway that you saw with the lab test results mapped to it? **DO THE RESULTS OF THE GENETIC TESTS VALIDATE THE RESULTS OF THE LAB TESTS?**

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 & SPR:g.9120T>A = p.R251X

WHAT DO YOU DO NOW THAT YOU KNOW? NOW THAT YOU'RE A-GROUND....

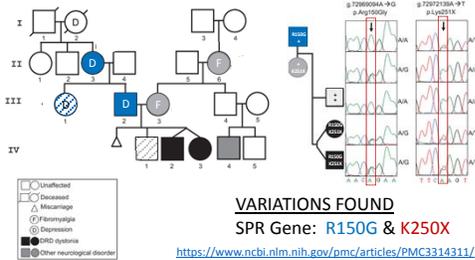
As a Clinician – “What do you do now?”
(hopefully you had an idea before the test was ordered, but not always....this is why we're doing the rest of this example)

As a Patient or Parent of a Patient – “What do I do now?”
A great reason to consult with a Genetic Counselor!

- Implications for the patient *beyond* this diagnosis:
The patient should consider discussing this with their primary care physician, dentist, other clinical professionals who may need to know for their care.
- Implications for others: “Should I tell family members?”



REVIEW OF FAMILY PEDIGREE & GENETIC VARIATION DATA



WHAT DO YOU DO NOW THAT YOU KNOW? NOW THAT YOU'RE A-GROUND....

As a Clinician – “What do you do now?”
(hopefully you had an idea before the test was ordered,
but not always...this is why we're doing the rest of this example)

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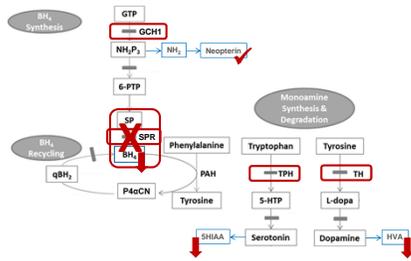
- Implications for the patient *beyond* this diagnosis:
The patient should consider discussing this with their primary care physician, dentist, other clinical professionals who may need to know for their care.
- Implications for others: “Should I tell family members?”

Often, the next question is – “What is wrong and how can it be fixed?”

- Understanding the potential impact of a genetic variant on the patient's physiology and phenotype (*molecular etiology and consequences*)



WHICH GENE WAS IMPLICATED IN THIS CASE?



Molecular Biology Research

7. Back on the MedGen record, **click the link for the gene identified as having variants in the twins.**

WHAT DOES THIS GENE NORMALLY DO?

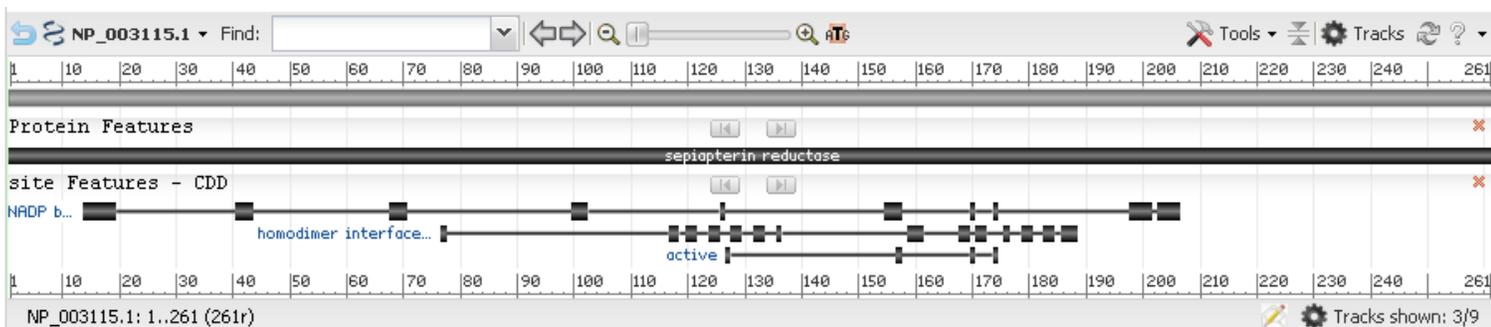
8. From the Gene record, **scroll down to the Expression section to see in which tissues this gene is expressed and**, since the protein is maintained within the cell, **where it functions.**

WHICH TISSUES FOUND TO EXPRESS THIS GENE CORRELATE WITH SOME OF THE TWINS' SYMPTOMS?

