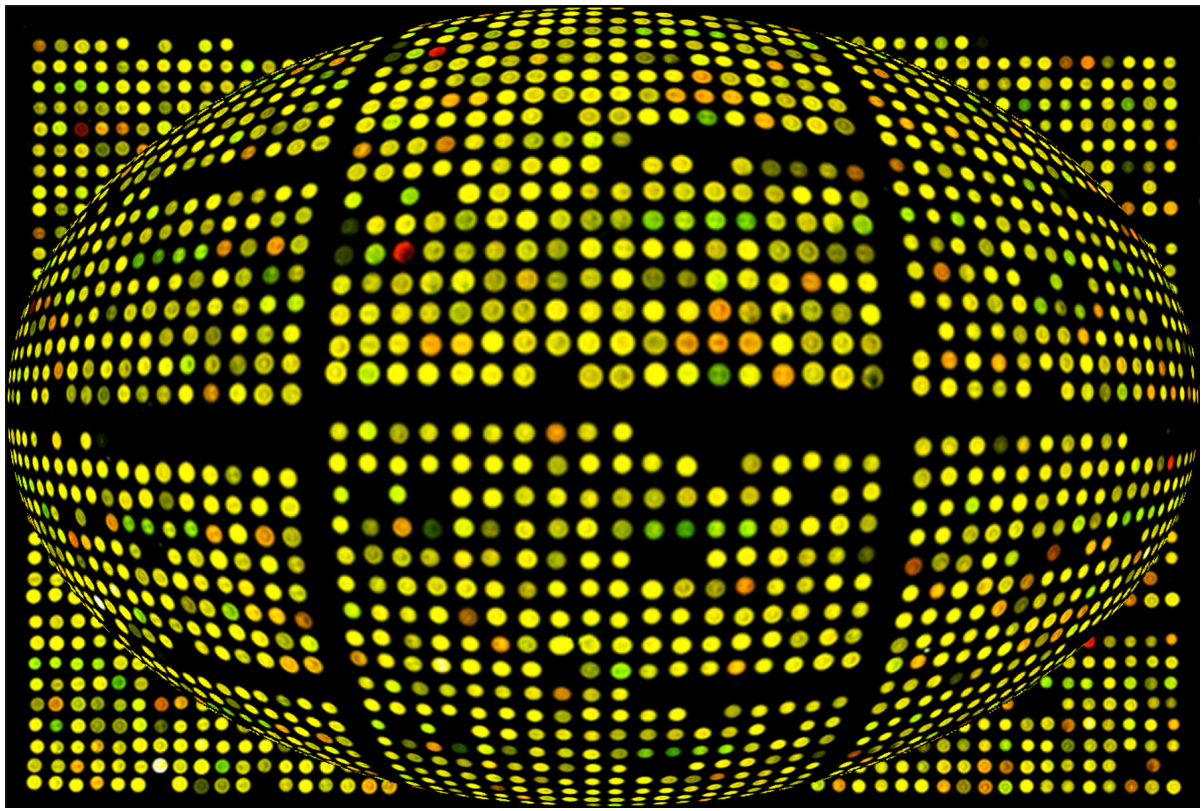
Array CGH diagnosing developmental disorders



Nigel P. Carter

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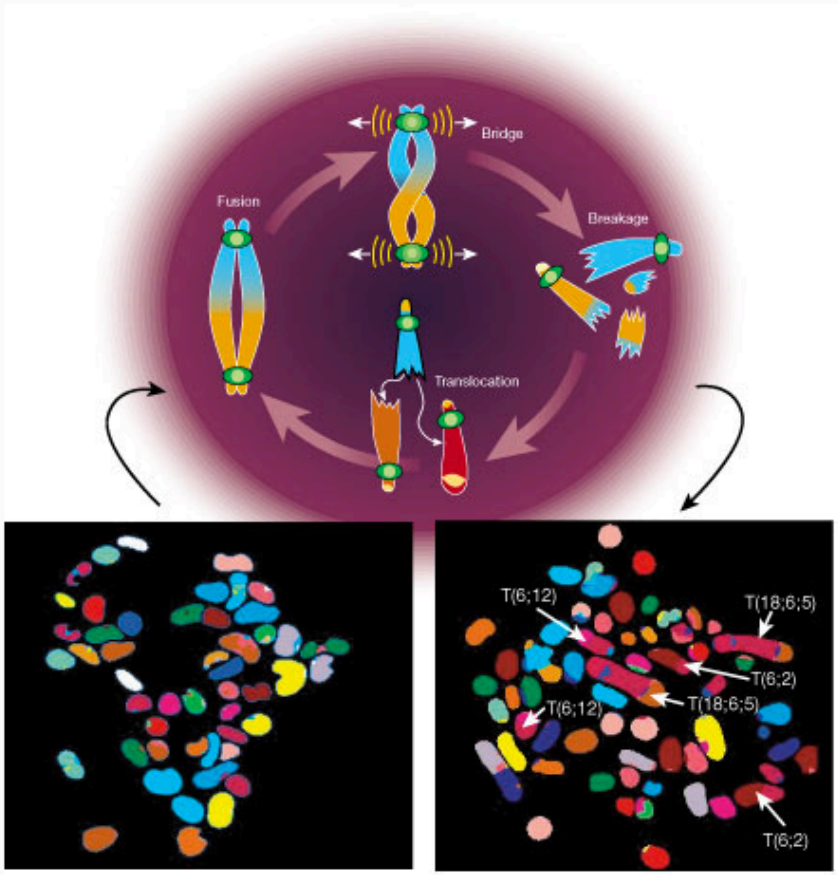
Introduction to Discovering Genomic Variation
November 2010

Solid Tumours

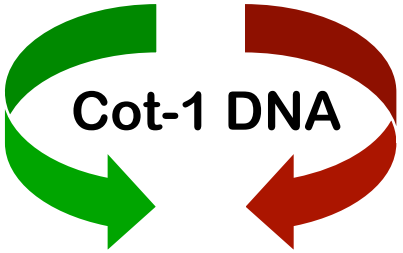


Conventional CGH

Comparative genomic hybridization for molecular cytogenetic analysis of solid tumors.
Kallioniemi A, Kallioniemi OP, Sudar D, Rutovitz D, Gray JW, Waldman F, Pinkel D.
Science. 1992 Oct 30;258(5083):818-21.
PMID: 1359641 [PubMed - indexed for MEDLINE]
Related citations

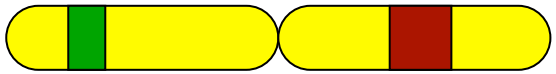
Test Genomic DNA

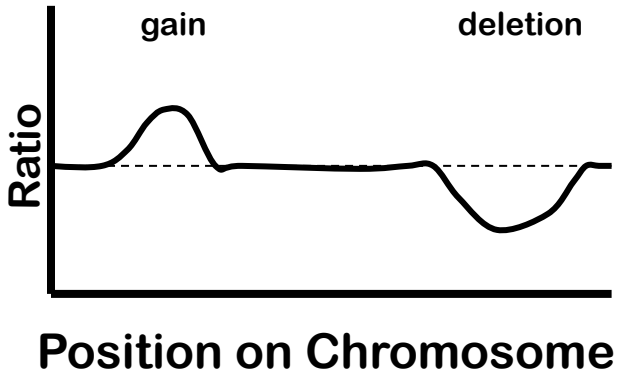
(Tumor DNA)



