DECIPH
GRCh37

Fred Sanger, 1918–2013

DECIPHER

Facilitating the discovery and interpretation of sequence and copy-number variation in genetic disorders

Jawahar Swaminathan, Ph.D.
Project Manager

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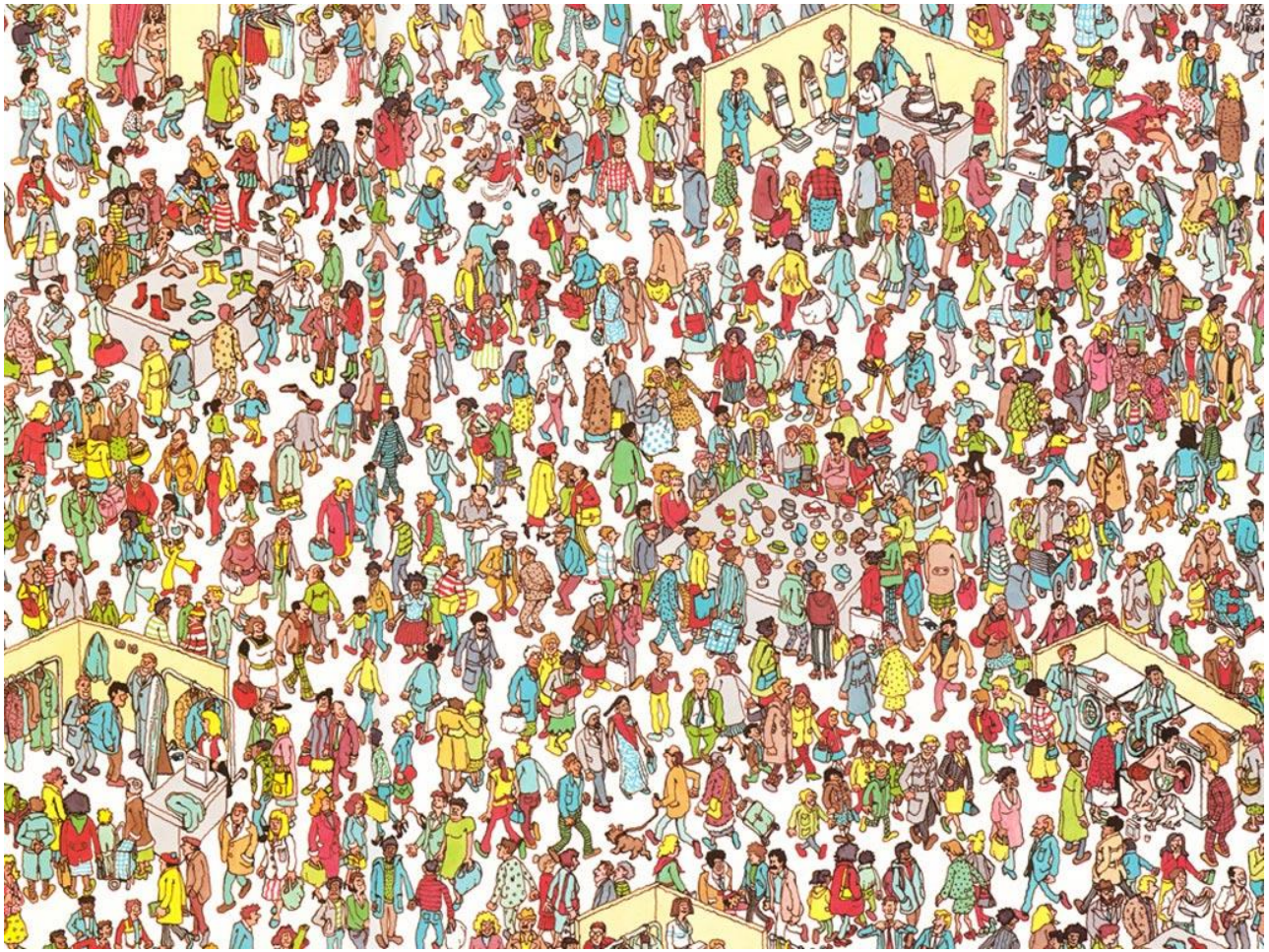
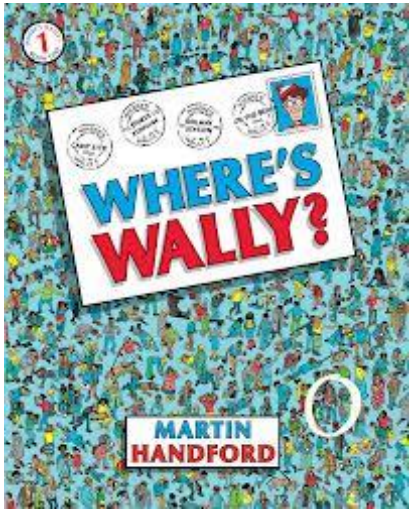
Identifying pathogenic variants amongst the background of normal variation in a genome





