

DECIPHER Tutorial

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The clinical details and the variant data presented in this worksheet are fictitious. They have been designed to assist you in learning how to upload data and use DECIPHER for analysis. DECIPHER has been designed so that usually the lab scientists will use the variant data to create an entry for an individual and this entry will then be edited by the clinician to add the clinical phenotype.

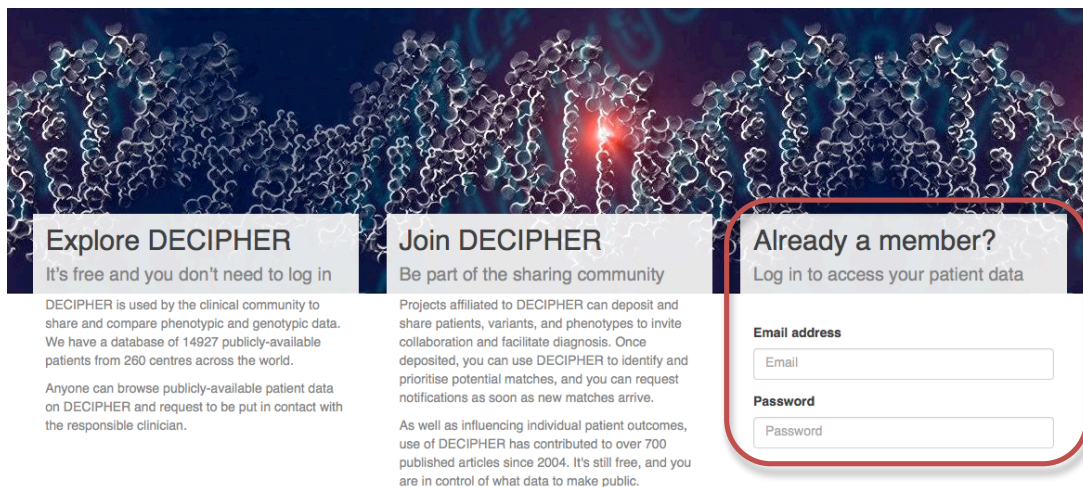
Please log into DECIPHER.

Web Address: <https://decipher.sanger.ac.uk>

Username: <as provided>

Password: <as provided/set up>

Software Requirements: Recent Internet Browser (IE10 or higher or newer versions of Firefox and Chrome). Will not work on IE8 or IE9.



Explore DECIPHER
It's free and you don't need to log in

DECIPHER is used by the clinical community to share and compare phenotypic and genotypic data. We have a database of 14927 publicly-available patients from 260 centres across the world.

Anyone can browse publicly-available patient data on DECIPHER and request to be put in contact with the responsible clinician.

Join DECIPHER
Be part of the sharing community

Projects affiliated to DECIPHER can deposit and share patients, variants, and phenotypes to invite collaboration and facilitate diagnosis. Once deposited, you can use DECIPHER to identify and prioritise potential matches, and you can request notifications as soon as new matches arrive.

As well as influencing individual patient outcomes, use of DECIPHER has contributed to over 700 published articles since 2004. It's still free, and you are in control of what data to make public.

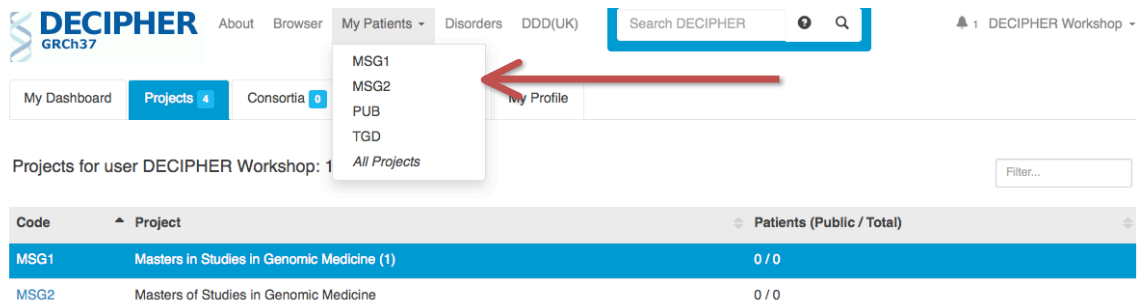
Already a member?
Log in to access your patient data

Email address

Password

Navigate to your project

Every user in DECIPHER is assigned to a project which is usually their place of work. Every project has users with designated roles of Clinician, Lab Scientist or member with read-write or read-only privileges. **For the purposes of this exercise your username above has clinician privileges to the MSG1 or MSG2 projects with read-write permissions.**



The screenshot shows the DECIPHER web interface. At the top, there is a navigation bar with the DECIPHER logo, 'About', 'Browser', 'My Patients', 'Disorders', and 'DDD(UK)'. A search bar is also present. Below the navigation bar, there are tabs for 'My Dashboard', 'Projects 4', and 'Consortia 0'. A dropdown menu is open under 'My Patients', showing options for 'MSG1', 'MSG2', 'PUB', 'TGD', and 'All Projects'. A red arrow points to the 'MSG1' and 'MSG2' options. Below the dropdown, there is a section titled 'Projects for user DECIPHER Workshop: 1' with a 'Filter...' button. A table below shows the following data:

Code	Project	Patients (Public / Total)
MSG1	Masters in Studies in Genomic Medicine (1)	0 / 0
MSG2	Masters of Studies in Genomic Medicine	0 / 0

Click on the “My Patients” link from the top of the page and choose either MSG1 or MSG2 (only one will be shown to you). This will load your patients from this project on the page (scroll down).

Create a patient record

Steps to creating a DECIPHER Patient

- 1. Patient Data:** Some basic information about the patient is required to be able to create a record in DECIPHER. These include age of the patient, sex, an internal reference that links this record in DECIPHER to the notes in the clinic, parental affected status, additional notes and so on. These fields may be edited at any time after the record has been created.
- 2. Variant data** – These are the variants (sequence or copy-number variants) that will have been identified by the reporting lab as the most likely finding from genetic testing. When these data are uploaded they are only visible to the submitting centre, unless the consent box is checked (see 6 below). The minimum information necessary to create a variant record are as follows:

- **For CNV:** Chromosome, Start, Stop, mean ratio and assembly (GRCh37).
 - **For Sequence variants:** Chromosome, Start, Reference Allele, Alternate Allele, Transcript (Ensembl or RefSeq) and assembly (GRCh37).
 - In addition, information about inheritance, pathogenicity and contribution of variant to phenotype may also be provided.
- 3. Phenotype** – usually the clinician will enter the patient’s phenotype selecting appropriate terms from the DECIPHER ontology selector. When these data are uploaded they are only visible to the submitting centre, unless the consent box is checked (see 5 below).
- 4. Editing/Revising the patient record** – patient information can be updated or revised at any time after creation as and when more information becomes available. If the patient has provided consent for their data to be shared anonymously, these changes are made immediately available to all users.
- 5. Reports** – both clinical and family reports can be printed from the DECIPHER entry for a given patient. The clinical report is a detailed report for the genetics record and shows minimal information about the position of the deposited variant and the karyotype.
- 6. Consent** – When the clinician discusses the results with the patient and/or family, this is an ideal opportunity to discuss the DECIPHER project and enquire whether the patient/family would like the result to be made anonymously available. If consent is given, this will enable the clinician to see whether the rearrangement overlaps with other patients (and if so to compare phenotypes). After discussion with the family, the clinician could then contact clinicians with similar patients in other centres to exchange information. This step facilitates the identification and delineation of new syndromes as well as encourages collaboration between clinician and researchers for diagnosis and new findings.

The following examples demonstrate how to create a patient record in DECIPHER with variant and phenotype information and analysing this information.

Example 1. Copy-Number Variant



Sofia is a 7 year old girl whom you have seen in your genetics clinic. She is the second child of healthy unrelated parents. She has periorbital fullness, bulbous nasal tip, long philtrum, wide mouth, full lips, full cheeks and small widely spaced teeth, supraaortic stenosis (SVAS), mild to moderate intellectual disability with relative cognitive strengths in verbal short term memory and

in language but extreme weakness in visuospatial construction (writing, drawing, pattern construction). Distinctive behavioural characteristics include anxiety, attention deficit hyperactivity disorder (ADHD), and overfriendliness. She has an apparently normal female karyotype, 46,XX.