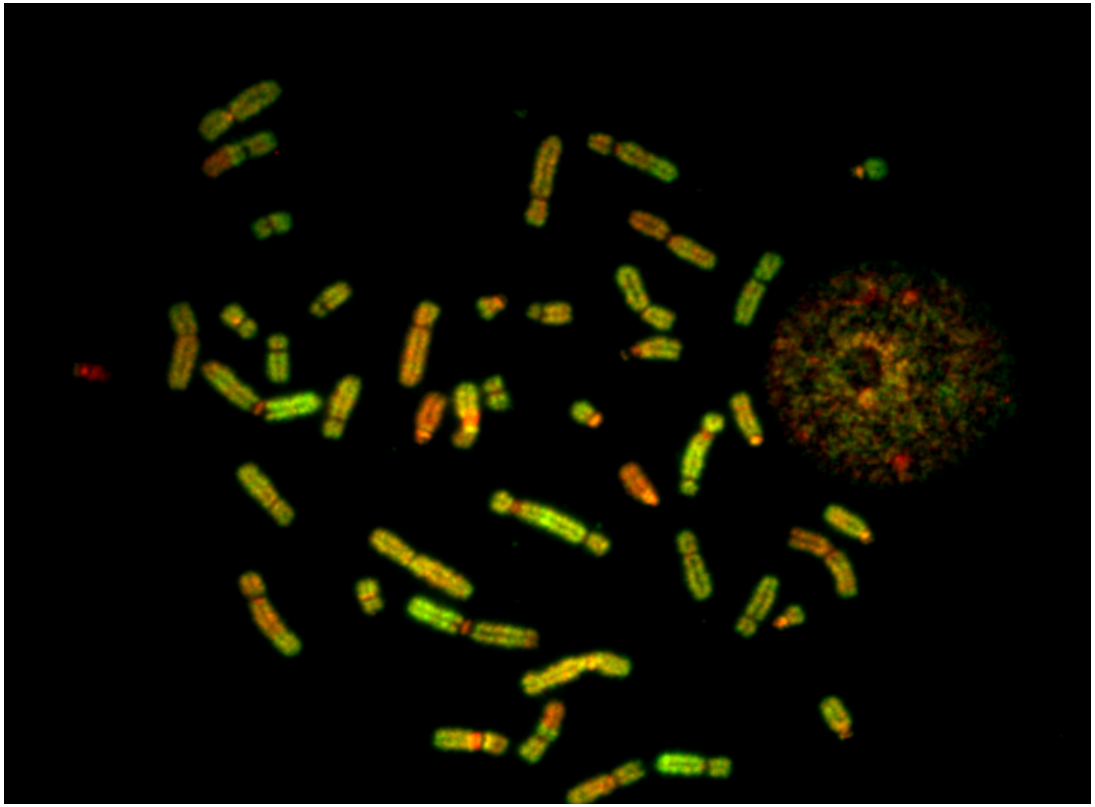
Reference

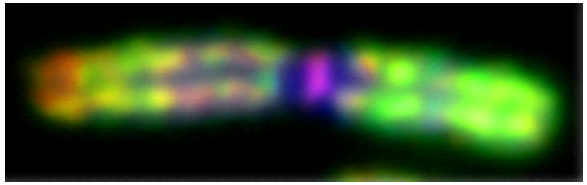
Genomic DNA

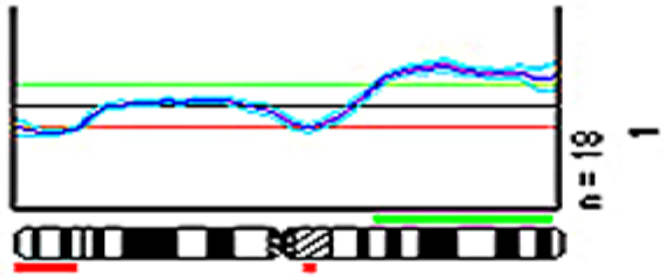




Conventional CGH

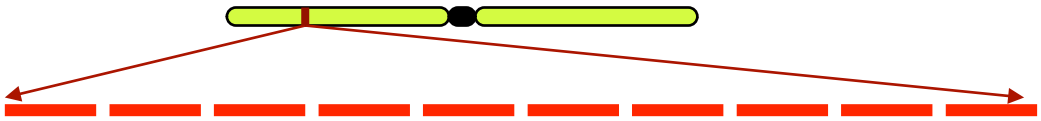






CGH On Microarrays

- Resolution of metaphase CGH ~ 3-5 Mb
- Improve resolution by replacing metaphase chromosomes as targets for CGH with spatially separated DNA clones spotted at high density onto glass slides

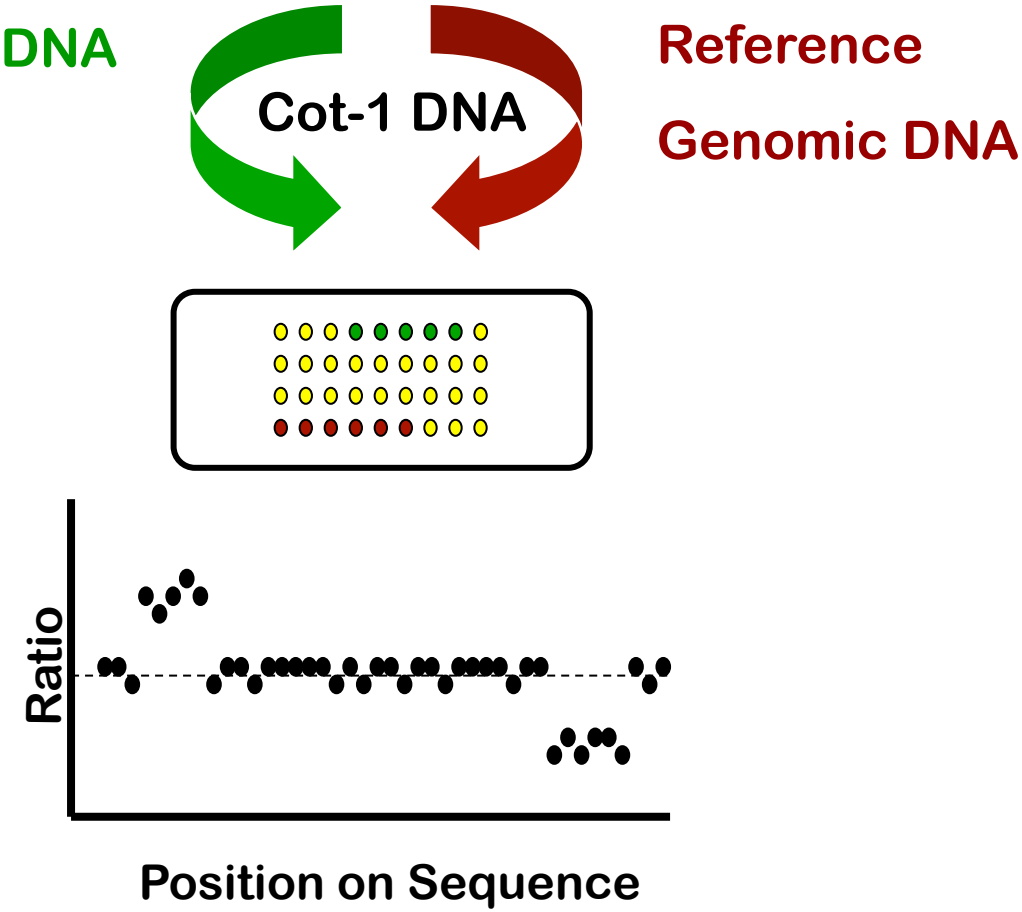


- Resolution will be dependent on clone size and density

Array-CGH

Test Genomic DNA

(Patient DNA)