9. From the Gene record, **click the “RefSeq Proteins” link** (on the right-hand side of the page). **Click “Graphics” to see defined regions on the protein sequence.** (If you want to learn more about the functional regions of the protein you can **click “Identify Conserved Domains”**.)

Based on the location of the twins' genetic variants and the description of the functional regions,

WHAT MIGHT THE GENETIC VARIATIONS DO TO THE PROTEIN STRUCTURE AND FUNCTION?



From either the Gene or Protein record, you can follow links to 3D Structures to examine the protein structure to see precisely where the amino acids affected by the genetic variations are located.

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

- An annotated 3D Structure: http://bit.ly/Twins_StructurePicture

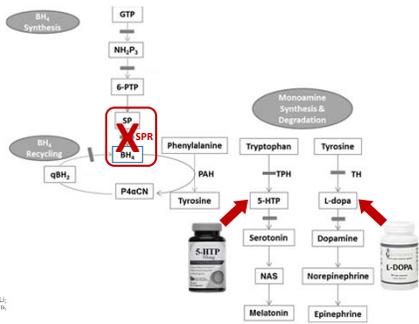
NOTES:

REVIEW OF MOLECULAR ETIOLOGY

What we've found so far:

- Alexis & Noah have Sepiapterin reductase deficiency with double heterozygous pathogenic variants in the SPR gene.
- SPR is the catalyst of the rate-limiting step for the production of a cofactor Tetrahydropterin (BH₄) which is critical for the synthesis of neurotransmitters & nitric oxide.
- SPR is expressed in tissues such as brain, muscle, vasculature, connective tissue, stomach, salivary gland, adrenal gland and pineal gland, among others.
- The two pathogenic variants cause the production of **very low or non-functional Sepiapterin reductase**.
 - SPR:p.R150G (*from the father's side*): Disrupts the formation of a wild-type salt-bridge causing the unfolding of the enzyme's 3D structure and targeting the protein for degradation.
 - SPR:p.K251X (*from the mother's side*): Causes the loss of the C-terminal tail including a D257, a critical binding residue for capturing, holding onto and coordinating the enzyme's substrate for catalysis.

HOW CAN ALEXIS & NOAH'S SYMPTOMS BE MANAGED?



HOW ARE THE BEERYS DOING NOW?



- Advocacy for:**
- Collaborative Patient Care
 - Genetic Testing
 - NIH Funding

COLLEGE!
& College athletics

RECAP

THE WORKFLOW THAT WE'VE USED IN THIS CASE STUDY WILL ALSO WORK FOR OTHER WELL-STUDIED AS WELL AS MANY POORLY-UNDERSTOOD DISORDERS.

- **MedGen** is a "health-related" **Information Hub**, providing links to:
 - Information about diseases/conditions
 - Links to scientific/clinical publications & patient education materials
 - Links to available genetic tests in NIH's Genetic Testing Registry
 - Links to information about relevant disease-associated genes
- **Gene** is a "gene-related" **Information Hub** providing information and links to more for just about anything that is currently known about:
 - Sequence, expression, structure & function of the genes and gene products
 - Links to specific, relevant literature
 - Links to sources of research reagents & experimental studies with data

NOW, IT'S YOUR TURN!

BASIC CASE

"A NOSEBLEED THAT WOULDN'T STOP"



Raven (23 y.o. female) & James (8 m.o. male)

A Mother & her Son were referred by a local clinic with a preliminary diagnosis of a Bleeding Disorder, likely Hemophilia

ADVANCED CASE

"WEARING A KILT ≠ ALCOHOLISM"



Jeff, 46 y.o. male

Preliminary Diagnosis:
Cirrhosis & Diabetes due to chronic alcoholism

TASKS TO DO & QUESTIONS TO ANSWER

- Find information for health care professionals and for patients/families.
- Identify diagnostics that should test the veracity of the preliminary diagnosis and characterize what is wrong.
- Based on an understanding of the molecular etiology, explain the patient's symptoms and select a successful therapy!
- Answer these questions:
 - What is wrong with my son/me?
 - Why is this happening?
 - What do we do now?
 - Should our family members be concerned?