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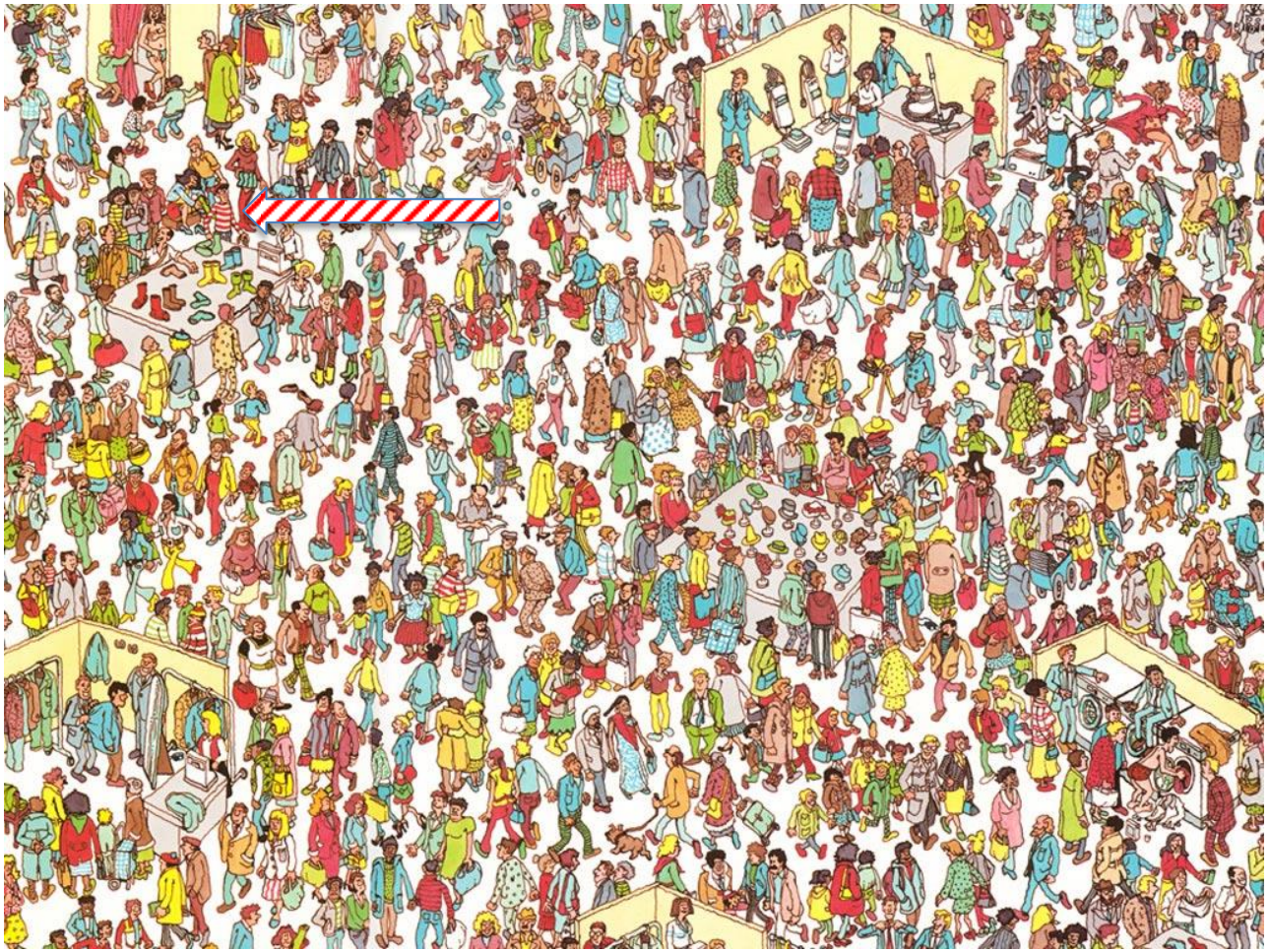
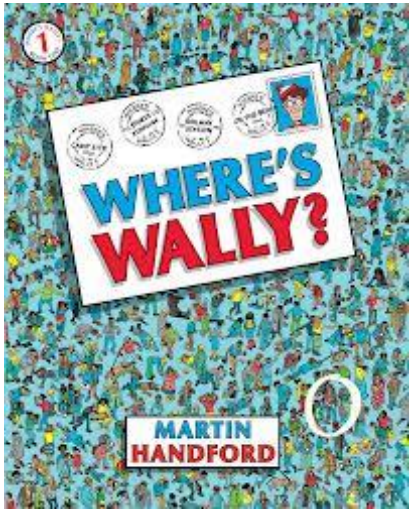
Identifying pathogenic variants amongst the background of normal variation in a genome





- Aiding the interpretation of genomic variants since 2004
- Primary Objective

  Facilitate identification and interpretation of pathogenic genetic variation in rare disorders

- Mission

  making genetic and phenotypic data discoverable to enable improved interpretation of variation that cannot be unambiguously interpreted in isolation

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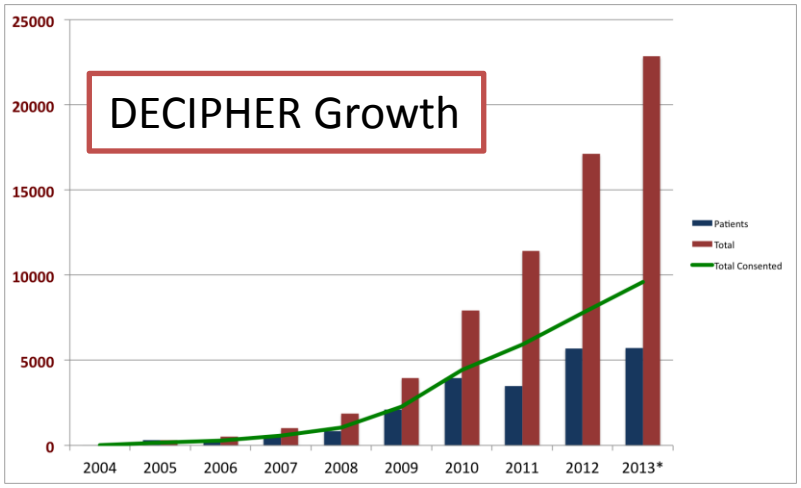
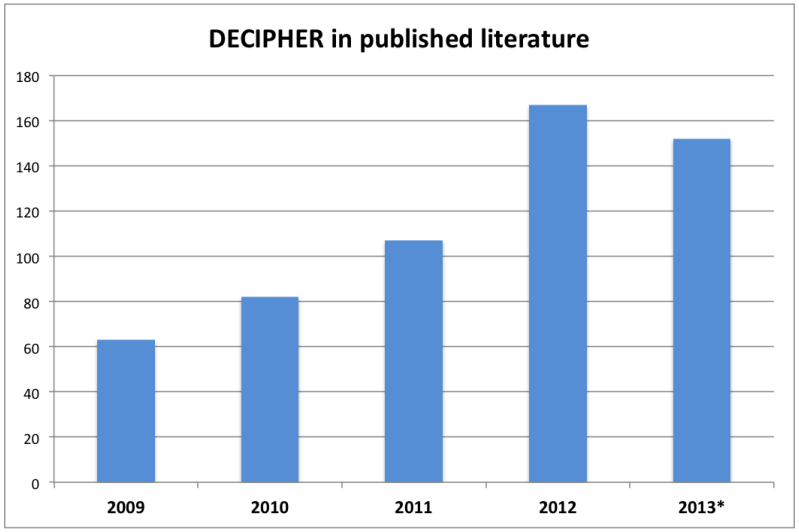
DECIPHER *at-a-glance*





DECIPHER by numbers

- **1900+ registered users**
- **200+ Consortium Centres in 40 countries**
- **22000+ patient records**
- **~40000 plausibly pathogenic CNV and Sequence variants with 80k associated phenotypes**
- **~9600 anonymised patients consented for public release**

Over 500 publications since 2009 have used DECIPHER data to aid variant discovery and diagnosis.

Facilitating Contact, Collaboration and Consultation amongst users

Peer-to-Peer
Within and between DECIPHER centres on patients on mutual interest using "Contacts" option.

External User to Peer
DECIPHER conduits contact and collaboration requests from external to registered users

Bulk anonymous data for research
Available to bona fide researchers under Data Access and Display agreements. Anonymised, encrypted file for research and method development.

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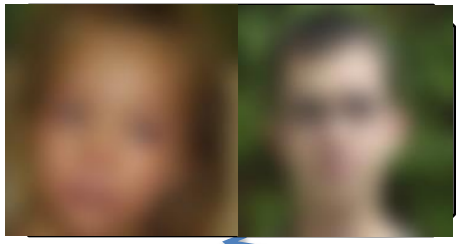
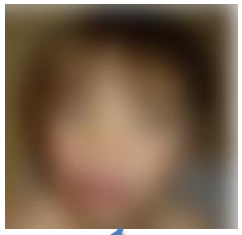
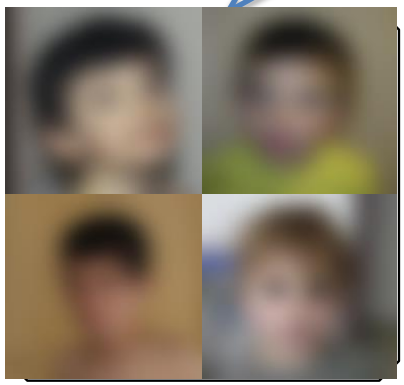