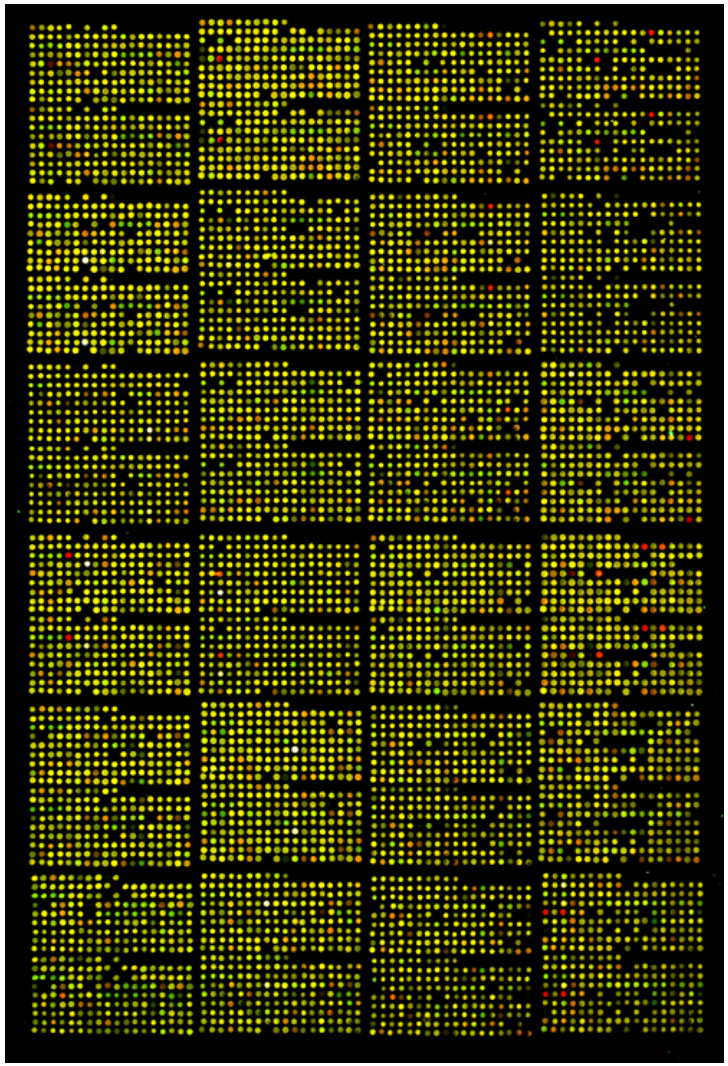


Reference

Genomic DNA

1Mb Resolution Array

- 167 BACs/PACs containing known oncogenes/tumour suppressor genes
- telomeric clone set (S. Knight, Oxford)

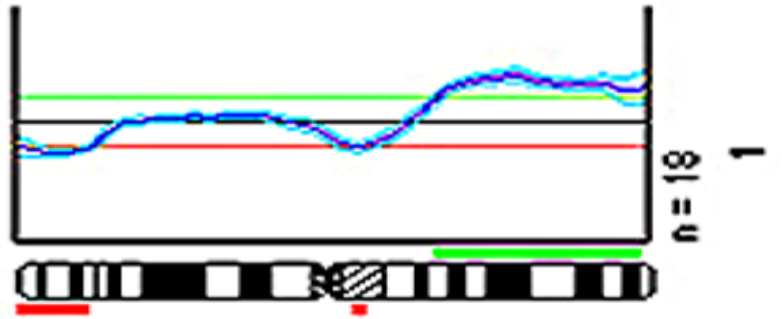


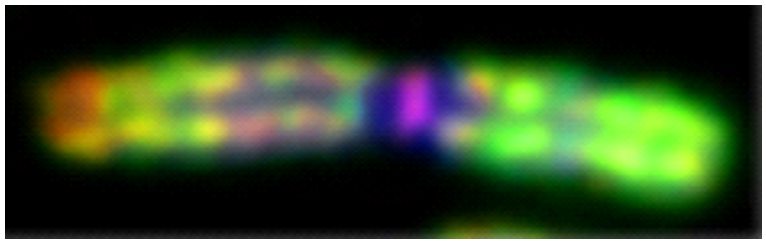
- 3523 clones
- all spotted in duplicate
- clone set publicly available