You arrange a genomic array analysis with the following result:

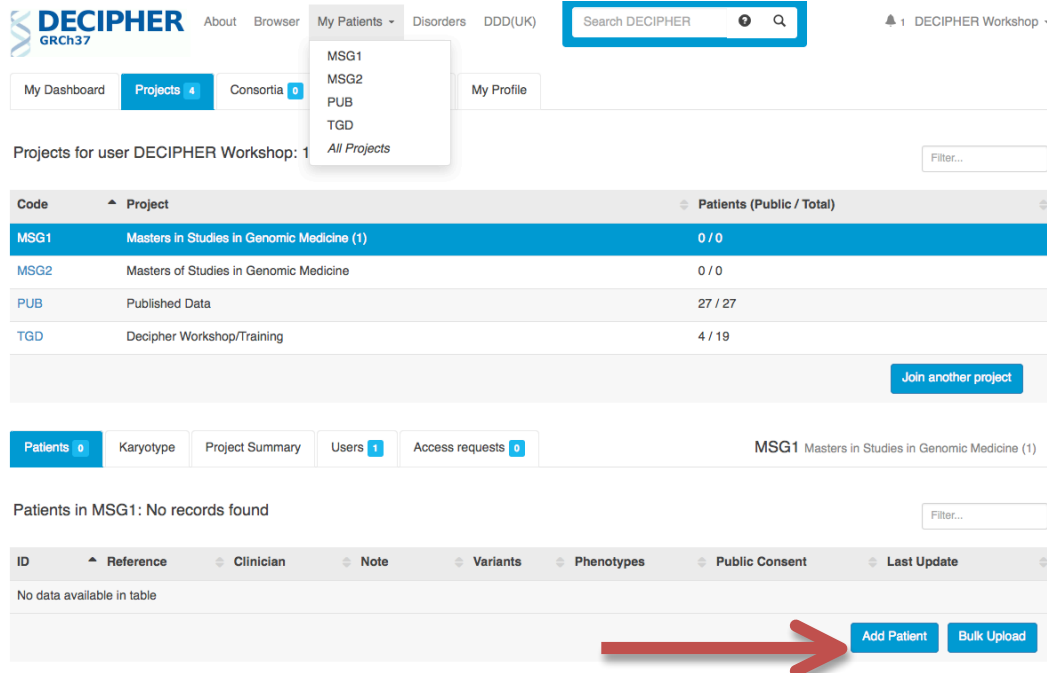
Array findings

Sophia was found to have a deletion on chromosome 7 starting at 71970679 and ending at 74254837 with a mean ratio of -0.95. You have conducted a trio analysis and arrays in the parents gave normal results. You have verified this deletion with aCGH and testing of both parents has revealed that this is a '*de novo*' deletion in Sophia.

Clinical features

Short stature, malar flattening, Everted lower lip, Small teeth, Aortic stenosis, intellectual disability, Short attention span, hyperactivity, short nose, delayed speech and language development

Create a patient record by clicking on Add Patient.



The screenshot shows the DECIPHER GRCh37 web application. The user is logged in as 'DECIPHER Workshop'. The 'My Patients' dropdown menu is open, showing options for MSG1, MSG2, PUB, TGD, and All Projects. The 'Projects' tab is active, displaying a table of projects for the user. The table has columns for Code, Project, and Patients (Public / Total). The MSG1 project is highlighted. Below the table, there is a 'Join another project' button. The 'Patients' tab is selected, showing 'Patients in MSG1: No records found'. At the bottom of the page, there are two buttons: 'Add Patient' and 'Bulk Upload'. A red arrow points to the 'Add Patient' button.

Code	Project	Patients (Public / Total)
MSG1	Masters in Studies in Genomic Medicine (1)	0 / 0
MSG2	Masters of Studies in Genomic Medicine	0 / 0
PUB	Published Data	27 / 27
TGD	Decipher Workshop/Training	4 / 19

ID	Reference	Clinician	Note	Variants	Phenotypes	Public Consent	Last Update
No data available in table							

You will be presented with a form in which you can enter the data for creating a patient record.

Add Patient ×

Age at initial presentation	7
Chromosomal sex *	46XX
Internal reference number or ID *	<My Name>
Mother is *	Unaffected with related or similar ph
Father is *	Unaffected with related or similar ph
Responsible clinician	DECIPHER Workshop
Note	
Public consent *	No

1. Enter the patient details with a unique internal reference (**your email address**) and Chromosomal Sex.
2. Choose parental affected status as “Unaffected with related or similar phenotype” for both parents.
3. Set “Responsible clinician” to your name from the dropdown.
4. Choose “No” for Public consent
5. Click “Save” to create a patient record.

Your patient record will be created as shown below.

Projects » TGD » Patient 300754 Print report

[Overview](#)
[Photos 0](#)
[Genotype 0](#)
[Phenotype 0](#)
[Karyotype](#)

[Citations 0](#)
[Contacts](#)

Age at initial presentation	7
Chromosomal sex	46XX
Internal reference number or ID	Jawahar
Mother is	Unaffected with related or similar phenotype
Father is	Unaffected with related or similar phenotype
Responsible clinician	DECIPHER Workshop
Note	
Public consent	No

[Edit Overview](#)

- Click on Genotype Tab

Overview Photos **0** Genotype **0** Phenotype **0** Karyotype Citations **0** Contacts

Copy-Number Variants: No records found Filter...

Location Interval Mean Ratio Genes Inheritance Pathogenicity Contribution Dosage (DS) Score DS Sampling Probability Shared Links

No data available in table

Add CNV

- Click on “*Add CNV*” to enter coordinate data

Add CNV

Chromosome *	7
Start *	71970679
End *	74254837
Genome assembly *	GRCh37/hg19
Mean ratio *	-0.95
or Copy Number	-select-
Confirmed by	Array
Inheritance *	Unknown
Pathogenicity	-select-
Contribution	-select-
Shared *	× TGD

- Fill in the popup window. Please note that you can either enter a Mean Ratio value or Copy Number. When completed click *save*

Overview Photos 0 Genotype 1 Phenotype 9 Karyotype Citations 0 Contacts

Copy-Number Variants: 1 to 1 of 1

Location	Interval	Mean Ratio	Genes	Inheritance	Pathogenicity Contribution ?	Dosage (DS) Score ?	DS Sampling Probability ?	Shared ?	Links
7 71970679 74254837	2.28 Mb	-0.95	52	Unknown	Click Here	-	-		View... Add CNV

- Click on the “Phenotype” tab to add the phenotypes recorded in “Clinical Features” above.

Human Phenotype Ontology

- Abnormality of head and neck
 - Abnormality of the head
 - Abnormality of the face
 - Abnormality of the mouth
 - Abnormality of the lip
 - Abnormality of lower lip
 - Everted lower lip vermillion (Everted lower lip)**
- Abnormality of the periorbital region
 - Abnormality of the eyelid
 - Ectropion
 - Ectropion of lower eyelids (Everted lower eyelids)

Patient 9

Patient phen

Phenotype

Aortic valve ste

Everted lower l

Global developo

Type in a phenotype term in the search box and click return. All terms matching the search term are shown highlighted. Choose the term you wish to add to the patient and either drag to the patient box on the right or click on the icon (without hat) to add to patient. Repeat for all the observed clinical features.