For everyone....

Start on PAGE 18: Welcome to your Patient(s)!



James (8 m.o. male) was referred to you by a local clinic....

Diagnosis: Bleeding Disorder, likely Hemophilia –
due to normal CBC and platelet levels

Symptoms: Significant Bruising, Relentless Nose-bleed, with a
possible history of bleeding issues in maternal line

Raven, James' 23 y.o. mother, has noticed frequent bruising on James' knees, palms and lower arms since he began crawling two months ago. Last night he pulled himself up to stand with the coffee table and fell - hitting his nose and causing a protracted nosebleed.

In discussions with Raven about her own health history, she mentioned that she had “heavy periods” her whole life (although she assumed it was normal and was too embarrassed to talk with anyone about it) and she also mentioned a “bleeding-issue” after natural childbirth which required a transfusion. Upon further questioning about their family history, she mentioned that two years ago her younger brother died after falling out of a tree due to severe bleeding.

You decide to check both the son and mother for the presence of a hereditary bleeding disorder.

For those interested in getting into a bit of protein biochemistry....

Start on PAGE 22: Welcome to your Patient!



Jeff, 46 year old American male of Scots descent has come to you for a second opinion...

Diagnosis: Cirrhosis of the liver and Type 1 Diabetes
due to chronic alcoholism

Key Symptoms: Elevated liver enzymes, excess ascites fluid and
an enlarged spleen (splenomegaly)

In the two months since his diagnosis, the insulin treatment and significant dietary changes have not seemed to improve things much, indeed his condition has deteriorated (severe fatigue). He claims he is not, nor has he been an alcoholic – used to have 1-2 glasses of beer a few times a week and had not had anything for a while before being diagnosed – *so he really doesn't think this diagnosis makes any sense.*

This case is based on a Medical Mystery published in the Washington Post and in an interview with Jeff on a Seattle TV News broadcast.

Welcome to your Patient(s)!

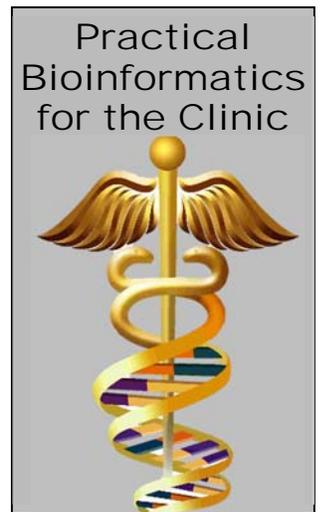


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You decide to check both the son and mother for the presence of a hereditary bleeding disorder.

Clinical Research

1. **Search MedGen with Hemophilia[ExactTitle]** to retrieve the disorder overview record.

In the “**Term Hierarchy**” section you can see more specific sub-types of “Hemophilia” -two major forms of hereditary disease are displayed. **Click the names of the diseases to open the MedGen records to read about each hereditary sub-type.**

WHAT IS/ARE THE MAJOR DIFFERENCES IN THE TWO SUB-TYPES OF HEREDITARY HEMOPHILIA?

2. To confirm a diagnosis of hereditary hemophilia and distinguish between the two major sub-types, **what laboratory test(s) could you order?**

(**Hint:** On the specific sub-type pages, check the **GeneReviews>Diagnosis** link and read through the sections.)

➤ **Lab Test results:** http://bit.ly/JamesRavens_LabTestResults

NOTES:

BASED ON YOUR RESEARCH AND THE RESULTS OF THE LAB TESTS, WHAT DO YOU THINK IS WRONG WITH JAMES AND RAVEN?

On the MedGen page for Hemophilia, in the “**Term Hierarchy**” section click the name of the disorder suggested by the results of the Lab Tests - this will take you to the page for James’ particular disorder.