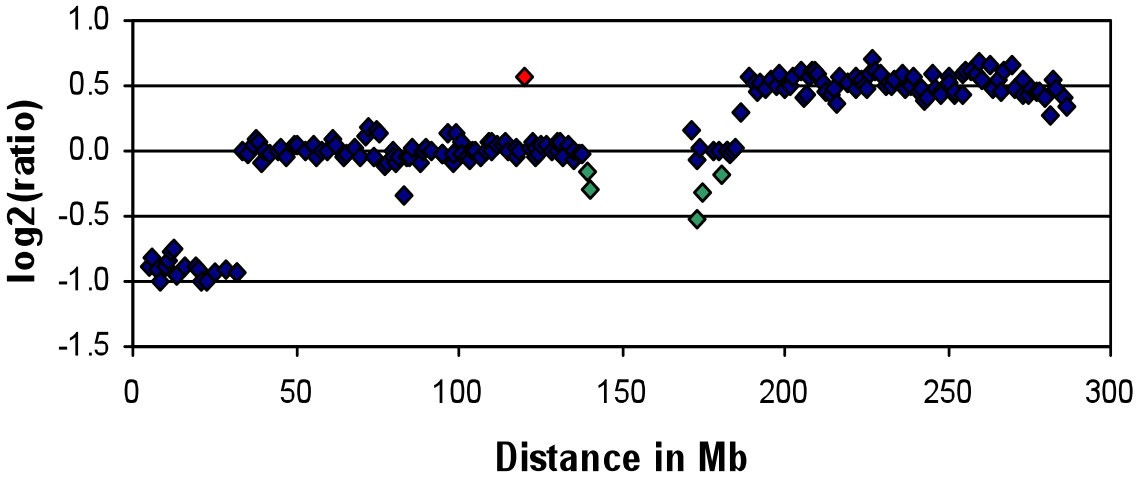
Heike Fiegler

Fiegler et al. (2003) Genes Chromosomes and Cancer 36:361-374

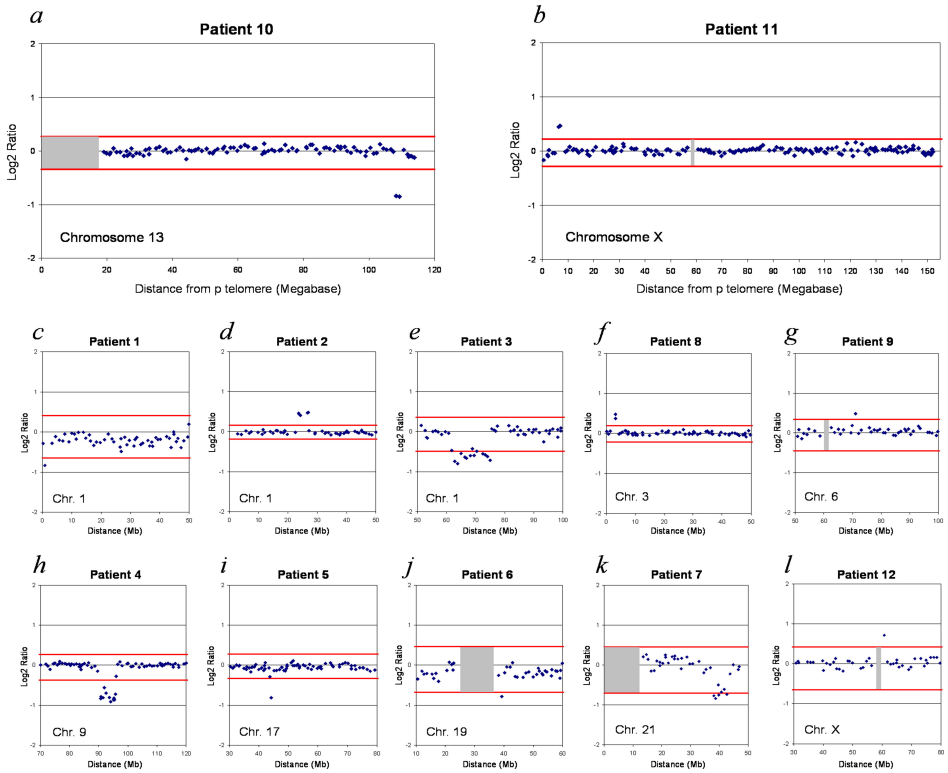
Hybridisation With 769P DNA







Copy number changes in patients with learning difficulty and dysmorphology



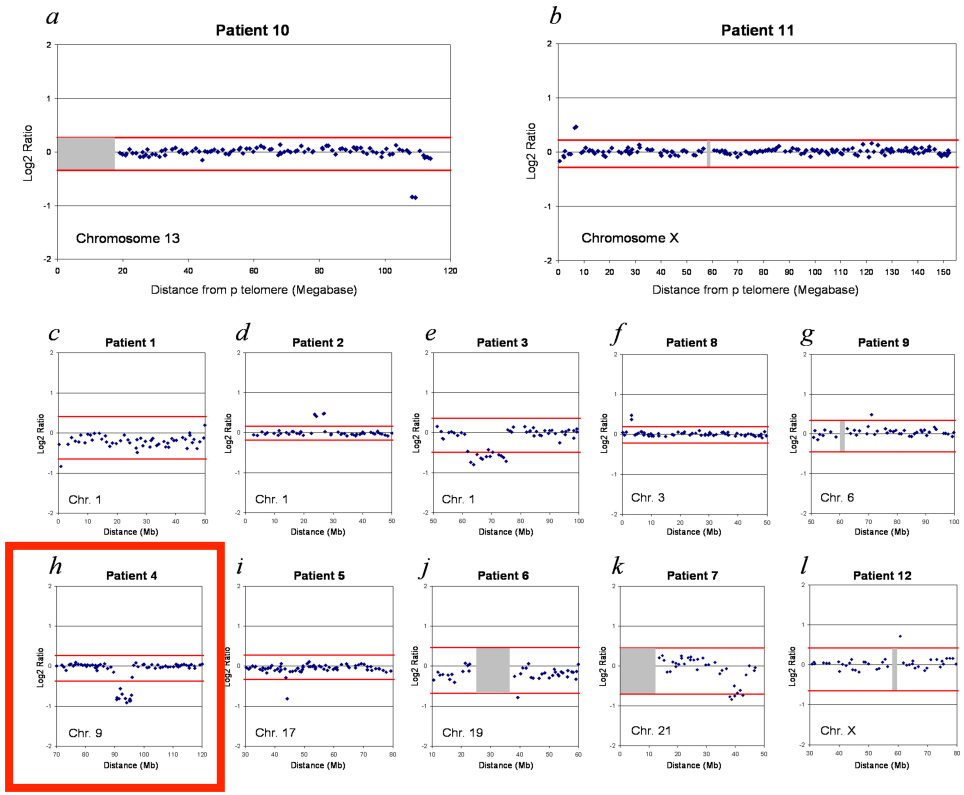
Shaw-Smith C, Redon R, Rickman L, Rio M, Willatt L, Fiegler H et al.,
J. Med Genet 2004; 41:241-248

50 patients

12 with one imbalance

None of the copy number changes are in common

Copy number changes in patients with learning difficulty and dysmorphology



50 patients

12 with one imbalance

J Med Genet 2004;**41**:241–248.

Inserm

Addenbrooke's NHS Trust

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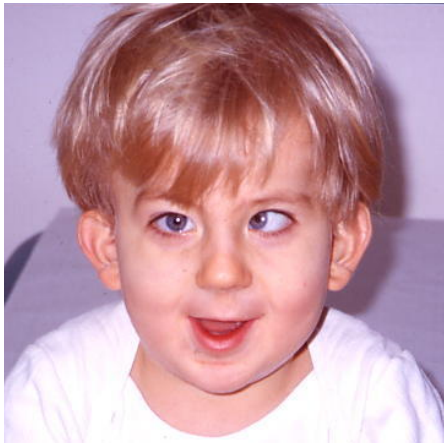
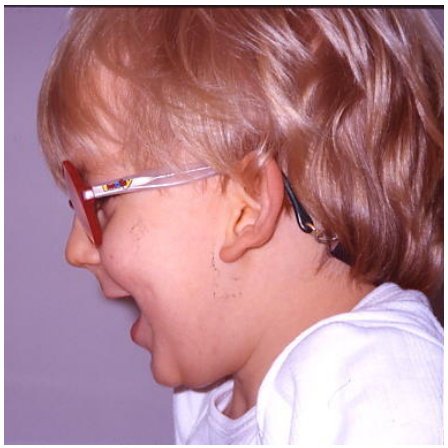
Deletion at 9q22.3



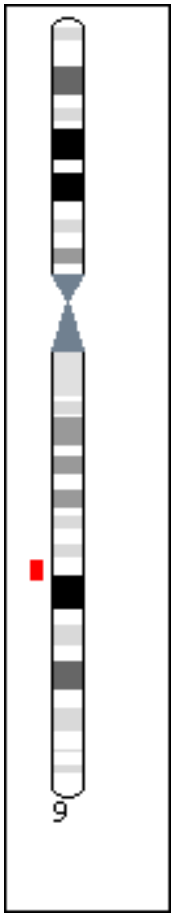


Feeding difficulties in the first months of life

Pre- and post-natal overgrowth
(weight, length, OFC > +3 SD)