Human Phenotype Ontology

- Abnormality of blood and blood-forming tissues
- Abnormality of connective tissue
- Abnormality of head and neck
- Abnormality of metabolism/homeostasis
- Abnormality of prenatal development or birth
- Abnormality of the abdomen
- Abnormality of the breast
- Abnormality of the cardiovascular system
- Abnormality of the ear
- Abnormality of the endocrine system
- Abnormality of the eye
- Abnormality of the genitourinary system
- Abnormality of the immune system
- Abnormality of the integument
- Abnormality of the musculature
- Abnormality of the nervous system
- Abnormality of the respiratory system
- Abnormality of the skeletal system
- Growth abnormality
- Neoplasm

Patient 9 Mother 0 Father 0

Patient phenotypes

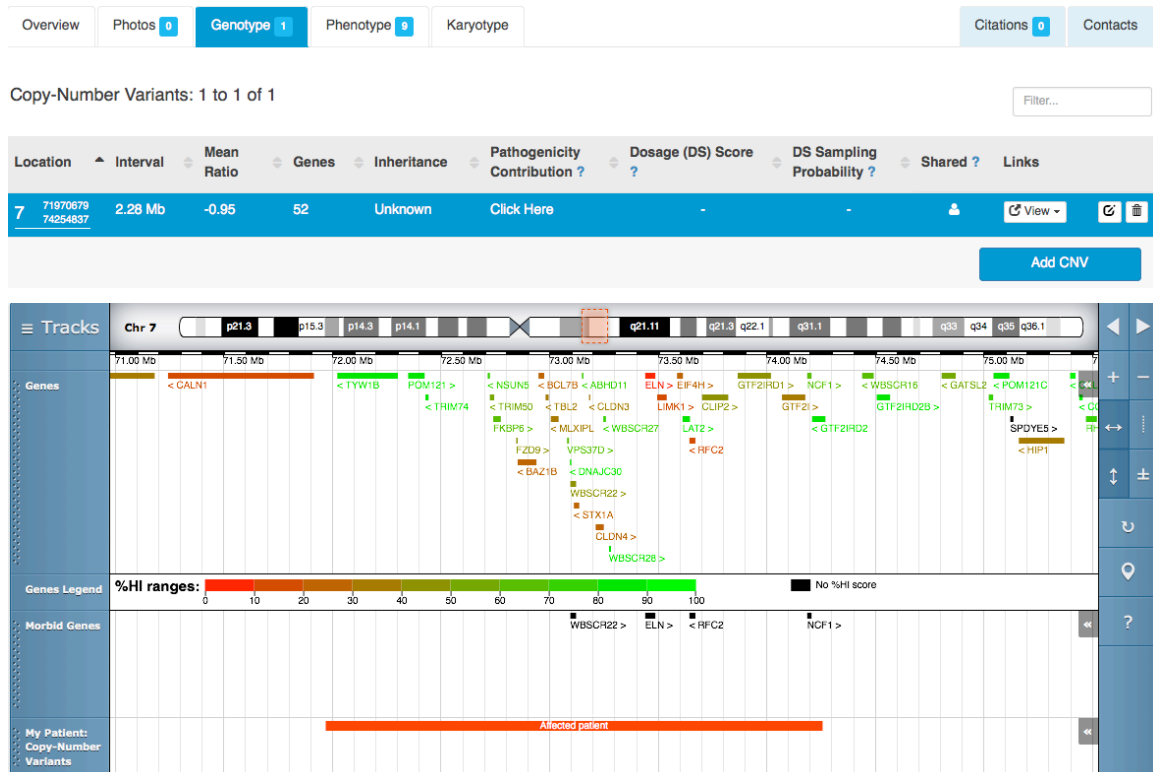
Phenotype	Observation	Code
Aortic valve stenosis	present	HP-0001650
Everted lower lip vermillion	present	HP-0000232
Global developmental delay	present	HP-0001263
Hyperactivity	present	HP-0000752
Intellectual disability	present	HP-0001249
Malar flattening	present	HP-0000272
Microdontia	present	HP-0000891

Analyse Patient

The patient record has now been created in DECIPHER. You can now analyse the patient variant and phenotype by finding genes affected by this CNV, find other patients in the database with overlapping deletions and shared phenotypes as well as visually examine the deletion seen in this patient using the built-in Genovese genome browser.

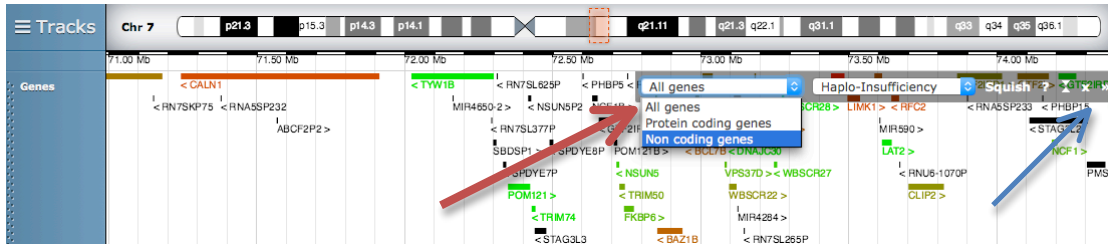
- Click on the “Genotype” tab, then click on the “Browser” tab on the page to load the Genovese browser. For a detailed look at genovese (not necessarily in this session) please refer to:

<https://decipher.sanger.ac.uk/assets/pdfs/BrowserGuide.pdf>



The genome browser has a number of tracks that may be turned on or off. By default the tracks shown are: genes, Patient CNVs, Patient SNVs (if any), DECIPHER CNVs, DECIPHER SNVs, Syndromes, Population CNVs and others. The genes are coloured by their prediction to be haploinsufficient. Reds indicate that the gene is likely to be dosage sensitive and that even disrupting a single copy of the gene could cause total loss of function of that gene.

Each track has a chevron “<<” on the right side. Click on these to see if there are additional filters available to fine tune the display. Shown below are the filters available for the genes track.



Click on the filters for the “DECIPHER: Copy-Number Variants” track.

Can you adjust the filters to show only “Losses” that are “Benign” and “Under 5Mb” in “All Patients”? Are there many (or any!) copy-number deletions that overlap the CNV seen in your patient? Change the filter to show only “Pathogenic” “losses”. Are there any recorded in this region that overlap your patient?

Other Questions?

- Click on the “Genes” tab next to “Browser”. This will load up a table of genes that overlap the patient variant.
 - *Question: How many genes are affected by this CNV? Hint: look at the number next to the tab that says “Genes”.*
 - *Answer Here:*
- Click on the checkboxes (OMIM, Morbid) to filter genes that are known to be associated with disease phenotype.

Genes: 1 to 4 of 4 (out of 52 total) Show: OMIM Morbid DDG2P Protein coding

Name	Location	Description	OMIM	Morbid	DDG2P ?	%HI ?	Links
ELN	7 73442119 73484237	elastin	✓	✓+	✓	8.62	View
RFC2	7 73645829 73668774	replication factor C (activator 1) 2, 40kDa	✓	✓	-	14.42	Ensembl HGNC
WBSR22	7 73097355 73119491	Williams Beuren syndrome chromosome region 22	✓	✓	-	49.23	UCSC Uniprot
NCF1	7 74188309 74203659	neutrophil cytosolic factor 1	✓	✓	-	67.53	View

- Morbid Genes are those known to be associated with a disease phenotype. Click on the “tick+” on the row for the ELN gene. This will pop-up a list of diseases known to be associated with this gene.