3. To assist you further in learning about this disorder, there are links to many relevant publications available in PubMed as well as to Clinical Trials. **Write in some PMIDs for interesting PubMed-listed articles.**

Click on the “**ClinicalTrials.gov**” link. **Are there any interesting Clinical Trials currently recruiting patients (such as a Gene Therapy trial)?**

Back on the MedGen page, you can find links to some helpful patient education materials linked from this page in the “**Consumer Resources**” section on the right-hand side of the page. **Write the names of some links to potentially helpful information you might like to share.**

Genetics Research

3. From the MedGen record, **find a genetic test that you could order for them. Write in the GTR ID.** (This should be a CLIA-certified clinical lab, with the nearest one to them in the state of Minnesota.)

➤ Genetic Test results: http://bit.ly/JamesRavens_GeneticTestResults

NOTES:

WHAT ARE THE RESULTS OF THE TEST FOR MOTHER AND SON - SPECIFIC GENE AND VARIATIONS?

HOW MAY THESE DIFFERENCES MANIFEST THEMSELVES AS DIFFERENCES IN THE SYMPTOMS/PHENOTYPE BETWEEN THE MOTHER AND SON (HINT: A FEMALE, XX, AND A MALE, XY)?

Molecular Biology Research

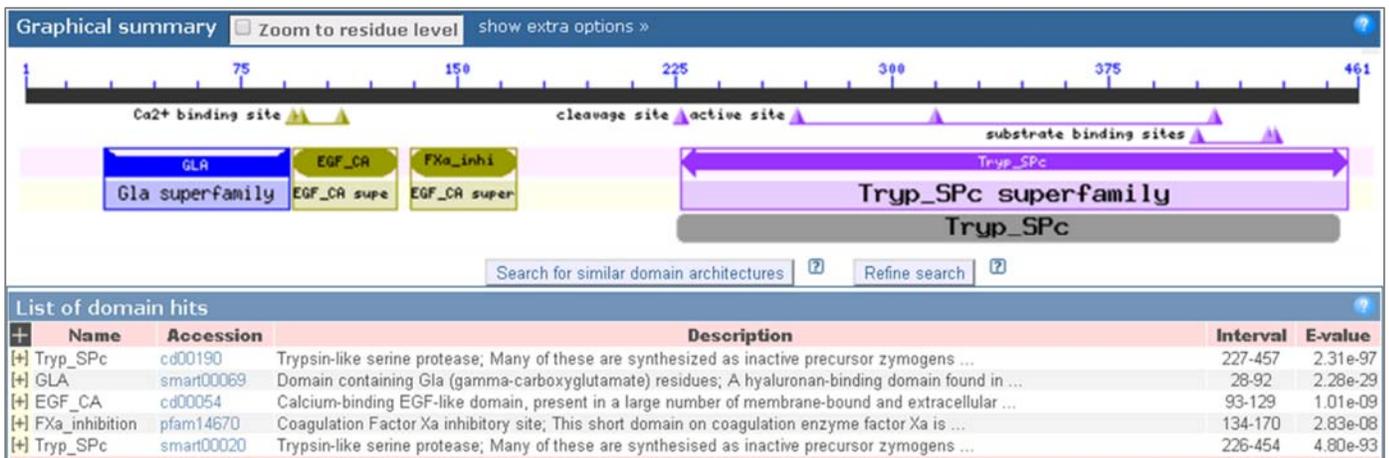
4. Back on the MedGen record, **click the Gene link for the one identified as having a variant in James and Raven. WHAT DOES THIS GENE NORMALLY DO?**

5. Scroll down to the “**Pathways from BioSystems**” section, **click the link for “Blood Clotting Cascade, organism-specific biosystem (from WikiPathways)”** to see the biological pathway in which the affected gene participates OR click here to see a **classic graphic of this pathway** from Lodish’s classic textbook Molecular Cell Biology (from NCBI’s Bookshelf).

WHAT DO YOU THINK THIS GENE’S MAJOR ROLE IS? WHY DO YOU THINK IT IS SO IMPORTANT?

6. Back on the Gene record, let’s take a look at a RefSeq Protein determine a potential effect for the identified genetic variant. **Click the RefSeq Proteins link** and then find and **click the “preprotein” isoform** (the one that is initially made and could be processed into the fully-functioning protein).

Click “Identify Conserved Domains” to see defined regions on the protein sequence.