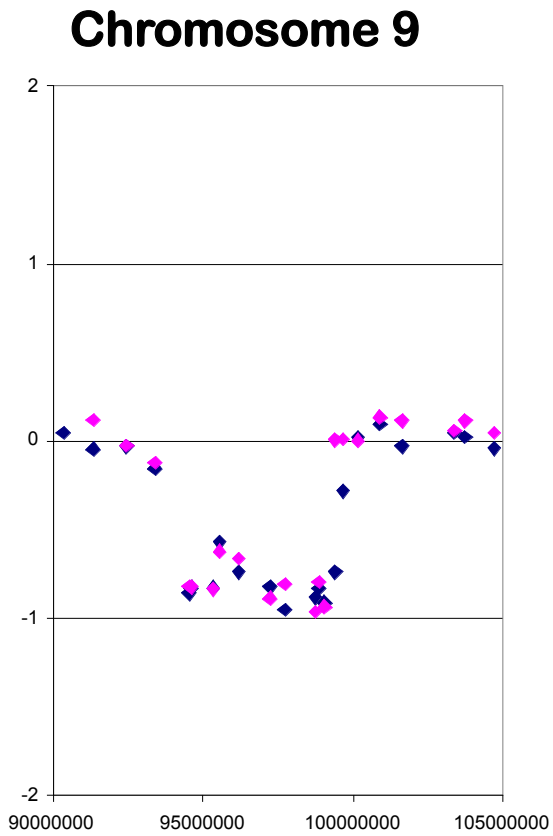
Psychomotor delay and hyperactivity
(still unable to walk unaided at six years of age, no speech)

Hypotonia, trigonocephaly, epicanthic folds, small mouth with a thin upper lip, thickened ears with ear lobule indentation, downslanting palpebral fissures, short neck, pectus excavatum, strabismus, umbilical hernia, thyroglossal cyst, advanced carpal maturation at birth and ventriculomegaly



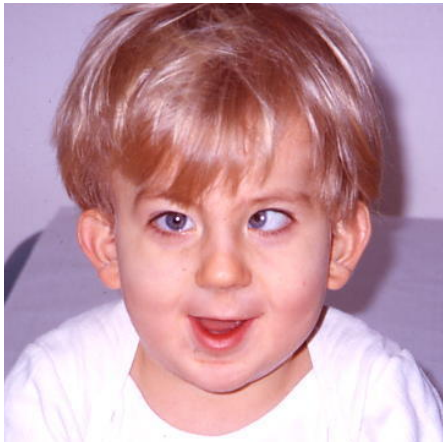
Is the *de novo* 9q22.3 deletion responsible for the phenotype?

Similar deletion at 9q22.3



Richard Redon, Laurence Colleaux

9q22.3 deletion Syndrome



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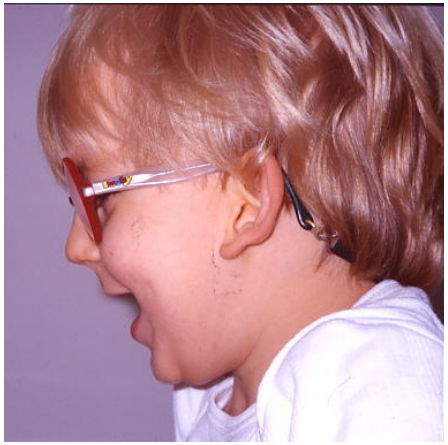
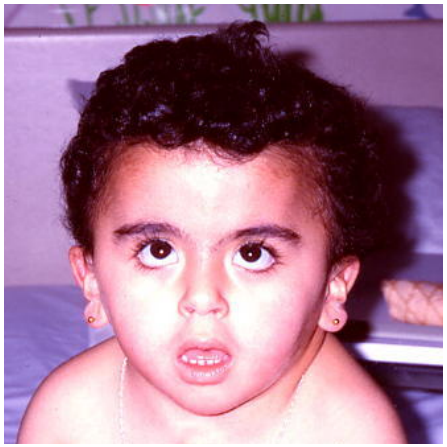
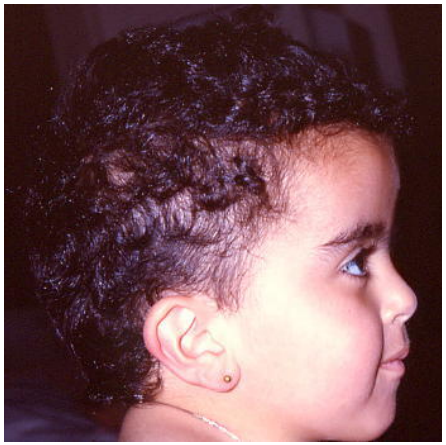




Hypotonia, trigonocephaly, epicanthic folds, small mouth with a thin upper lip, thickened ears with ear lobule indentation, downslanting palpebral fissures, short neck, pectus excavatum, strabismus, umbilical hernia, thyroglossal cyst, advanced carpal maturation at birth and ventriculomegaly



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European Journal of Human Genetics (2006) 14, 759–767

www.nature.com/ejhg

ARTICLE

Interstitial 9q22.3 microdeletion: clinical and molecular characterisation of a newly recognised overgrowth syndrome

Richard Redon[1,3], Geneviève Baujat[2,3], Damien Sanlaville[2], Martine Le Merrer[2], Michel Vekemans[2], Arnold Munnich[2], Nigel P Carter[1], Valérie Cormier-Daire[2] and Laurence Colleaux*[,2]

Introduction to Discovering Genomic Variation
November 2010

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http://decipher.sanger.ac.uk/

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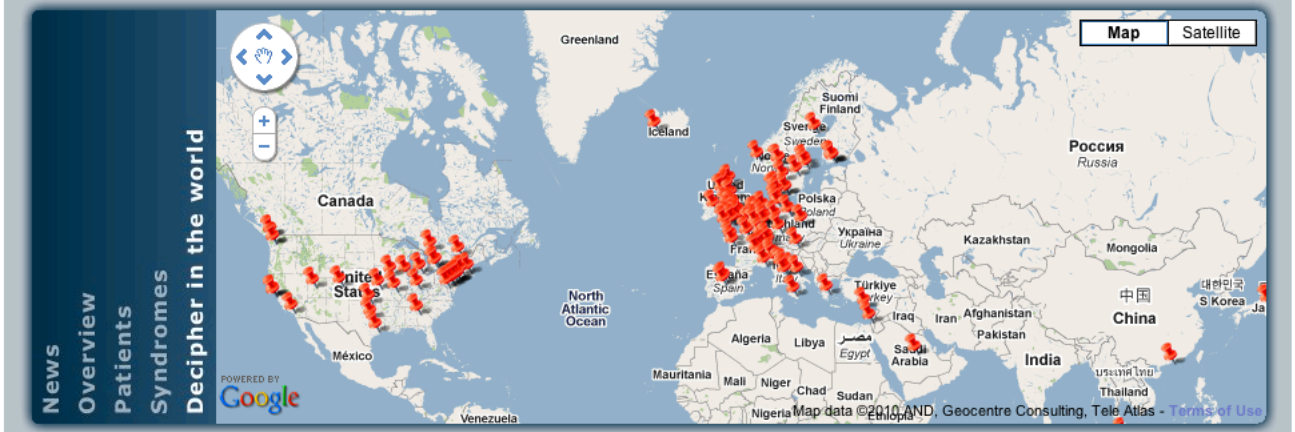

Welcome to DECIPHER V5.0

The DECIPHER website has been completely re-written from the ground up with the aim of improving speed and making tasks intuitive. You will have noticed the new home page with the sliding "pleats" that give you basic information about centres, syndromes, patients and any news.