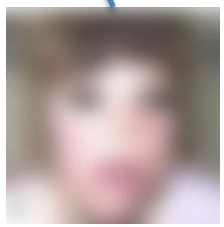


DECIPHER Data from Belgium, Netherlands



A novel microdeletion syndrome at 9q21.13 characterised by mental retardation, speech delay, epilepsy and characteristic facial features

Eur J Med Genet
March 2013



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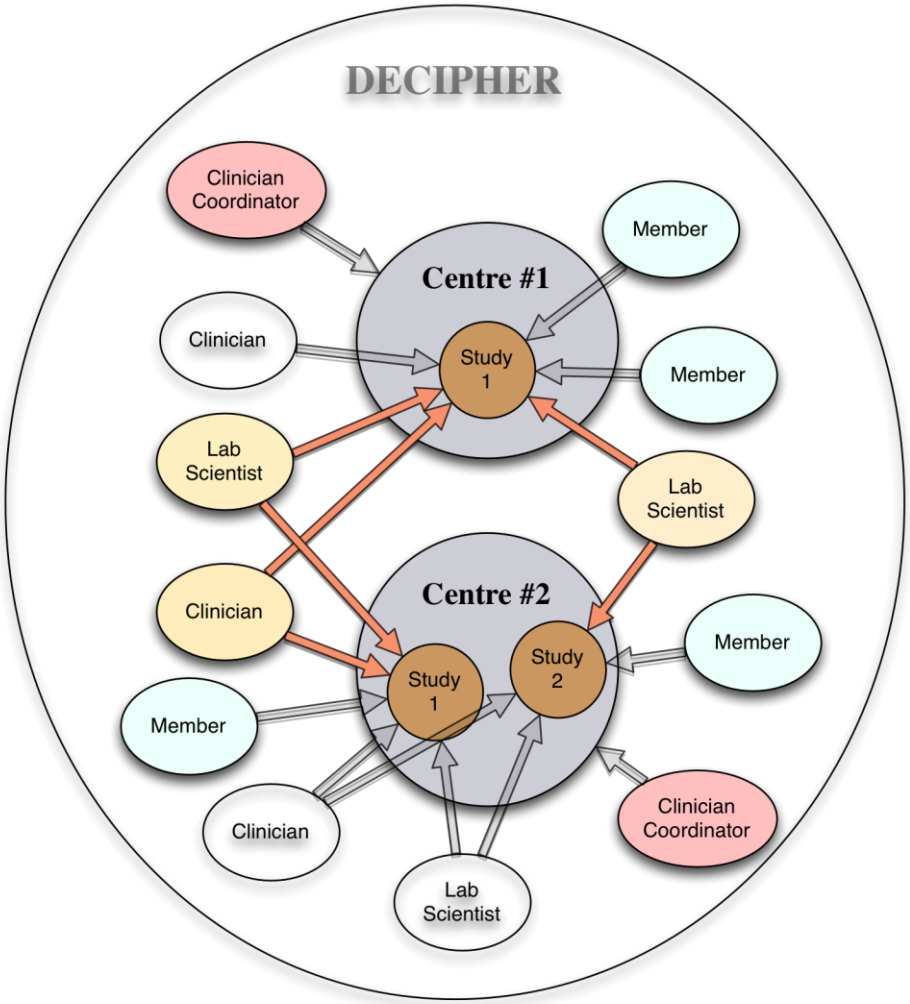
Infrastructure

- Level 4 secure MySQL database storage
- User-authenticated access rights and privileges
- Asynchronous and bulk-data entry
- Consortium composition
  - Centre
    - Study/Studies
      - Users
        - » User Role (Coordinator/Clinician/Scientist/Member)
        - » User Right (Read-Write/Read Only)

Anatomy of a DECIPHER Centre

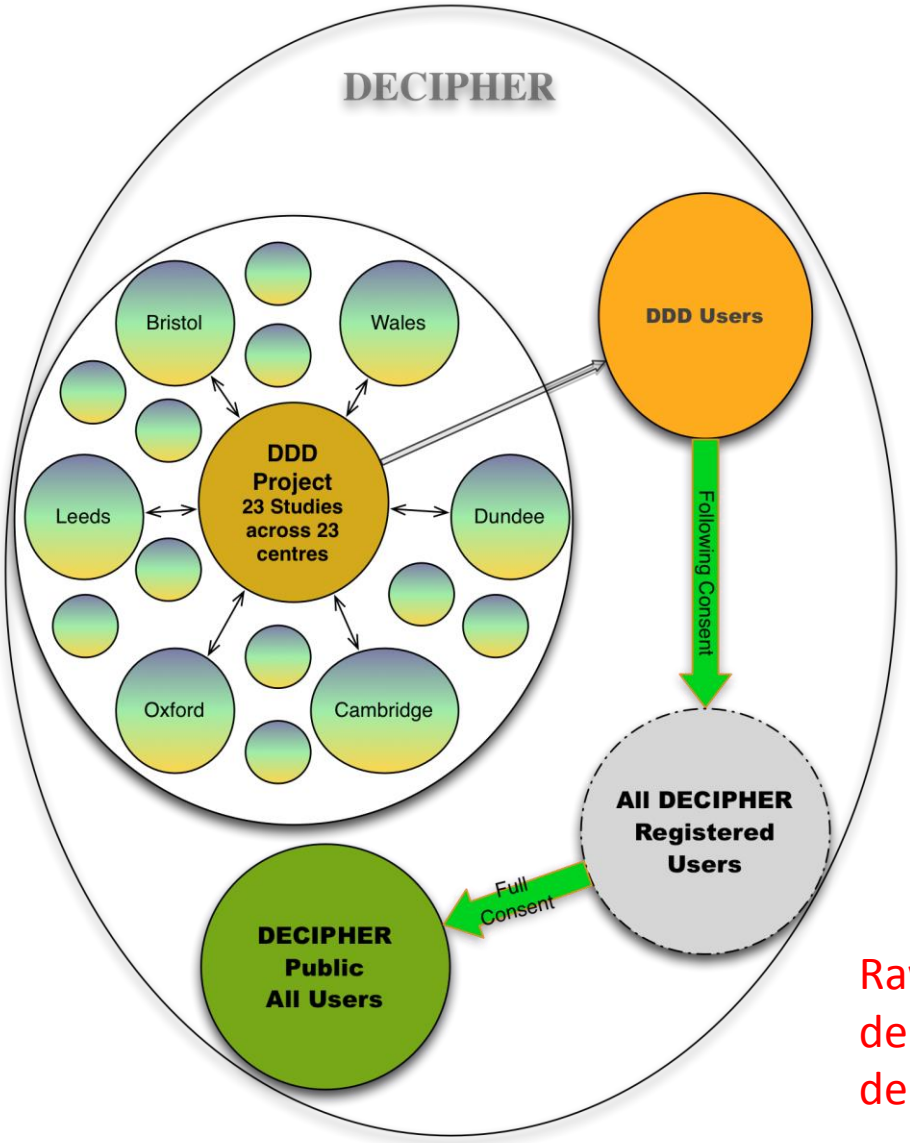


Centre
Academic centre affiliated to a hospital
Study
One or more projects within a centre
Coordinator
Senior clinical geneticist responsible for the DECIPHER centre
Clinicians
Senior clinicians responsible for referred patients
Lab Scientists
Lab scientists entering variant information
Members
Associated junior doctors, nurses etc. within the centre/study assisting data entry and analysis