○ *Question: What diseases are associated with the ELN gene that overlaps the deletion found in your patient?*

○ *Answer here:*

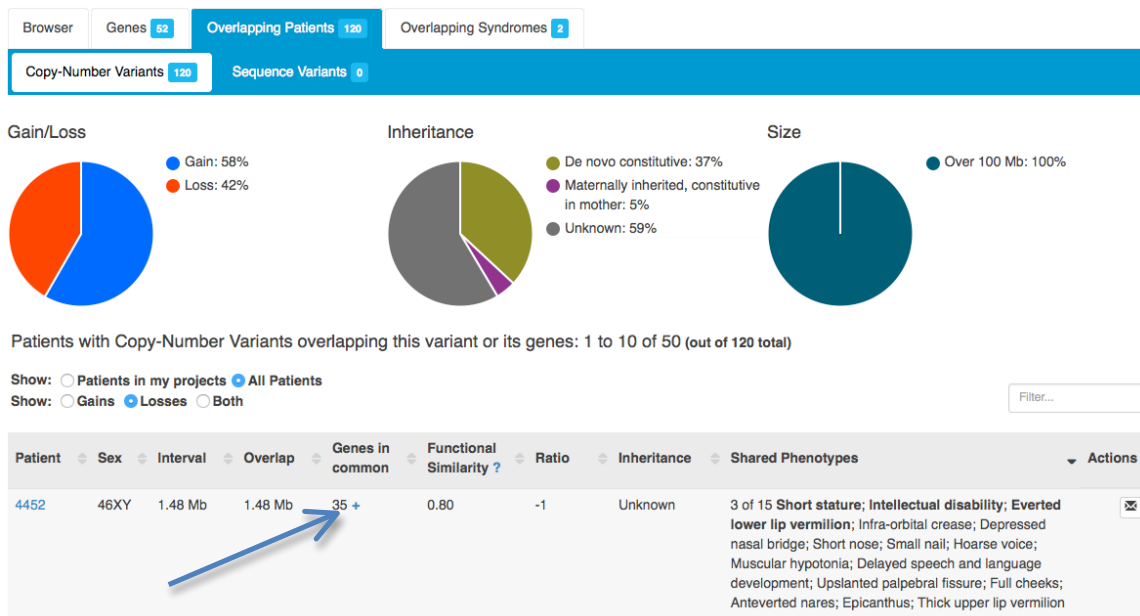
- Haploinsufficiency is a prediction of the ability of a gene to continue to retain function when a mutation disrupts one copy of the gene. Uncheck the OMIM and Morbid boxes and click on the “%HI” column header to sort by this value. Lower values (e.g. 0-10%) indicate a gene is more likely to exhibit haploinsufficiency, higher values (e.g. 90-100%) indicate a gene is more likely to NOT exhibit haploinsufficiency.

- *Question: Does your patient CNV affect any haploinsufficient gene/s? If so, which one/s? Which is the most haploinsufficient gene in this list? Hint: Lowest values. What diseases are associated with the two most haploinsufficient genes in the list? Hint: Click on the “tick” on the morbid column to be taken to the OMIM website where you can find more information about the phenotype.*

○ *Answers here:*

Information: Find out more about the genes by clicking on the “view” button and going to various external resources.

- Click on “Overlapping Patients” tab next to the “Genes” tab.



Sort the table of overlapping patients on “shared phenotypes” by clicking on the “shared phenotypes” so that most shared phenotypes are shown first and in **bold**.

Question: Are there any patients in DECIPHER with more than 2 or 3 common phenotypes?

Question: Are any of the previously identified haploinsufficient genes in our patient common to the other patients? Hint: Click on the “+” sign on the genes in common column for any patient to see a list of common genes, then click on the OMIM and Morbid checkboxes to filter.

- Close the common genes window and then click on the “Syndromes” tab

Question: Are there any syndromes that overlap our patients CNV?

Question: What syndrome(s) does Sophia have? Hint: Click syndrome name to get to the syndrome entry.

Browser Genes **52** Overlapping Patients **120** **Overlapping Syndromes 2**

Syndromes with Copy-Number Variants overlapping this variant or its genes: 1 to 2 of 2

Syndrome	Location	Interval	Copy Number	Links
7q11.23 duplication syndrome	7 <small>72744455 74142672</small>	1.40 Mb	3	View
Williams-Beuren Syndrome (WBS)	7 <small>72744455 74142672</small>	1.40 Mb	1	View

Syndromes » [Williams-Beuren Syndrome \(WBS\)](#)

Overview Genotype **1** Citations **6** Phenotypes **7** Karyotype

Last modified: 2014-07-02

Clinical - Characteristic facial features include periorbital fullness, bulbous nasal tip, long philtrum, wide mouth, full lips, full cheeks and small widely spaced teeth. Individuals have mild to moderate intellectual disability or learning difficulties with relative cognitive strengths in verbal short term memory and in language but extreme weakness in visuospatial construction (writing, drawing, pattern construction). Distinctive behavioural characteristics include anxiety, attention deficit hyperactivity disorder (ADHD), and overfriendliness. Congenital heart disease occurs in 80%, with the majority having supravalvular aortic stenosis (SVAS), and a smaller proportion having a discrete supravalvular pulmonary stenosis.

The microdeletion on 7q11.23 encompasses the elastin gene (ELN) which is also mutated in isolated SVAS. Other symptoms include hernias, visual impairment, hypersensitivity to sound, chronic otitis media, malocclusion, small or missing teeth, renal anomalies, constipation, vomiting, growth deficiency, infantile hypercalcemia, musculoskeletal abnormalities, diabetes and a hoarse voice. Risk for hypertension has been linked to the location of the distal deletion breakpoint, with hypertension being significantly less prevalent in WBS patients with a deletion that includes NCF1 (p=0.02), a gene coding for the p47phox subunit of the NADPH oxidase. This likely arises through life-long reduced angiotensin II-mediated oxidative stress.

Also look at the phenotypes associated with this syndrome. Are any of the phenotypes recorded for our patient similar to that often seen in patients with WBS?

Phenotypes: 1 to 7 of 7

Filter...

Phenotype	Code
Aortic valve stenosis	HP:0001650
Everted lower lip vermillion	HP:0000232
Intellectual disability	HP:0001249
Malar flattening	HP:0000272
Microdontia	HP:0000691
Short attention span	HP:0000736
Short stature	HP:0004322

With all the information that you have seen so far in DECIPHER, would you be confident that your patient displays characteristics of WBS? Can you now go back to the patient record, edit the Copy-Number variant and fill up the sections regarding pathogenicity and contribution fields?

Copy-Number Variants: 1 to 1 of 1

Filter...

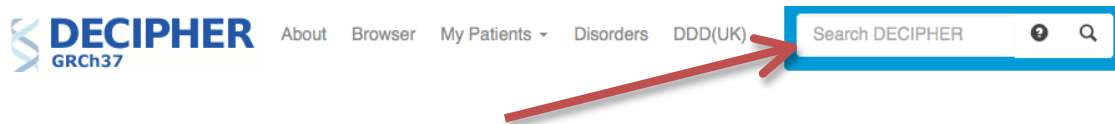
Location	Interval	Mean Ratio	Genes	Inheritance	Pathogenicity Contribution ?	Dosage (DS) Score ?	DS Sampling Probability ?	Shared ?	Links
7 71970679 74254837	2.28 Mb	-0.95	52	De novo constitutive	Click Here	-	-		View  

[Add CNV](#)

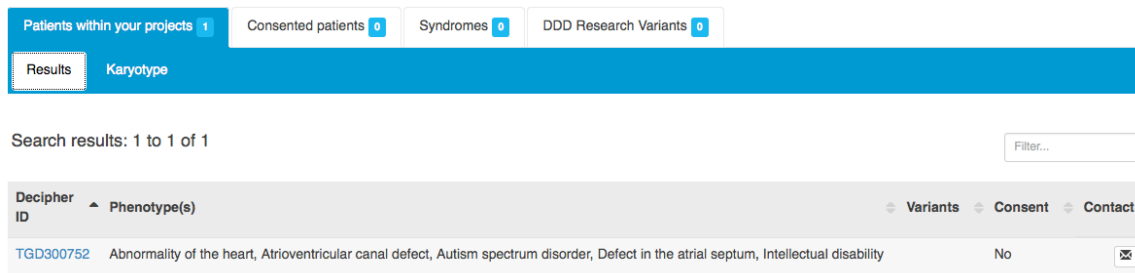
Independent Exercise 1 (25 minutes)

In this exercise we will not be creating a new patient but searching for, and finding an existing patient for analysis.

Click on the “Search DECIPHER” box on the top right of the page. In the box please type in “**ref: Tutorial1**” and click on search. (Please type in exactly as written including the prefix ref:).



The search results will look somewhat like that shown below. Click on the search result to open up a new browser tab with the patient record loaded.