When you log in, you will see a new tab appear "My patients" - click on this to see all your existing patients. You can now search for any patient number, lab id number, note or any text using the Filter search box. Each page is designed to look similar with tabs having clear functions - just click on them and see what each does - it should be obvious. The exception is the "Aberrations" tab which has even more functional tabs to try.

If you have any difficulties just email decipher@sanger.ac.uk as usual.

We hope you enjoy using the new DECIPHER V5.0

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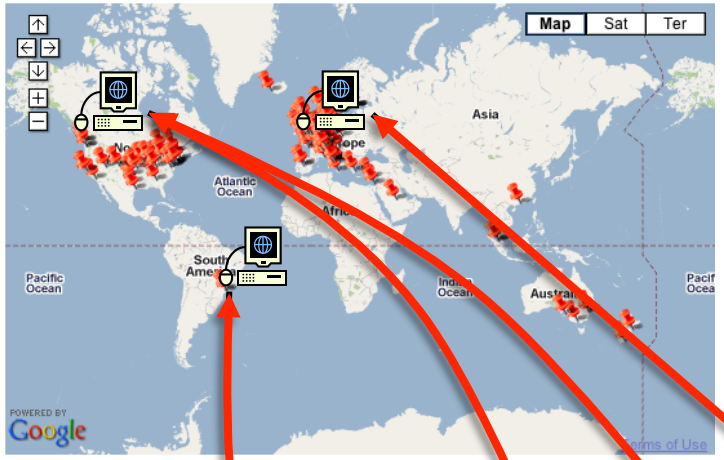

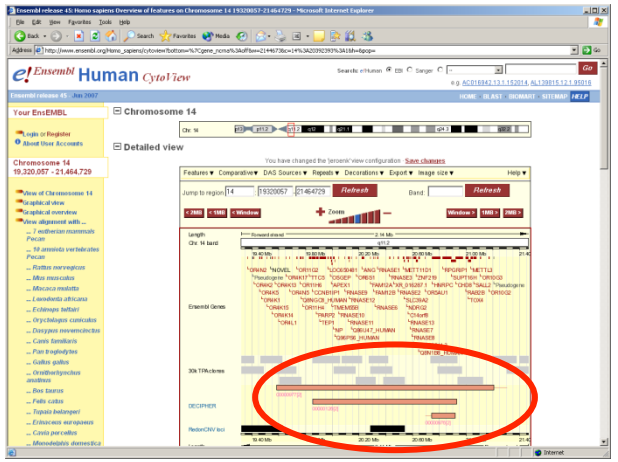

DECIPHER

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A A A A

Patients » ASMP » ASMP000126

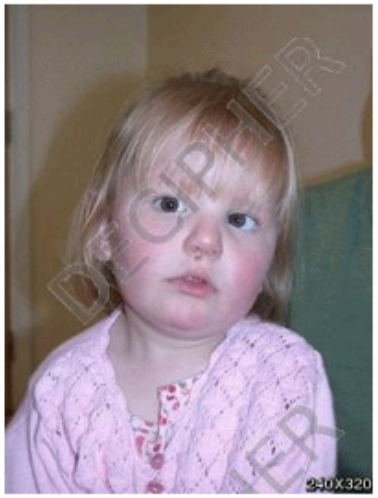
Patient ASMP000126

Print Report

Overview | Aberrations (1) | Phenotypes (5) | Citations (1) | Karyotype

Age at Initial Presentation	2
Chromosomal Sex	46,XX
Patient lab ID	19396 B02/0789
Clinician	
Patient is	Affected
Note	-
Consent	✔

Edit info



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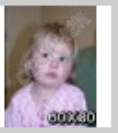
«  »

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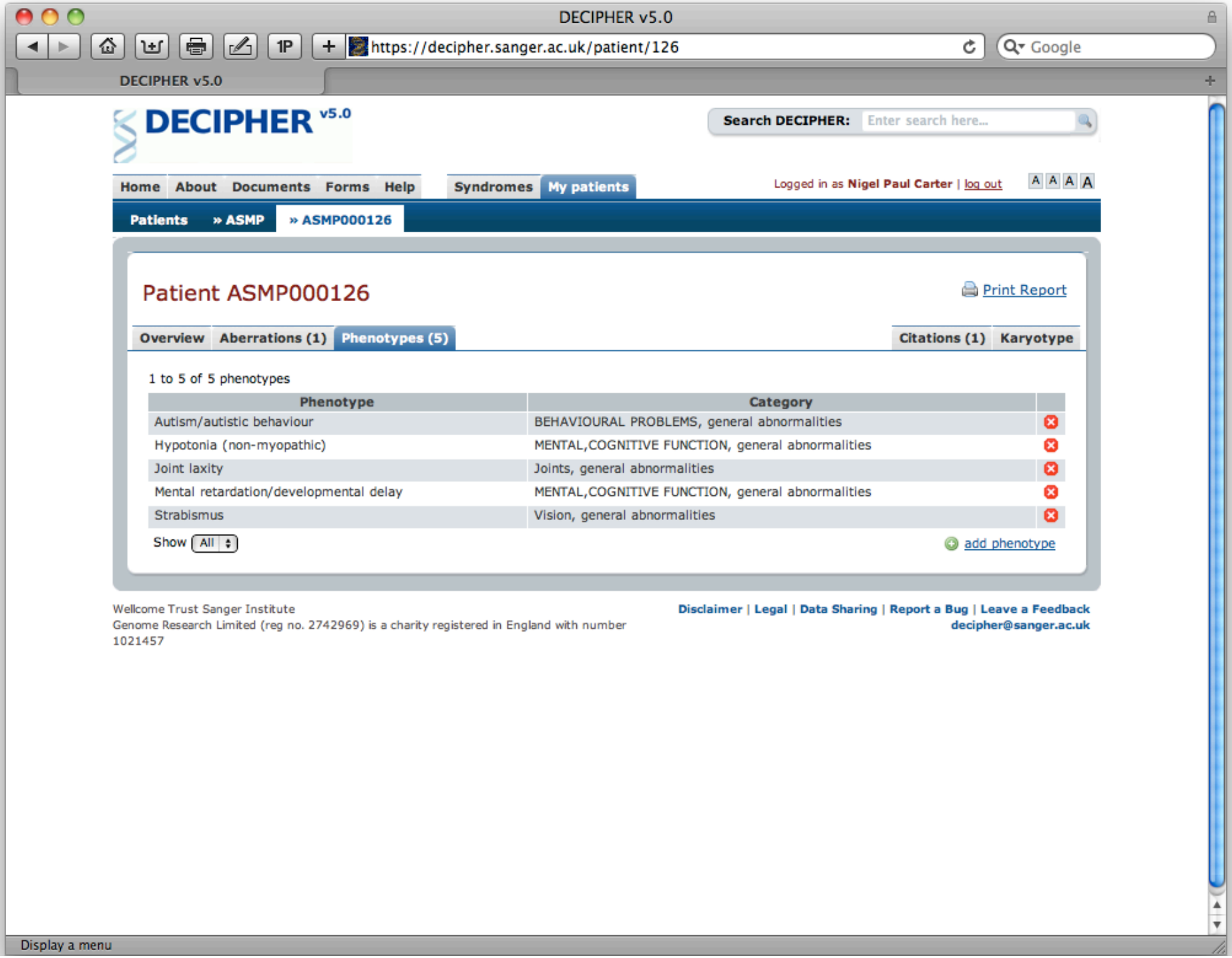
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» ASMP000126
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Overview
Aberrations (1)
Phenotypes (5)
Citations (1)
Karyotype
1 to 5 of 5 phenotypes
Phenotype
Category
Autism/autistic behaviour
BEHAVIOURAL PROBLEMS, general abnormalities
Hypotonia (non-myopathic)
MENTAL,COGNITIVE FUNCTION, general abnormalities
Joint laxity
Joints, general abnormalities
Mental retardation/developmental delay
MENTAL,COGNITIVE FUNCTION, general abnormalities
Strabismus
Vision, general abnormalities
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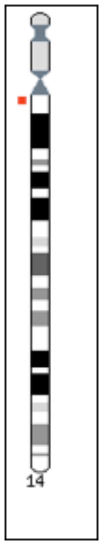
Patients » ASMP » ASMP000126