DECIPHER Access

- **Centre/Study/User/Role model and multiple access layers.**
- **Users can be members of multiple studies across multiple centres**

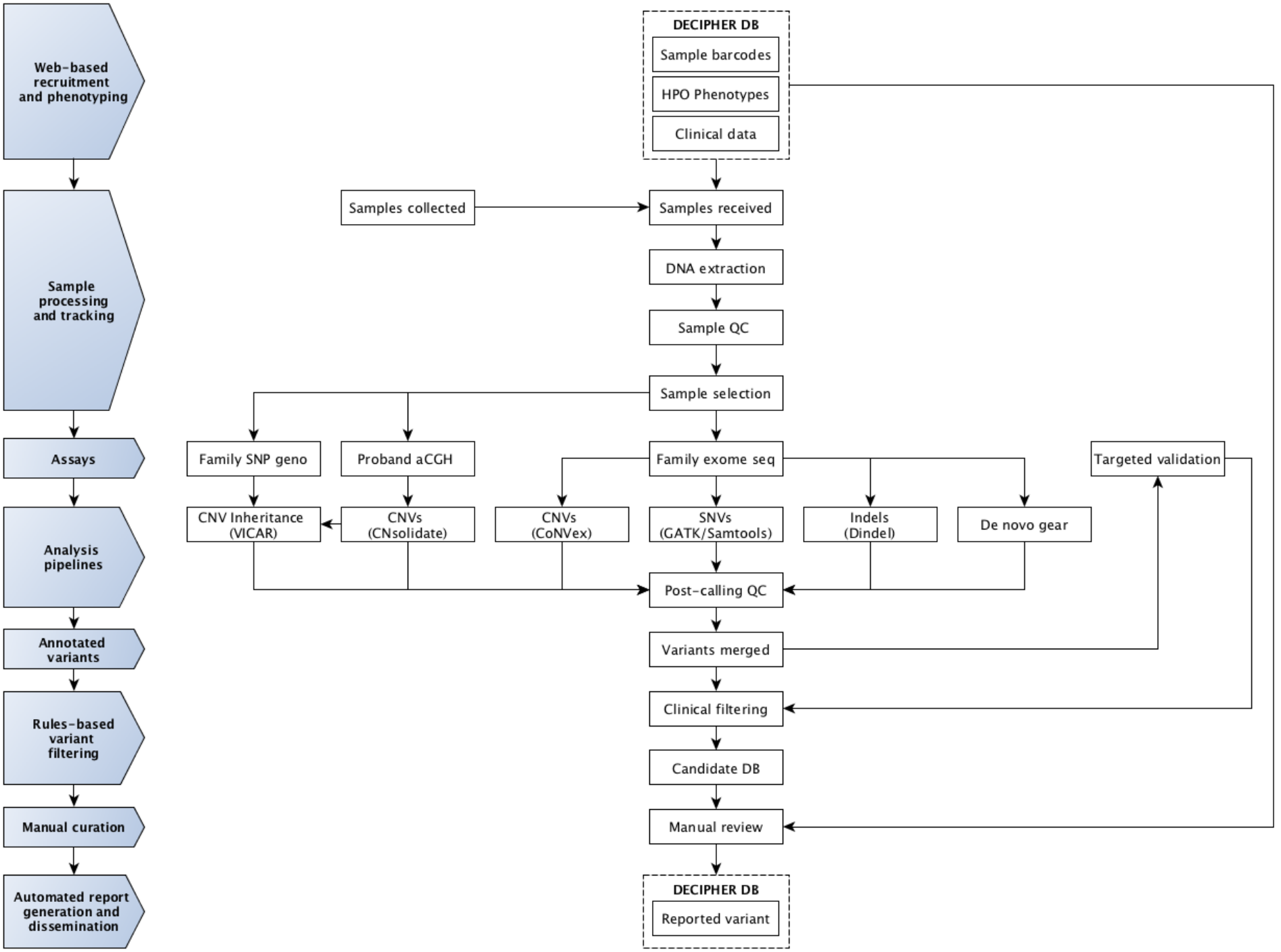
Supporting a larger multi-study project (DDD)



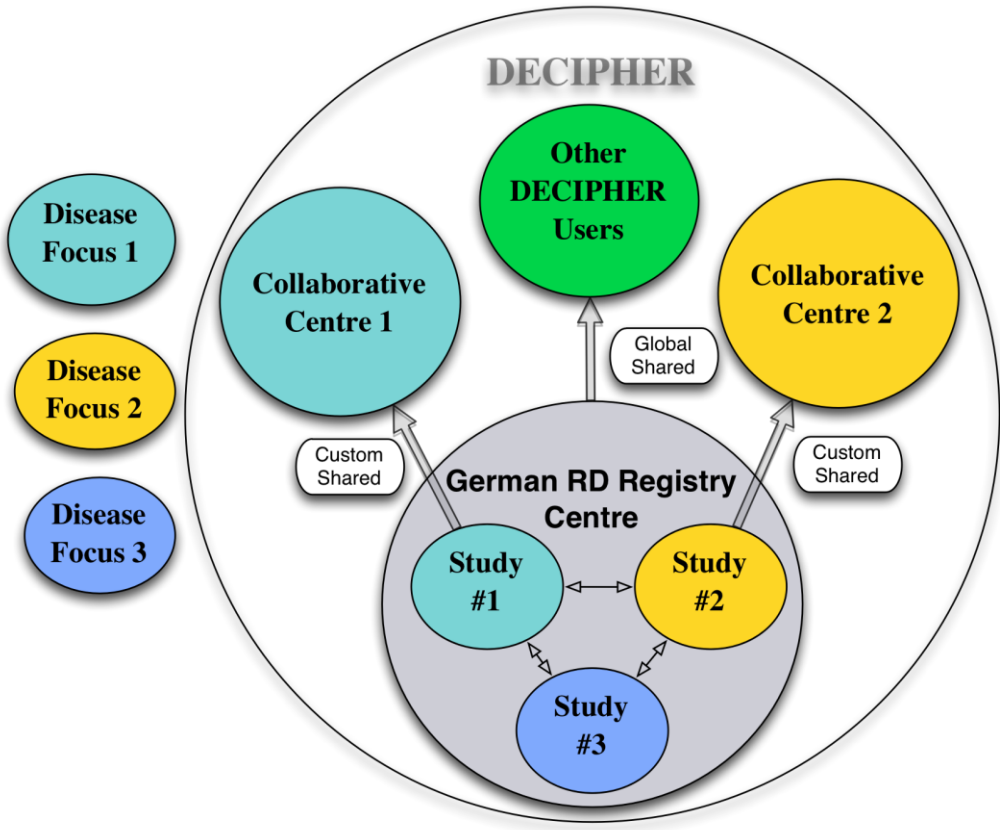
DDD Project in DECIPHER

- *Study Access and User Accounts*
- *Custom Forms for Data Entry*
  - Patient Recruitment
  - Patient Information and followup
  - Sample Registration/Tracking
- *Report Notification and Download*
- *Results download and analysis using DECIPHER tools*
- *Validation and Confirmation of Results*
- *Feedback on Pathogenicity*