Decipher ID	Phenotype(s)	Variants	Consent	Contact
TGD300752	Abnormality of the heart, Atrioventricular canal defect, Autism spectrum disorder, Defect in the atrial septum, Intellectual disability		No	

The patient is an 8-year-old boy referred for genetic testing with the following clinical features:

Abnormality of the heart, atrioventricular canal defect, autism spectrum disorder, defect in the atrial septum, intellectual disability

The mother also shares “defect in the atrial septum” with the child. Paternal phenotypes recorded include “abnormal cardiogram, facial abnormalities, low-set ears and thrombasthenia”.

Hint: See the phenotype tab for this patient! Parental phenotypes are recorded in separate tabs.

Array CGH analysis has reported two potential variants.

- A de novo 533kb deletion in Chromosome 8 between 11484468 and 1207511.
- Paternally inherited 134 kb duplication in Chromosome 10 between 135243079 and 13577503.

Using Decipher, can you predict which is the CNV that most likely contributes to the patient phenotype? Can you also judge which CNV is likely to be more pathogenic?

Hints: For each of the recorded CNVs, please find out which genes are deleted/duplicated and if any of the genes are known to be associated with a disease phenotype (Morbidity), and are haploinsufficient (HI Score) – see the genes table for each copy-number variant.

Another clue will come from the predicted dosage sensitivity scores (DS Score) column on each of the variant row. A high positive score indicates that the copy-number variant is more likely to be pathogenic than a copy-number variant with a lower positive score, or a negative score.

Also do any of the overlapping patients for each of these CNVs have similar phenotypic presentation? – See the overlapping patients table for each of the variants

More Hints: Click between the two CNVs to load up information relevant to that CNV in the Browser, Genes, Overlapping Patients tabs.

Record your answers below and reasons why:

Exercise 2 (Creating a Sequence Variant in DECIPHER)

In this exercise we will be creating a new patient record, entering sequence variant information and analysing the patient record.

Go to your Project in DECIPHER by Clicking on the “My Patients” tab and choosing either MSG1 or MSG2 (You will see only one of these). This will load up your project and list all patients in your project.

Code	Project	Patients (Public / Total)
MSG1	Masters in Studies in Genomic Medicine (1)	0 / 1
MSG2	Masters of Studies in Genomic Medicine	0 / 1
PUB	Published Data	27 / 27
TGD	Decipher Workshop/Training	4 / 19

[Join another project](#)

[Patients 1](#) | [Karyotype](#) | [Project Summary](#) | [Users 1](#) | [Access requests 0](#)
MSG2 Masters of Studies in Genomic Medicine

Patients in MSG2: 1 to 1 of 1



In the filter box, type in your email address (or the name you used to create the patient record in Exercise 1). This should then only show you your patient.

- Click on this record to open up the patient in a new browser tab.
- Click on the “Genotype Tab”
- Click on “Add Sequence Variant” to open up the input form.

DECIPHER will accept valid HGVS codes to speed up deposition. In the absence of this you can add the location and the mutation yourself. For the purposes of this exercise, please

- Set “Genome assembly” to GRCh37
- Type/paste in the following code into “HGVS”
 - NM_001080517.1:c.3856del
- Moving to the next field on the form will automatically populate items on this form.
- Click on “Save” to create the variant. You will see something like shown below.

Sequence Variants: 1 to 1 of 1 Filter...

Location	Gene	Allele	Transcript	Consequence	Inheritance Genotype	Pathogenicity Contribution ?	Shared ?	Links
3	9517302 9517302	SETD5	T>	ENST00000402198 c.3856delT	frameshift_variant (1286 S/X) p.Ser1286LeuTer84	Unknown	Click Here	View Alert Share Delete

[Add Sequence Variant](#)

This is a summary of the information about the variant including location, transcript and predicted consequence of the variant. There are links further down the row to view this region in other resources such as Ensembl or ExAC. The predicted consequence suggests

that the variant causes a frameshift mutation leading to mis-production of the protein coded by this gene. The highlighted box on the gene name is a link out to the DECIPHER gene pages and provides collated information extracted from other patients that have openly accessible variants in this gene.

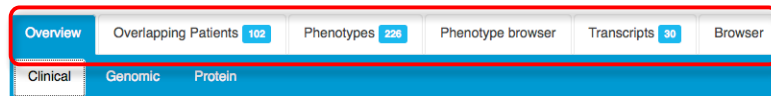
Click on the gene name. This opens up a new browser tab with gene page for this gene (SETD5).

SETD5 3:9439299-9520924

Forward strand gene: SET domain containing 5

Also known as: [ENSG00000168137](#), [FLJ10707](#)

DECIPHER holds 16 sequence variants in this gene, in 16 public patients



OMIM: [615743](#)

Morbid: [615761](#)

Gene Tests: [Click to Search GeneTests](#)

%HI: [12.87 ?](#)

DDG2P: [Yes](#)

LSDB: [Yes](#)

Gene disorders: -

Find literature associated with this gene on PubMed ([Click to Search](#))

Find other entries in DECIPHER that contain this gene ([Click to Search](#))

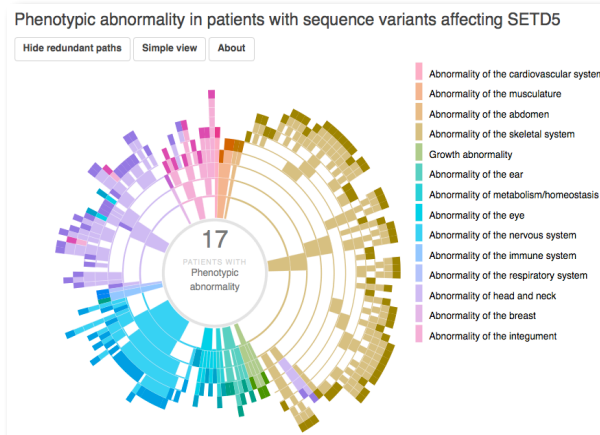
Click on the “Phenotypes” tab as shown in the boxed area above. This table is a summary of all phenotypes (and their ascendant terms) recorded for all openly accessible patients with a sequence variant in this gene.

Phenotypes associated with 16 consented patients with Sequence Variants in SETD5: 1 to 10 of 226 Filter...

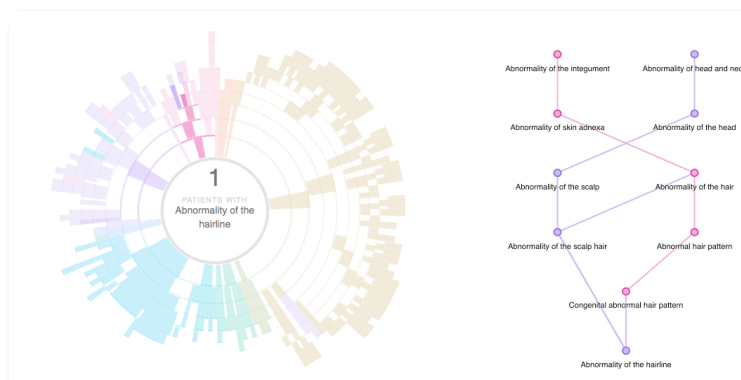
Code	Phenotype	Affected patients with Sequence Variants in SETD5	Percentage of phenotyped patients with Sequence Variants in SETD5	Affected patients in DECIPHER	Percentage of 12703 phenotyped patients in DECIPHER	p value ?	Odds ratio ?
HP:0011343	Moderate global developmental delay	4	25.00%	174	1.37%	5.27×10^{-05}	24.54 (7.84 - 76.87)
HP:0001805	Thick nail	1	6.25%	1	0.01%	1.26×10^{-03}	Infinity

You can sort the columns by clicking on the headers. Click on the “?” sign on the p-value and Odds ratio column headers to learn more about the significance of these values.