WHERE IN THE ABOVE SCHEMATIC IS JAMES AND RAVEN’S GENETIC VARIANT LOCATED?

Make sure you are using the position of the affected amino acid in the protein sequence.

If you don't remember what it is.....go back and look at your notes or the Genetic Test Lab Report.

WHAT WOULD YOU PREDICT THIS GENETIC VARIATION MIGHT DO TO THE PROTEIN STRUCTURE AND FUNCTION?



SUMMARY: WHAT IS HAPPENING IN JAMES?

**WHY IS RAVEN'S "PHENOTYPE" (SYMPTOMS) DIFFERENT FROM JAMES'?
SHOULD RAVEN BE CONCERNED?**

- InfoGraphic Answer: http://bit.ly/JamesRavens_Answer

Welcome to your Patient!

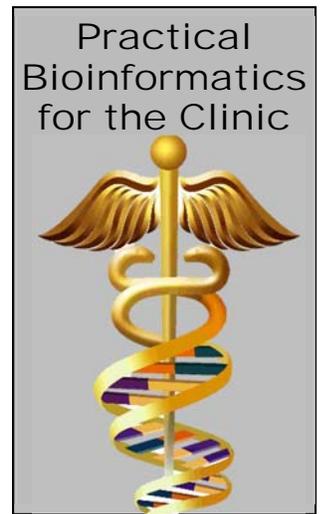


Jeff, 46 year old American male of Scots descent has come to you for a second opinion...

Diagnosis: Cirrhosis of the liver and Type 1 Diabetes due to chronic alcoholism

Key Symptoms: Elevated liver enzymes, excess ascites fluid and an enlarged spleen (splenomegaly)

In the two months since his diagnosis, the insulin treatment and significant dietary changes have not seemed to improve things much, indeed his condition has deteriorated (severe fatigue). He claims he is not, nor has he been an alcoholic – used to have 1-2 glasses of beer a few times a week and had not had anything for a while before being diagnosed – *so he really doesn't think this diagnosis makes any sense.*



Clinical Research

1. **Search MedGen with these symptoms:**

cirrhosis AND diabetes AND ascites AND splenomegaly

WHAT IS A POSSIBLE DIAGNOSIS FOR JEFF?

2. To **confirm this diagnosis, WHAT LABORATORY TEST(S) WOULD YOU ORDER?**
(Hint: Check the **GeneReviews>Diagnosis** Link or take a look at PubMed articles listed in the **Recent clinical studies>Diagnosis** section.)

➤ **Lab Test results:** http://bit.ly/Jeffs_LabTestResults

NOTES:

Based on your research and the results of the Lab Test, **WHAT DO YOU THINK IS WRONG WITH JEFF?**

To assist you further in learning about this disorder, there are links to many relevant **publications available in PubMed** as well as to **Clinical Trials**. In addition, you can find links to some helpful **Patient Education Materials**.



You discuss the diagnosis and hand Jeff some Patient Education materials.

He has heard that this is may be a genetic condition. He has a twin sister and a brother and is concerned that they may be effected.

He'd like to have a DNA test to see if the cause of his disease is genetic and also see if he can find out specifically what is wrong with him on a personal level, even though it may not change his prognosis or therapy.

Genetics Research

3. From the MedGen record, **find a genetic test that you could order for him.**
(For this case-study, this should be a CLIA-certified clinical lab in California.)

➤ **Genetic Test results:** http://bit.ly/Jeffs_GeneticTestResults

NOTES:

WHAT IS THE SPECIFIC GENE AND VARIATION IDENTIFIED IN JEFF?