Raw sequence data from DDD exome sequencing deposited in EGA. Filtered variants & phenotypes deposited in DECIPHER


Web-based recruitment and phenotyping
Sample processing and tracking
Assays
Analysis pipelines
Annotated variants
Rules-based variant filtering
Manual curation
Automated report generation and dissemination
DECIPHER DB
Sample barcodes
HPO Phenotypes
Clinical data
Samples collected
Samples received
DNA extraction
Sample QC
Sample selection
Family SNP geno
Proband aCGH
Family exome seq
Targeted validation
CNV Inheritance (VICAR)
CNVs (CNsolidate)
CNVs (CoNVex)
SNVs (GATK/Samtools)
Indels (Dindel)
De novo gear
Post-calling QC
Variants merged
Clinical filtering
Candidate DB
Manual review
DECIPHER DB
Reported variant

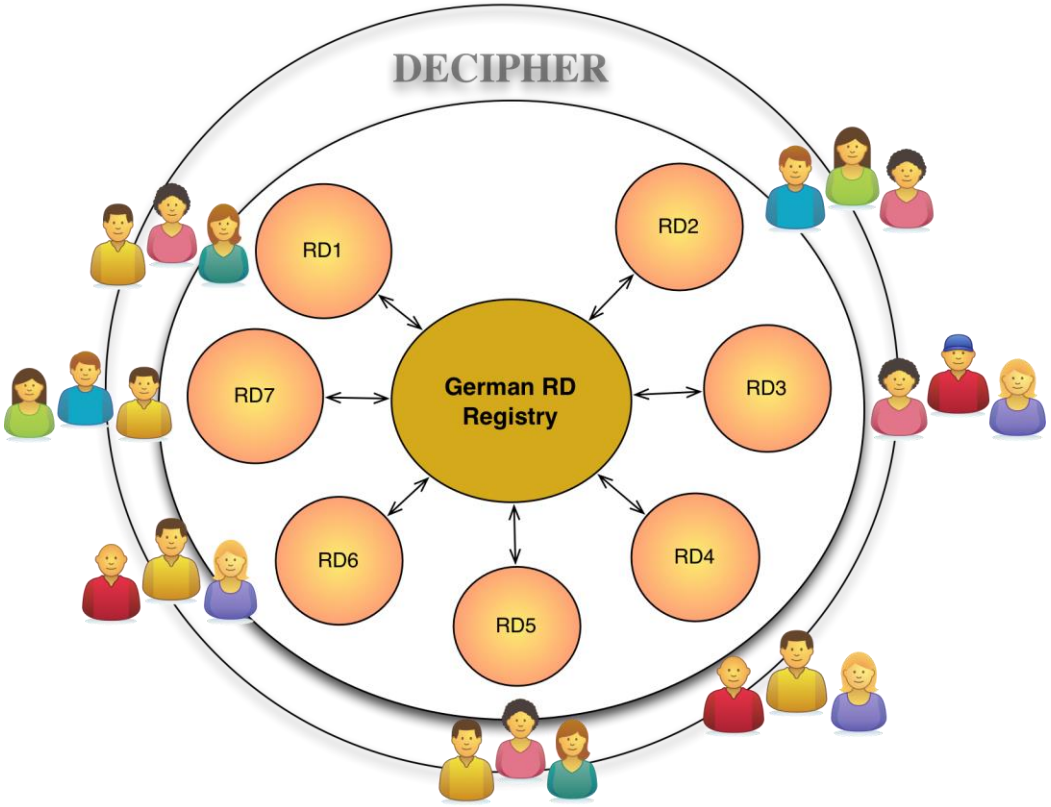
Conceptualising an RD Initiative - 2



- **All patients in a single centre**
- **Multiple studies within centre**
- **Users in Centre have access to one or more studies**
- **Studies may be shared with other external collaborators**

Data from any rare disease study that collects phenotype-linked genotype data (CNV or sequence variant) can be analysed and shared from within DECIPHER.

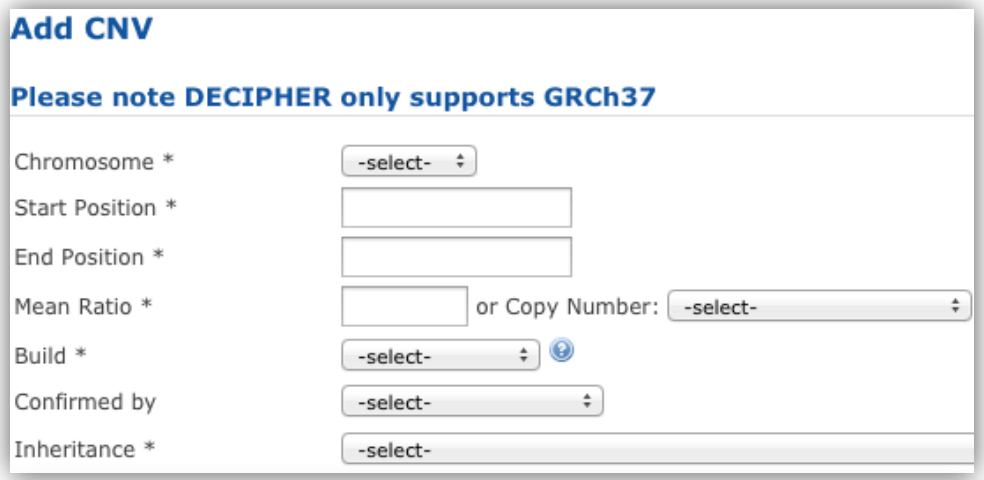
Conceptualising an RD Initiative - 3

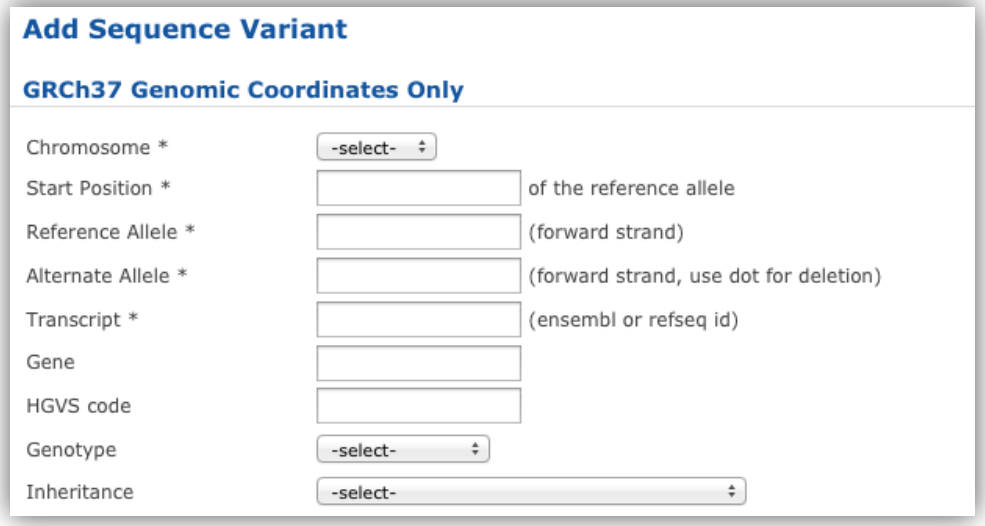


- A Rare Disease “super” centre with many centres.
- Each centre can have >1 studies
- Each centre specialised on disease/gene/geographical etc
- Users of centre “own” patient data
- Read-Only access to data from other centres.
- Users can be in multiple centres.