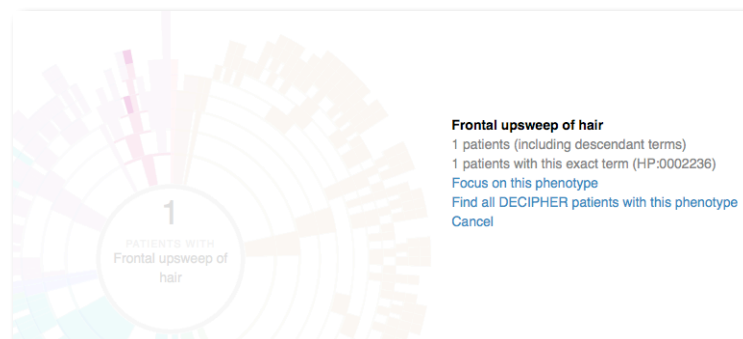
Next click on the “Phenotype Browser”. This is a visual representation of the phenotypes observed in patients with openly accessible sequence variants in SETD5.



This is an interactive tool, with the right side pane showing the top-level phenotype terms and the left side displaying a phenogram. As you move your mouse over the right side list of terms, equivalent arcs are highlighted on the phenogram. Moving the mouse over the phenogram shows individual terms and the phenotype ontology path leading to the term on the right side.

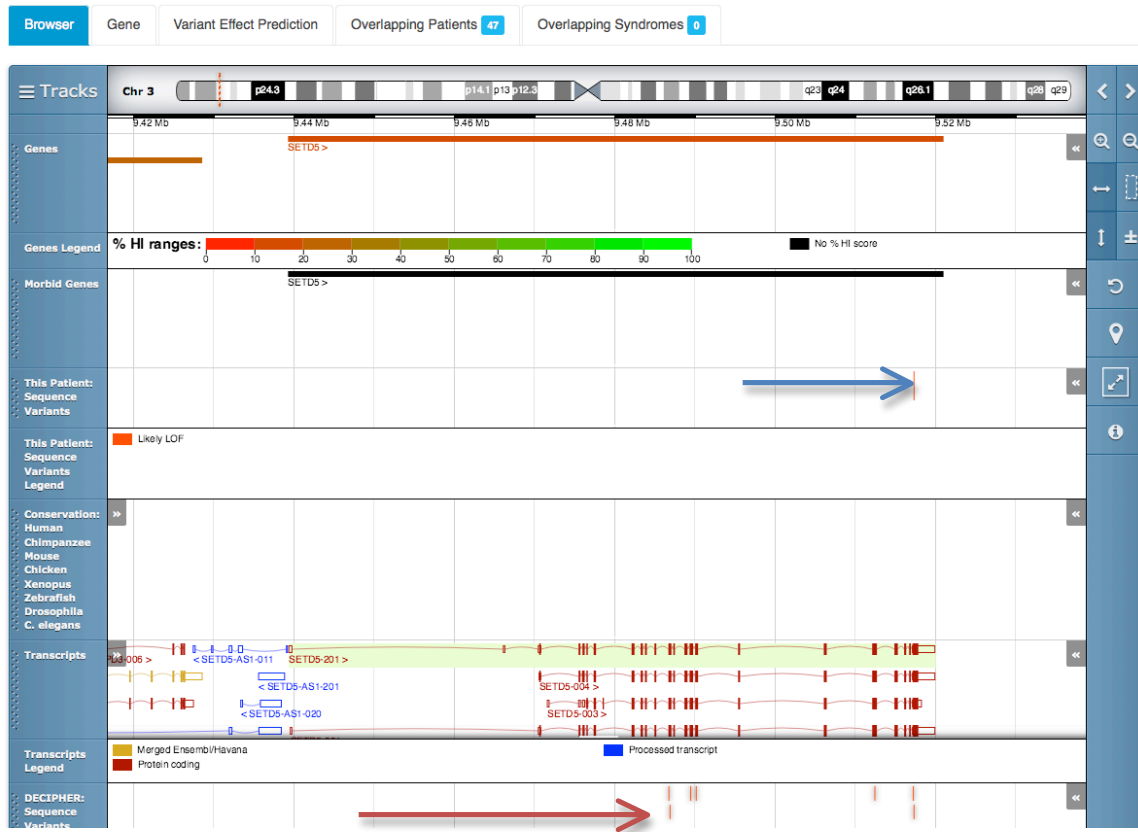


Click on any term to activate a menu that allows you to drill down into the term and redraw a new phenogram, or conduct a search in DECIPHER for other patients with this phenotype and having a variant (CNV or SNV) that involves this gene.



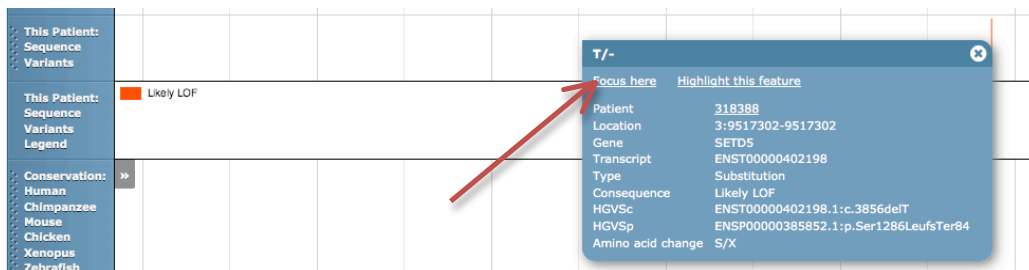
Close the gene browser tab and go back to the patient record you just created.

Click on the sequence variant row and then on the browser tab below to see this variant in context of other data.



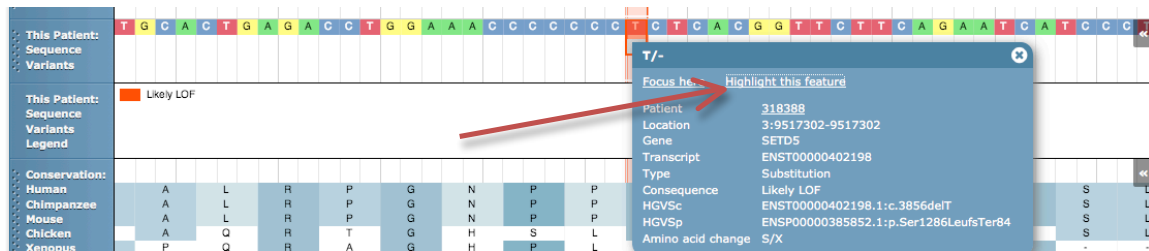
This variant is on gene SETD5 and is represented by a single vertical line as indicated above (blue arrow). Other patients in DECIPHER with sequence variants in the same gene are in the track “DECIPHER: Sequence Variants” as indicated by the red arrow. The transcript in which this variant was recorded is shown on the “Transcripts” track with a highlighted background.

At this zoom level it is difficult to see details of the sequence variant on other overlapping sequence variants in DECIPHER. To zoom in directly on the recorded sequence variant, click on the vertical line showing the position of your variant to open a pop-up menu. Now choose “Focus here” from the pop-up menu.



The browser view changes to show more detail of the sequence variant. Close the pop-up menu by clicking on the “X”. These include showing the variant on the genomic

sequence and zoomed in views of sequence conservation at this position across different species. Click on the Sequence variant on our patient as before to bring up the pop-up menu and click on “Highlight this feature”.



The highlight feature draws a vertical line at this position through the browser making it easier for comparing data. This menu is available on all tracks and features by simply clicking on the feature of interest. Close the pop-up menu by clicking on the “X”.

Scroll down to the “DECIPHER: Sequence Variants” track. *Does our variant overlap another variant in DECIPHER?* If so, click on this variant to see more information in a pop-up window. Click on the patient ID for this patient from the pop-up menu to see the other patient in a new browser tab. *What is the predicted pathogenicity of this overlapping variant in the other patient?*

Did you notice a “Contacts Tab” on this other patient? This is to facilitate communication between users on a variant/patient of interest.

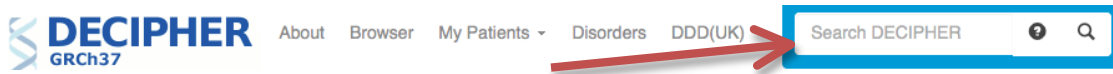
Close the new tab and come back to your own patient record. Further down along on the genome browser you should have tracks titled ExAC and dbSNP and ClinVar. *Do any of these have a variant recorded at the position of your variant (the highlighted region)?* You can click on any of these overlapping variants in the overlap region to get more information.