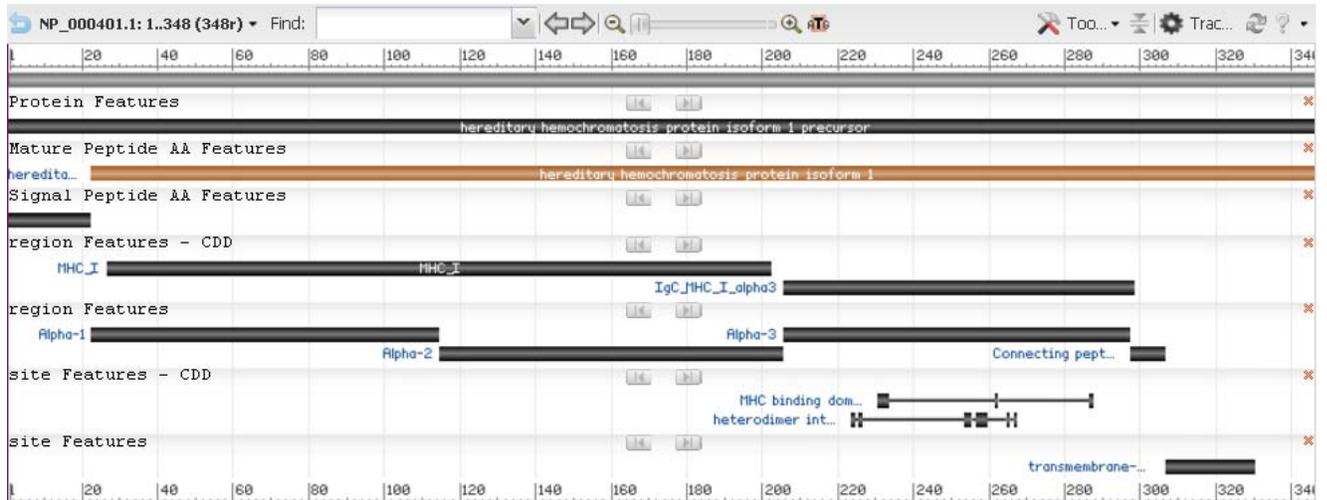
Molecular Biology Research

4. Back on the MedGen record, **click the gene link for the one identified as having a variant in Jeff.**
WHAT DOES THIS GENE NORMALLY DO?

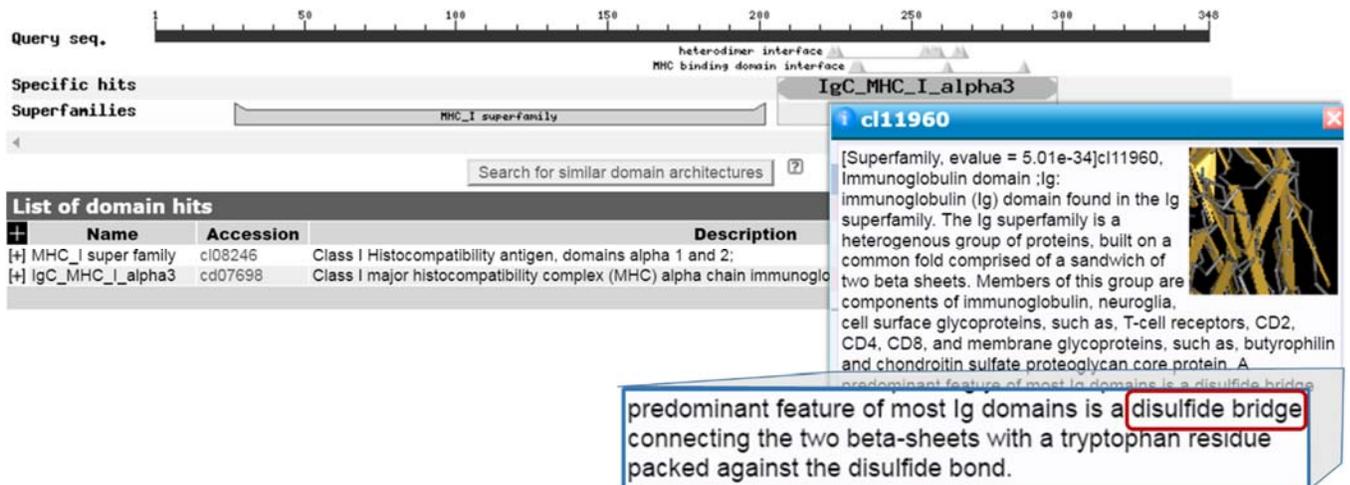
5. From the Gene record, scroll down to the Expression section to see in which tissues this gene is expressed and also where it functions.

WHICH TISSUES FOUND TO EXPRESS THIS GENE CORRELATE WITH SOME OF JEFF'S SYMPTOMS?