DECIPHER supports different sharing modes with access control

DECIPHER: Data Entry





Deposition of patient variant (sequence/CNV)

- Secure, password Protected
- User authenticated deposition
- Asynchronous entry of patient information
- Ontology for phenotype entry (HPO)
- **Bulk upload (Sequence/CNV)**
- Explicit consent for anonymous sharing

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DECIPHER: Data Discovery

Search By

- Chromosomal Location
- Gene Symbol
- Phenotype
- DECIPHER ID
- Internal ID

Results Filtered By

- Patients in own study (Consented/Unconsented)
- Patients within larger group (Consented for sharing within group)
- Other consented patients (publicly consented)

Patients within your studies | Karyotype

1 to 2 of 2 entries

Decipher ID	Variant	Phenotypes
273915	gain 4:1559100-2119236	Intellectual disability, Microcephaly, Small for gestational age, Abnormal bleeding, Sandal gap, Delayed speech and language development, Synophrys, Abnormality of the face, Tall stature, Long face, Aplasia/hypoplasia affecting the eyelid
273915	4:1806119 G>A	Intellectual disability, Microcephaly, Small for gestational age, Abnormal bleeding, Sandal gap, Delayed speech and language development, Synophrys, Abnormality of the face, Tall stature, Long face, Aplasia/hypoplasia affecting the eyelid

10 per page

Consented patients | Karyotype

1 to 10 of 75 entries

Decipher ID	Variant	Phenotypes
260581	gain 4:68345-2246643	Thin upper lip vermilion, Macrocephaly, Hypertelorism, Long philtrum, Abnormality of toe
256909	gain 4:29099-9734585	Thin upper lip vermilion, Hypertelorism, Broad nasal tip, Long philtrum, Telecanthus, Long eyelashes, Upslanted palpebr Autism, Intellectual disability, Depressed nasal bridge

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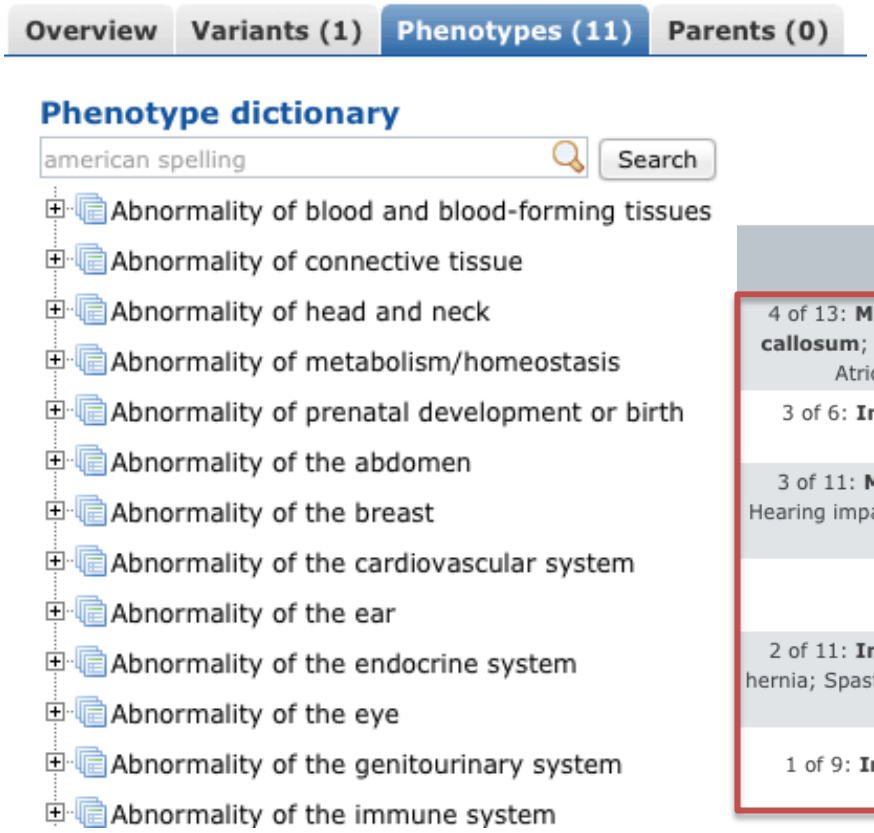
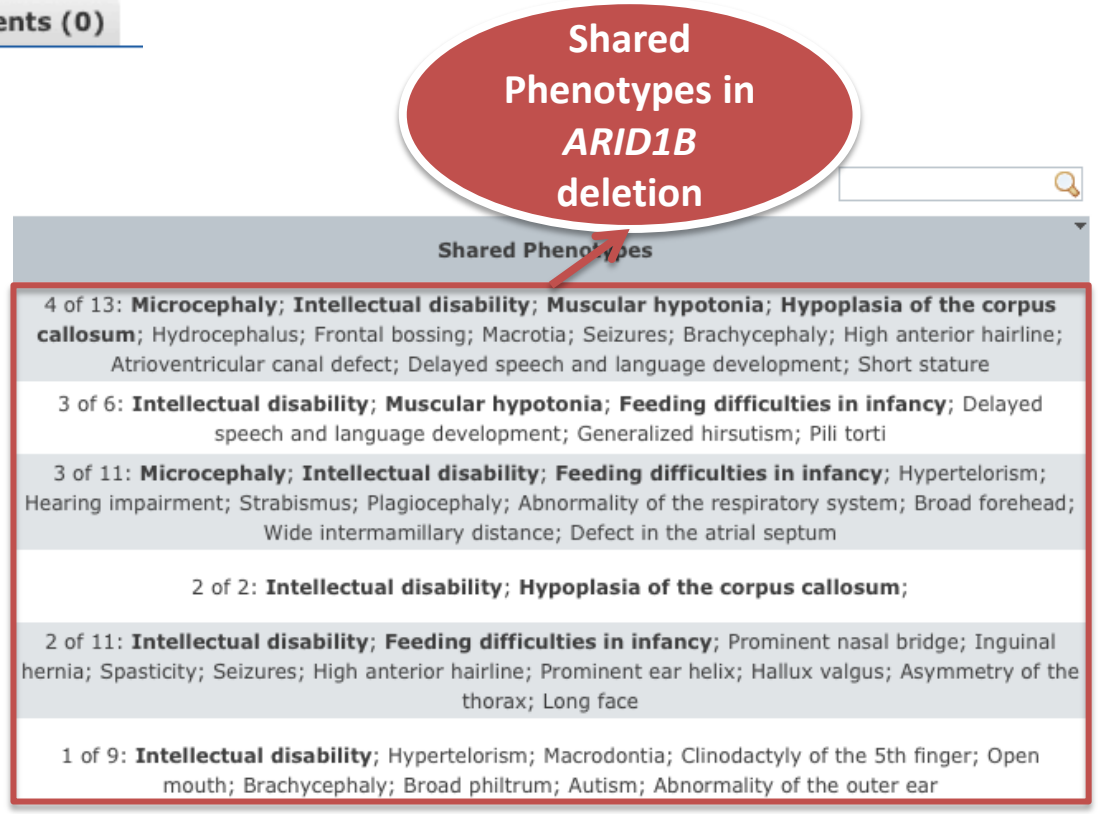
DECIPHER: Features