There are other tabs next to the “Browser” tab. Click through the “Gene” tab to see information about SETD5. The “Variant Effect Prediction” tab has information about the different predicted consequences for the other transcripts for SETD5. The chosen transcript is highlighted in bold. Click on “Overlapping Patient” and then on “Sequence Variants” subtab below. *Are there any other patients in DECIPHER with a variant on the same gene?*

Exercise 3 – Analysis of Sequence Variants

In this exercise, we will not be creating a new patient record but searching for, finding and then analysing sequence variants in an existing record.

Click on the “Search DECIPHER” box on the top right of the page. In the box please type in “ref: Tutorial2” and click on search. (Please type in exactly as written including the prefix ref:).



The search results will look somewhat like that shown below. Click on the search result to open up a new browser tab with the patient record loaded.

Search results for 'ref:GC Course2' ([Refine Search](#))

Patients within your projects 1 Consented patients 0 Syndromes 0 DDD Research Variants 0

Results Karyotype

Search results: 1 to 1 of 1

Decipher ID	Phenotype(s)	Variants	Consent	Contact
TGD300753	Global developmental delay, Horseshoe kidney, Hypertension, Intellectual disability, Seizures, Short palm	No		<input type="text" value="x"/>

Click on the patient row to open up the patient record in a new browser tab.

Overview Photos 0 Genotype 3 Phenotype 6 Karyotype

Age at initial presentation	10
Chromosomal sex	46XX
Internal reference number or ID	GC Course2
Mother is	Of unknown phenotype
Father is	Affected with related or similar phenotype
Responsible clinician	DECIPHER Workshop
Note	
Public consent	No

The patient is a 10 year old female of European (non-finnish) descent with three reported sequence variants (see the “Genotype” tab and 6 recorded phenotypes that include *Global developmental delay*, *Horseshoe kidney*, *Intellectual disability*, *Seizures*, *Short palm* and *Hypertension*). The lab has reported the three sequence variants in this patient:

- Heterozygous maternally inherited missense mutation in BRCA2

- ENST00000380152: c.5744C>T (p.Thr1915Met)
- b) De novo heterozygous missense mutation in VHL
 - NM_000551.3:c.250G>T (p.Asp9Asn)
- c) Heterozygous paternally inherited frameshift mutation in SCN2A
 - ENST00000375437: c.1827delC (p.Ser610LeufsTer31)

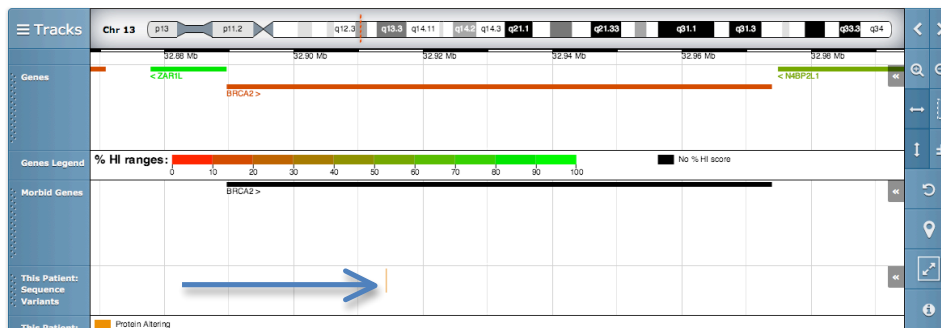
Click on the genotype tab and then click on the BRCA2 mutation row that has been reported.

Sequence Variants: 1 to 3 of 3 Filter...

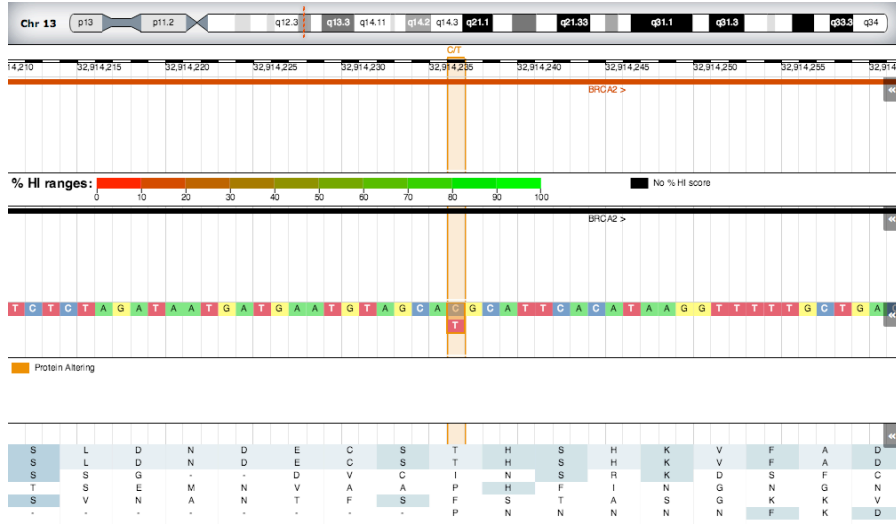
Location	Gene	Allele	Transcript	Consequence	Inheritance Genotype	Pathogenicity Contribution ?	Shared ?	Links
2 166179621 166179621	SCN2A	C>-	ENST00000375437 c.1827delC	frameshift_variant (609 D/X) p.Ser610LeufsTer31	Paternally inherited, constitutive in father Heterozygous	Click Here		View
3 10183556 10183556	VHL	G>A	ENST00000256474 c.25G>A	missense_variant (9 D/N) p.Asp9Asn	De novo constitutive Homozygous	Click Here		View
13 93914298 93914298	BRCA2	C>T	ENST00000380152 c.5744C>T	missense_variant (1915 T/M) p.Thr1915Met	Maternally inherited, constitutive in mother Heterozygous	Click Here		View

[Add Sequence Variant](#)

By default the Geniverse browser is loaded with tracks necessary for sequence analysis.



Click on the “My Patients: Sequence Variants” feature on the browser that shows the position of the variant and choose “Highlight this feature” from the pop-up menu. Then also click on “Focus here” on the pop-up menu. The region zooms in to show the variant on the primary genome sequence as shown below.



Question: What is the haploinsufficiency score of the BRCA2 gene? Hint: Click on the gene on the gene track to open the pop-up menu that has these values?

Answer:

Question: Are there any other known variants at this position in other resources? Hint: Scroll down on the genome browser and look at the ExAC and other tracks. Click on any of the items on these tracks to know more about it.

Answer:

Question: If there is an existing overlapping variant at the same position in the ExAC track, what is the frequency at which it is found in European non-finnish population? Hint: you can click on the overlapping ExAC variant to see the pop-up menu.

Answer:

Next click on the following icon on the genome browser from the right side to go back to previous view.



Next click on the “Variant Effect Prediction” tab.

Browser Gene **Variant Effect Prediction** Overlapping Patients 12 Overlapping Syndromes 0

For every sequence variant deposited in DECIPHER, the Ensembl Variant effect predictor (VEP) is run. This process predicts consequences for the variant across all transcripts known for the gene in which the variation has been recorded. The transcript that matches the input transcript is highlighted in bold.

Sequence variant gene: 1 to 2 of 2 Filter...

HGNC & Ensembl Transcript	HGVS	Position	AA	SIFT ?	Polyphen ?	VEP Consequence
BRCA2 ENST00000380152	ENST00000380152.3:c.5744C>T ENSP00000369497.3:p.Thr1915Met	1915	T/M	Tolerated (0.64)	Benign (0.001)	missense_variant
BRCA2 ENST00000544455	ENST00000544455.1:c.5744C>T ENSP00000439902.1:p.Thr1915Met	1915	T/M	Tolerated (0.64)	Benign (0.001)	missense_variant

Question: What are the SIFT and Polyphen predictions of the functional impact of this variant?