6. From the Gene record, click the RefSeq Proteins link, then the one entitled "isoform 1 precursor". (hint, hint – it's at the bottom of the list) Click Graphics to see defined regions on the protein sequence.



Then, click "Identify Conserved Domains" to display a graphic displaying more specific information about the main functional regions on this protein.



Based on the location of Jeff's genetic variant and the description of the functional regions, WHAT EFFECT MIGHT THE VARIANT HAVE ON THE PROTEIN STRUCTURE &/OR FUNCTION?

7. From both the Gene and Protein records, there are links to 3D Structures....**examine a structure to see precisely where the amino acid affected by the genetic variation is located.**

➤ An annotated 3D Structure: http://bit.ly/Jeffs_StructurePicture

NOTES:

WHAT DO YOU THINK THE CHANGE IN AMINO ACID MIGHT DO TO THE PROTEIN?



SUMMARY: WHAT IS WRONG WITH JEFF?

➤ InfoGraphic Answer: http://bit.ly/Jeffs_Answer

HOW TO KEEP UP WITH IT ALL & LEARN MORE

1) Outreach & Education Site:

<https://www.ncbi.nlm.nih.gov/home/learn.shtml>

2) News & Social Media Sites



3) Courses, Webinars & Tutorials



4) Help & Technical Support: info@ncbi.nlm.nih.gov

NCBI Workshops | References & Resources

THE NATIONAL CENTER FOR BIOTECHNOLOGY INFORMATION, a.k.a. THE “NCBI”

<http://www.ncbi.nlm.nih.gov>

ABOUT THE NCBI

About the NCBI FactSheet: ftp://ftp.ncbi.nih.gov/pub/factsheets/Factsheet_AboutNCBI.pdf

NCBI Handbook Chapter: <http://www.ncbi.nlm.nih.gov/books/NBK148949/>

YouTube 20th Anniversary Video: <https://www.youtube.com/watch?v=kyKGn6lh3EM>

List of many of NCBI's Databases: <http://www.ncbi.nlm.nih.gov/gquery/>

NCBI Resources Factsheet: ftp://ftp.ncbi.nih.gov/pub/factsheets/Factsheet_NCBI_Overview.pdf

Outreach & Education Site: <http://www.ncbi.nlm.nih.gov/education/>

NCBI NEWS & SOCIAL MEDIA:

NCBI News Site: <http://www.ncbi.nlm.nih.gov/news>

NCBI Insights Blog: <http://ncbiinsights.ncbi.nlm.nih.gov>

Facebook: <https://www.facebook.com/ncbi.nlm>

Twitter: [@NCBI](https://twitter.com/NCBI)

YouTube Channel: <https://www.youtube.com/user/NCBINLM>

LinkedIn: <https://www.linkedin.com/company/3595640>

EMail Address: info@ncbi.nlm.nih.gov

RESOURCES MENTIONED IN TODAY'S PRESENTATION

CLINICAL RESEARCH

MedGen – Aggregated information about medical genetic conditions and phenotypes

Homepage: <http://www.ncbi.nlm.nih.gov/medgen>

Help Doc: <http://www.ncbi.nlm.nih.gov/medgen/docs/help/>

NCBI Handbook Chapter: <http://www.ncbi.nlm.nih.gov/books/NBK159970/>

FactSheet: ftp://ftp.ncbi.nlm.nih.gov/pub/factsheets/Factsheet_MedGen.pdf

Genetic Testing Registry (GTR) – NIH's registry of genetic tests and laboratories

Homepage: <http://www.ncbi.nlm.nih.gov/gtr>

Help Doc: <http://www.ncbi.nlm.nih.gov/gtr/docs/help/>

YouTube Playlist: <http://www.youtube.com/playlist?list=PL1C4A2AFF811F6F0B>

FactSheet: ftp://ftp.ncbi.nih.gov/pub/factsheets/Factsheet_GTR.pdf

CLINICAL DECISION SUPPORT & PATIENT EDUCATION MATERIALS

PubMed – A database of published biomedical and scientific citations and abstracts