Drag-and-Drop HPO Phenotype Entry

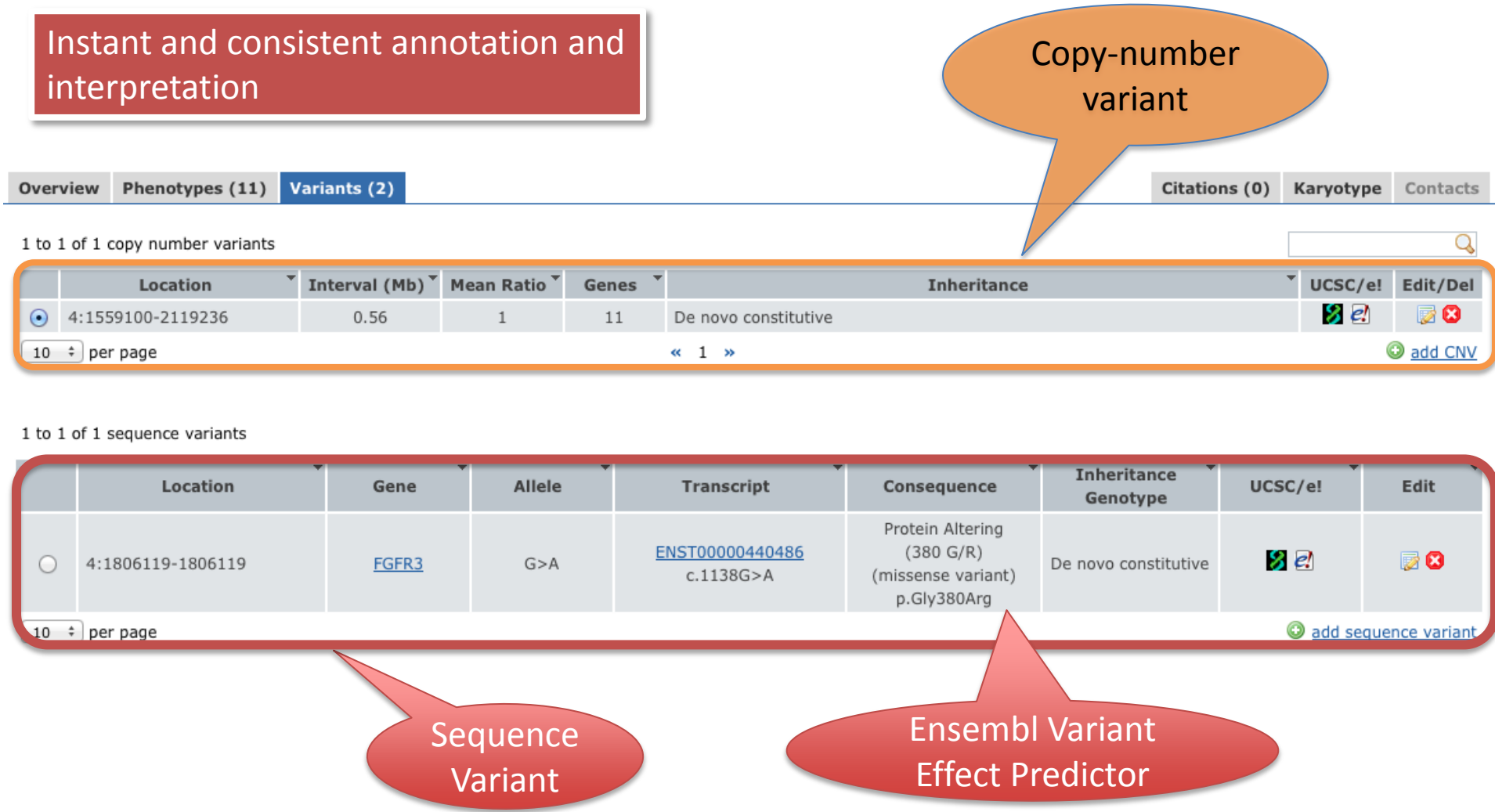


Identifying patient clusters with genotype-phenotype overlaps



DECIPHER: Features

Instant and consistent annotation and interpretation



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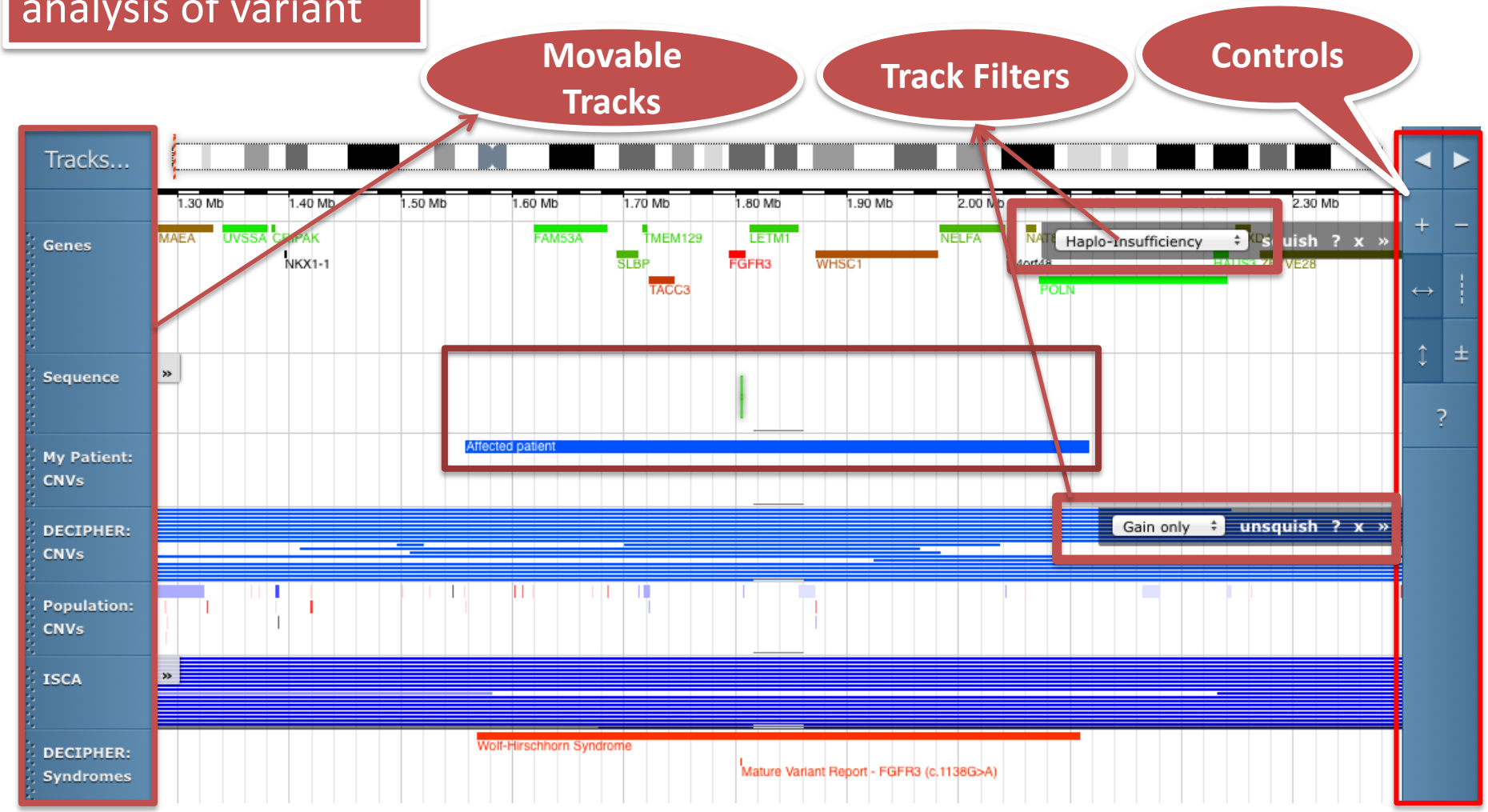
DECIPHER: Features