Answer:

Now let us go and see if there are any overlapping patients in DECIPHER with shared phenotypes. Click on the “Overlapping Patients” tab. There are two sub-tabs which delineate CNVs that overlap our variant and other sequence variants that have been recorded in DECIPHER for the same gene. Click through both the sub-tabs and sort on the column “Shared phenotypes” by clicking on it to bring up patients in DECIPHER with the most shared phenotypes. **Set up the filter shown below to “Patients not in my projects” (otherwise you will see all the patients being created in this tutorial session)!**

Browser Gene Variant Effect Prediction **Overlapping Patients 14** Overlapping Syndromes 0

Copy-Number Variants 11 Sequence Variants 3

Gain/Loss

- Gain: 27%
- Loss: 73%

Inheritance

- De novo constitutive: 50%
- Unknown: 50%

Size

- 0.1-1 Mb: 27%
- 1-10 Mb: 36%
- 10-100 Mb: 36%

Patients with Copy-Number Variants overlapping this variant, or gene BRCA2: 1 to 10 of 11

Show: Both **Patients not in my projects** Filter...

Patient	Sex	Interval	Functional Similarity ?	Ratio	Inheritance	Shared Phenotypes	Actions
252508	46XY	5.23 Mb	0.01	-0.5	Unknown	1 of 7 Intellectual disability; Webbed neck; Hypertelorism; Pectus excavatum; Constipation; Proportionate short stature; Abnormality of the vertebrae	✕
254873	46XY	6.29 Mb	0.01	0.58	De novo constitutive	1 of 3 Intellectual disability; Abnormality of the forehead; Tics	✕

Question: Are there any patients in DECIPHER that have copy-number or sequence-variants that overlap our patient BRCA2 variant? Are there many shared phenotypes?

Answer:

Given that this heterozygous sequence variant is predicted to be benign by SIFT and PolyPhen2, and that none of the overlapping patients in DECIPHER share many phenotypes with our patient and that heterozygous occurrence of this variant occurs as a high percentage in ExAC, would you conclude that this variant is probably not significant?

Independent Work

Using the same approach as the one above, can you analyse the two other variants reported for this patient and answer the following questions?

VHL

- *What is the haploinsufficiency value for VHL gene?*

Answer:

- *What are the predicted SIFT and PolyPhen2 predictions for the VHL variant? Did you notice that the predictions disagree?*

Answer:

- *Are there variants in ExAC for this VHL variant?*

Answer:

- *Are there many shared phenotypes in overlapping patients (“not in my projects filter” ON), if so what are the top 2-3 shared phenotypes?*

Answer:

SCN2A

- *What is the haploinsufficiency value for SCN2A gene?*

Answer:

- *Are there variants in ExAC for this SCN2A variant? If so, is it commonly seen in the European non-finnish population? How many times has been seen in this population?*

Answer:

- *Are there many shared phenotypes in overlapping patients (“not in my projects filter” ON), if so what are the top 2-3 shared phenotypes?*

Answer:

- *Looking at the Gene-specific page for SCN2A (click on gene name on variant), are there any phenotypes that specifically stand out as being significant? Hint: Look at the Phenotypes tab for the SCN2A gene page and look at phenotypes with lowest p-values.*

Answer:

General

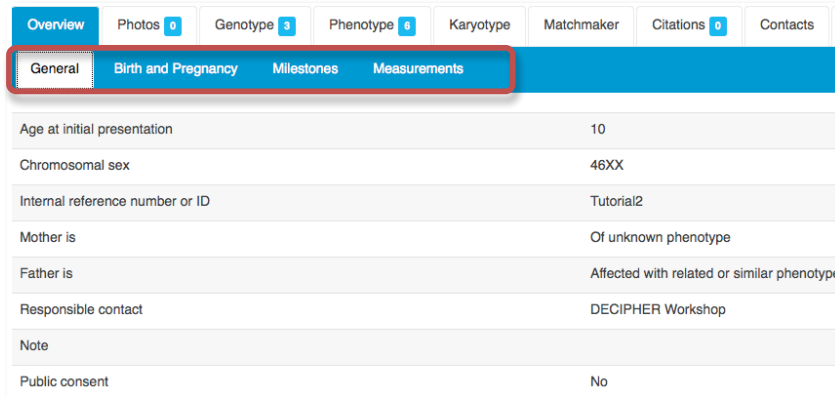
- *Which variant, in your opinion, explains seizures in this patient? Hint: Click on the “Gene” tab and then the “Clinical” tab and then click on one of the “morbid” entries to see associated disease phenotypes for this gene.*
- *Which of the two variants (SCN2A and VHL) would you classify as being more pathogenic and representative of patient phenotype?*

Answer:

Please use the area below for any notes you may wish to make!

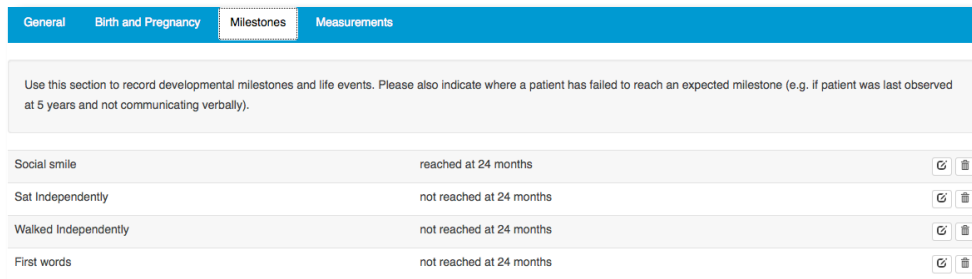
Addendum

Decipher now supports the entry of extended patient information. While creating a patient record, additional sub-tabs are available under the Patient Overview Section as shown below.











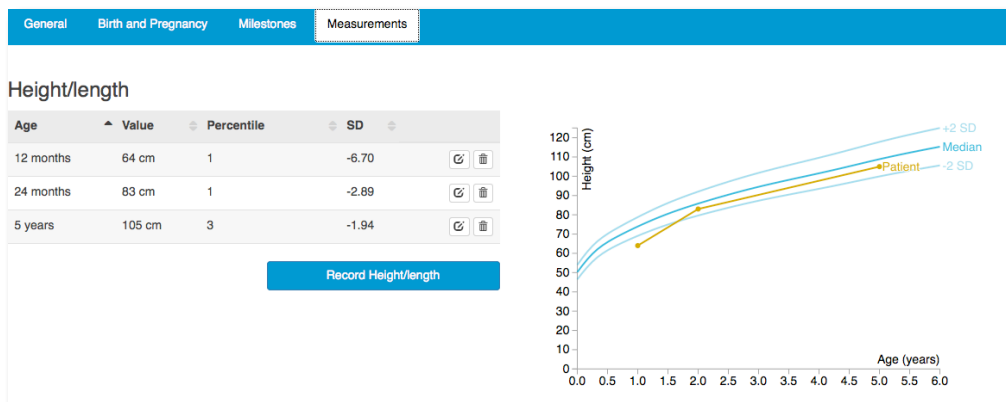
Overview	Photos 0	Genotype 3	Phenotype 6	Karyotype	Matchmaker	Citations 0	Contacts
General	Birth and Pregnancy	Milestones	Measurements				
Age at initial presentation	10						
Chromosomal sex	46XX						
Internal reference number or ID	Tutorial2						
Mother is	Of unknown phenotype						
Father is	Affected with related or similar phenotype						
Responsible contact	DECIPHER Workshop						
Note							
Public consent	No						

Additional information including details of birth and pregnancy, developmental milestones and measurements may be entered for the patient here.



Use this section to record developmental milestones and life events. Please also indicate where a patient has failed to reach an expected milestone (e.g. if patient was last observed at 5 years and not communicating verbally).

Social smile	reached at 24 months		
Sat independently	not reached at 24 months		
Walked independently	not reached at 24 months		
First words	not reached at 24 months		



Height/length

Age	Value	Percentile	SD
12 months	64 cm	1	-6.70
24 months	83 cm	1	-2.89
5 years	105 cm	3	-1.94

[Record Height/length](#)