Patient ASMP000126

Print Report

Overview | Aberrations (1) | Phenotypes (5) | Citations (1) | Karyotype

arr 14q11.2(19,853,959-20,930,827)del dn



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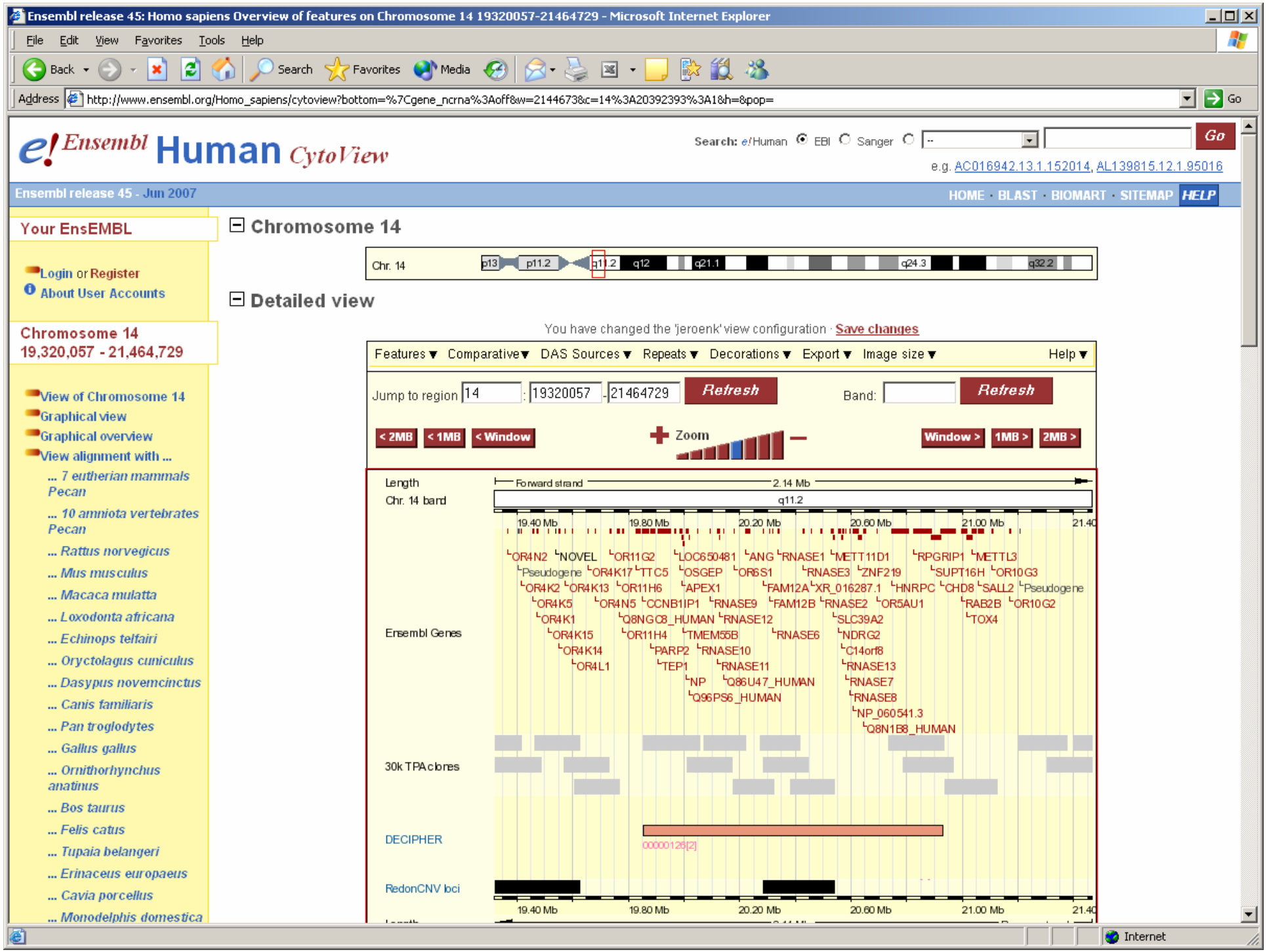
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Chromosome 14
19,320,057 - 21,464,729
View of Chromosome 14
Graphical view
Graphical overview
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... 10 amniota vertebrates Pecan
... Rattus norvegicus
... Mus musculus
... Macaca mulatta
... Loxodonta africana
... Echinops telfairi
... Oryctolagus cuniculus
... Dasypus novemcinctus
... Canis familiaris
... Pan troglodytes
... Gallus gallus
... Ornithorhynchus anatinus
... Bos taurus
... Felis catus
... Tupaia belangeri
... Erinaceus europaeus
... Cavia porcellus
... Monodelphis domestica
Chromosome 14
Chr. 14
p13 p11.2 q11.2 q12 q21.1 q24.3 q32.2
Detailed view
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q11.2
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Ensembl Genes
OR4N2 NOVEL OR11G2 LOC650481 ANG RNASE1 METT11D1 RPGRIP1 METTL3
Pseudogene OR4K17 TTC5 OSGEP OR6S1 RNASE3 ZNF219 SUPT16H OR10G3
OR4K2 OR4K13 OR11H6 APEX1 FAM12A XR_016287.1 HNRPC CHD8 SALL2 Pseudogene
OR4K5 OR4N5 CCNB1IP1 RNASE9 FAM12B RNASE2 OR5AU1 RAB2B OR10G2
OR4K1 Q8NGC8_HUMAN RNASE12 SLC39A2 TOX4
OR4K15 OR11H4 TMEM55B RNASE6 NDRG2
OR4K14 PARP2 RNASE10 C14orf8
OR4L1 TEP1 RNASE11 RNASE13
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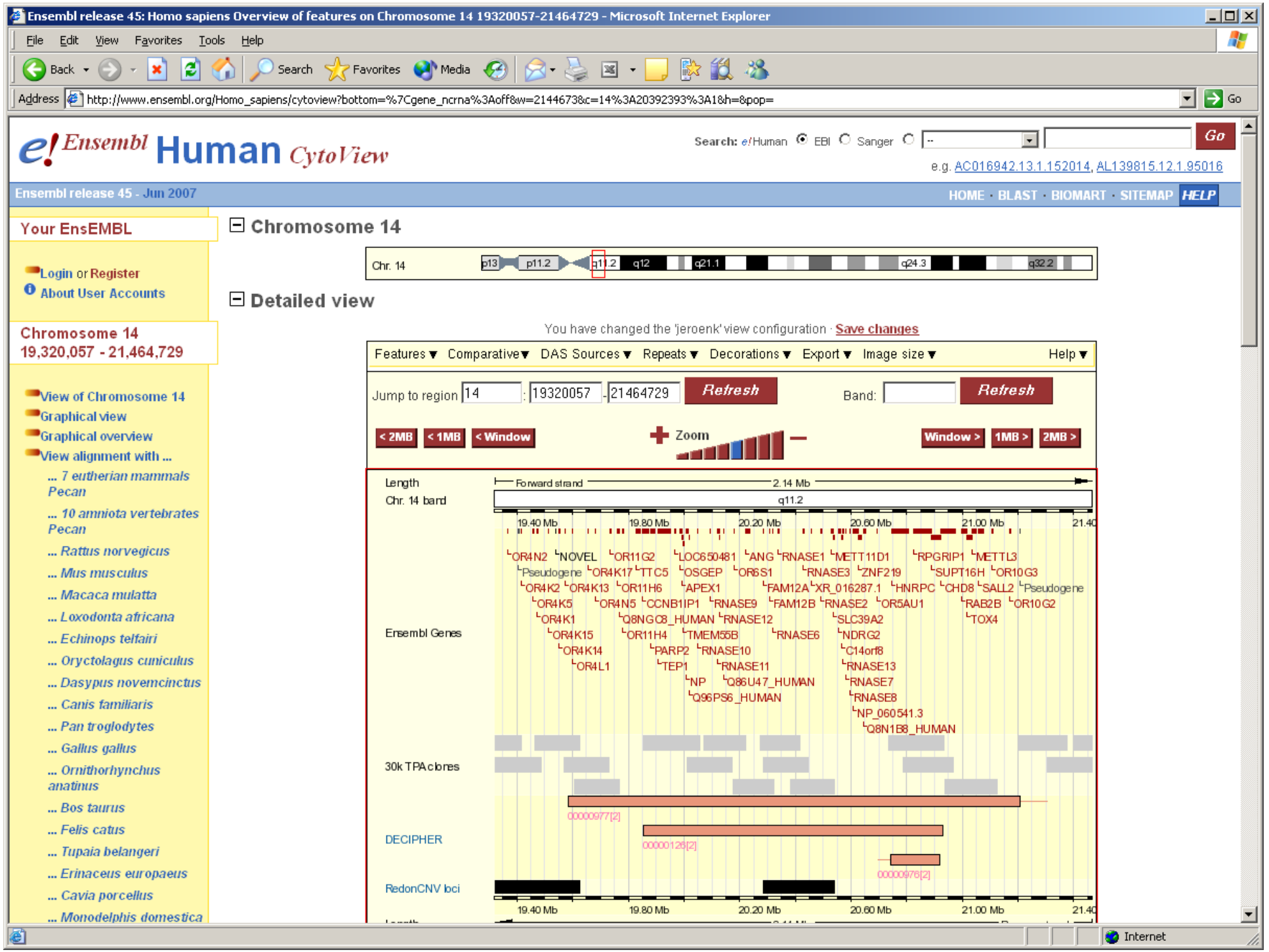
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... Rattus norvegicus
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... Oryctolagus cuniculus
... Dasypus novemcinctus
... Canis familiaris
... Pan troglodytes
... Gallus gallus
... Ornithorhynchus anatinus
... Bos taurus
... Felis catus
... Tupaia belangeri
... Erinaceus europaeus
... Cavia porcellus
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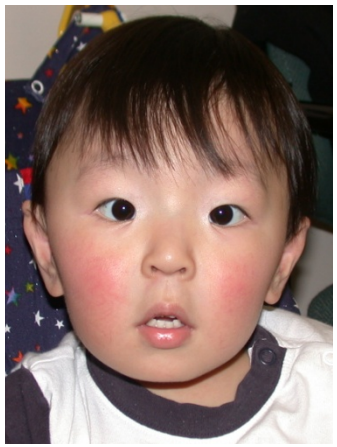
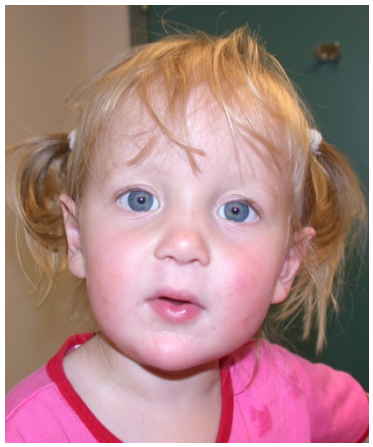
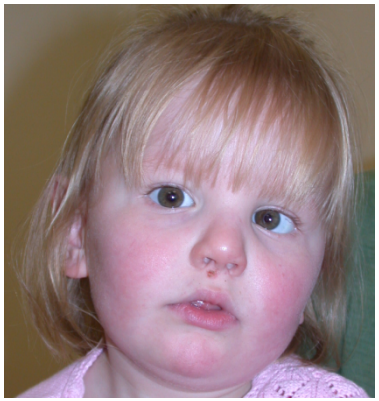
19.40 Mb 19.80 Mb 20.20 Mb 20.60 Mb 21.00 Mb 21.40
Ensembl Genes
30k TPAclones
DECIPHER
RedonCNV loci