Homepage: <http://www.ncbi.nlm.nih.gov/pubmed>

Help Doc: <http://www.ncbi.nlm.nih.gov/books/NBK3827/>

YouTube Playlist: <https://www.youtube.com/playlist?list=PLBD13A2628C7A9965>

NCBI Handbook Chapter: <http://www.ncbi.nlm.nih.gov/books/NBK153385/>

FactSheet: ftp://ftp.ncbi.nih.gov/pub/factsheets/Factsheet_PubMed.pdf

PubMed Central (PMC) – A database of free, full-text biomedical and scientific manuscripts

Homepage: <http://www.ncbi.nlm.nih.gov/pmc>

Help Doc: <http://www.ncbi.nlm.nih.gov/books/NBK3825/>

YouTube 10th Anniversary Video: <https://www.youtube.com/watch?v=Z0oPcHr9bE8>

NCBI Handbook Chapter: <http://www.ncbi.nlm.nih.gov/books/NBK153388/>

Books – Free books, reports and documents about life science and healthcare.

Homepage: <http://www.ncbi.nlm.nih.gov/books>

Help Doc: <http://www.ncbi.nlm.nih.gov/books/NBK3833/>

NCBI Handbook Chapter: <http://www.ncbi.nlm.nih.gov/books/NBK169440/>

FactSheet: ftp://ftp.ncbi.nih.gov/pub/factsheets/Factsheet_Books.pdf

Books/GeneReviews – Expert-authored, peer-reviewed information about human diseases

GeneReviews “Homepage”: <http://www.ncbi.nlm.nih.gov/books/NBK1116/>

PubMed Health – Information for consumers and clinicians on diseases and conditions.

Homepage: <http://www.ncbi.nlm.nih.gov/pubmedhealth/>

NLM’s ClinicalTrials.gov – A registry and results database of clinical studies

Homepage: <http://clinicaltrials.gov>

NLM’s Medline Plus – Consumer information about diseases, conditions, and wellness issues

Homepage: <http://www.nlm.nih.gov/medlineplus/>

NLM’s Genetics Home Reference – Consumer-friendly information about genetic variations and health

Homepage: <http://ghr.nlm.nih.gov>

JHU’s OMIM – A compendium of human genes and genetic phenotypes

Homepage: <http://www.ncbi.nlm.nih.gov/omim> or <http://www.omim.org>

MOLECULAR ETIOLOGY RESEARCH

Gene – Aggregated information with links to genomic, expression, homolog, structure and function data

Homepage: <http://www.ncbi.nlm.nih.gov/gene>

Help Doc: <http://www.ncbi.nlm.nih.gov/books/NBK3839/>

NCBI Handbook Chapter: <http://www.ncbi.nlm.nih.gov/books/NBK169435/>

FactSheet: ftp://ftp.ncbi.nih.gov/pub/factsheets/Factsheet_Gene.pdf

Conserved Domains Database (CDD) – A database of protein domains with sequence fingerprints

Homepage: <http://www.ncbi.nlm.nih.gov/cdd>

Help Doc: http://www.ncbi.nlm.nih.gov/Structure/cdd/docs/cdd_how_to.html

NCBI Handbook Protein Resources Chapter: <http://www.ncbi.nlm.nih.gov/books/NBK169830/>

FactSheet: ftp://ftp.ncbi.nih.gov/pub/factsheets/Factsheet_CDD.pdf

Structure – A database of 3D macromolecular structures and complexes from the Protein Database

Homepage: <http://www.ncbi.nlm.nih.gov/structure>

Help Doc: http://www.ncbi.nlm.nih.gov/Structure/MMDB/docs/mmdb_help.html

NCBI Handbook Protein Resources Chapter: <http://www.ncbi.nlm.nih.gov/books/NBK169830/>

FactSheet: ftp://ftp.ncbi.nih.gov/pub/factsheets/Factsheet_Structure.pdf

EMERGING RESOURCE

ClinVar – A collection of assertions about the relationships of genomic variations with human health

Homepage: <http://www.ncbi.nlm.nih.gov/clinvar>

Help Doc: <http://www.ncbi.nlm.nih.gov/clinvar/docs/help/>

NCBI Handbook Chapter: <http://www.ncbi.nlm.nih.gov/books/NBK174587/>

FactSheet: ftp://ftp.ncbi.nih.gov/pub/factsheets/Factsheet_ClinVar.pdf