Real-time interactive graphical analysis of variant



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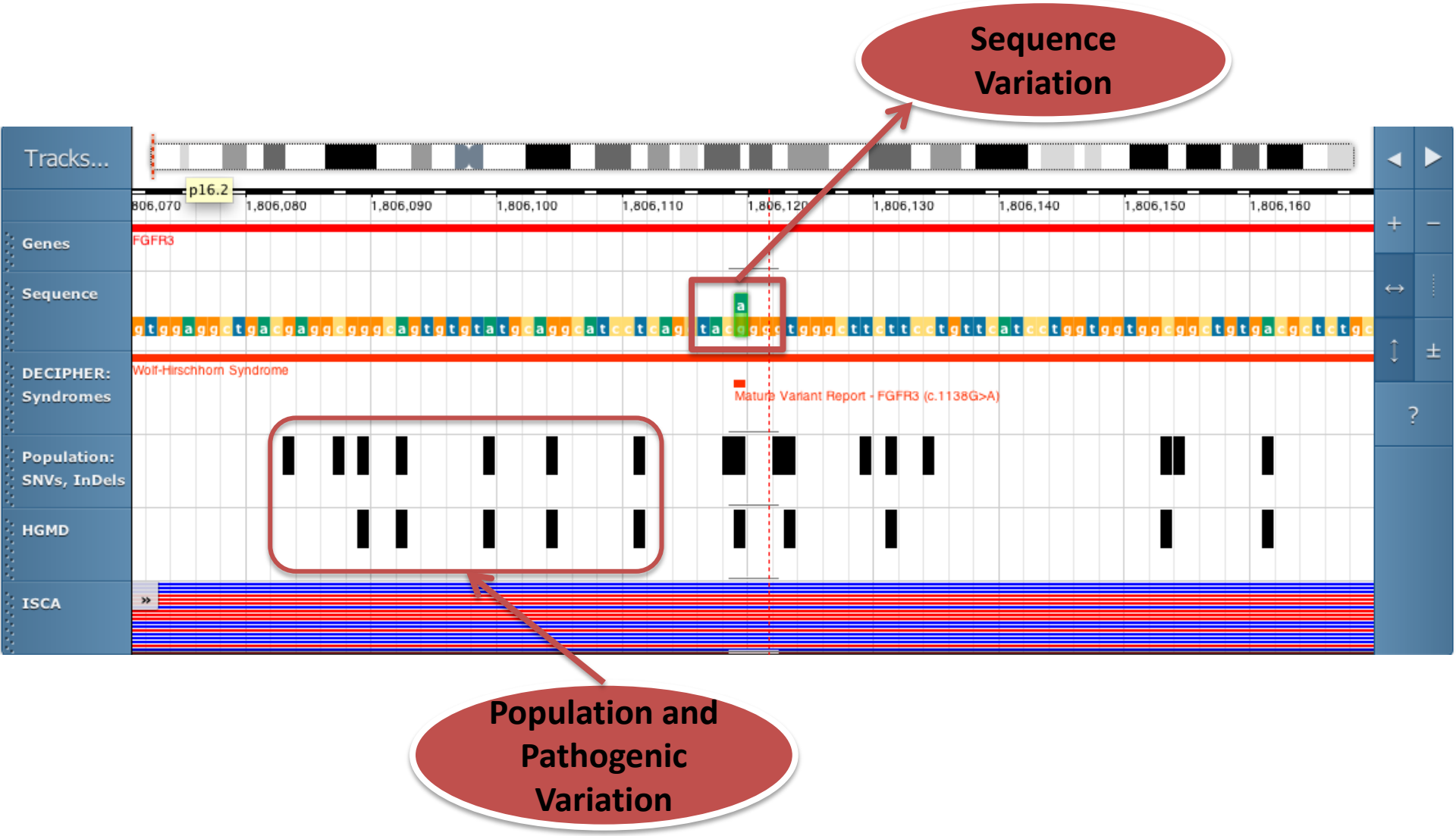
DECIPHER: Features



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DECIPHER: Features

Prioritising plausibly pathogenic genes using sortable columns

Browser | Graph | Genes (11) | Patient overlap (146) | Syndrome overlap (2)

All (11) | OMIM (9) | Morbid (3)

1 to 10 of 11 entries

Filter...

Name	Location	Description	OMIM	Morbid	DDG2P ?	%HI ?	DBs
FGFR3	4:1795034-1810599	fibroblast growth factor receptor 3	✓	✓	✓	4.9	
POLN	4:2073645-2243848	polymerase (DNA directed) nu	✓	-	-	91.1	
NAT8L	4:2061239-2070816	N-acetyltransferase 8-like (GCN5-related, putative)	✓	✓	-	47.3	
C4orf48	4:2043689-2045697	chromosome 4 open reading frame 48	✓	-	-	-	
NELFA	4:1984441-2043630	negative elongation factor complex member A	✓	-	-	61.1	
WHSC1	4:1873151-1983934	Wolf-Hirschhorn syndrome candidate 1	✓	-	-	21.8	

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On-going developments

- Notification mechanisms (E-Mail alerts on matching variant discovery)
- Phenotype-entry app (Tablet/Hospital Management Systems)
- Patient Portal

We are open and receptive to ideas and suggestions about how to use DECIPHER to improve the interpretation of plausibly pathogenic variants

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DECIPHER Publications

REPORT

DECIPHER: *D*atabase of Chromosomal *I*mbalance and *P*henotype in *H*umans Using *E*nsembl *R*esources

Am. J. Hum. Genet (2009).
doi: 10.1016/j.ajhg.2009.03.010

DECIPHER: web-based, community resource for clinical interpretation of rare variants in developmental disorders

Human Molecular Genetics (2012).
doi: 10.1093/hmg/dds362

DECIPHER: database for the interpretation of phenotype-linked plausibly pathogenic sequence and copy-number variation

Nucleic Acids Res. (2014).
doi: 10.1093/nar/gkt937

Acknowledgements

- **Patients and families for permission to include their data in DECIPHER**
- **Members of the DECIPHER consortium**

Supported by wellcome trust

wellcome trust sanger institute

DECIPHER People