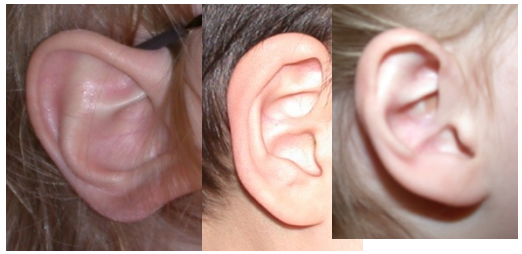
International Collaboration

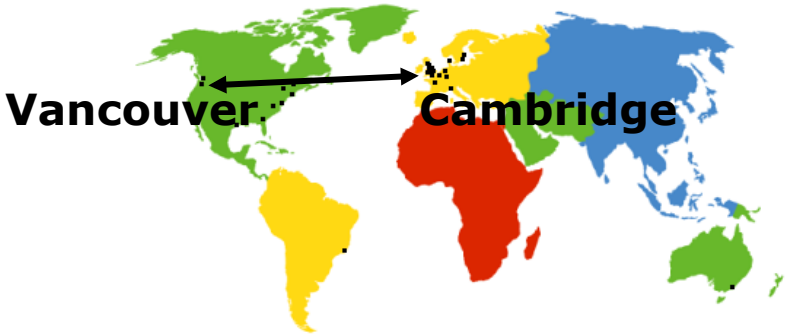
Del 14q11.2 Syndrome











- **Symptoms/Phenotype**
  - Developmental delay
  - Autism spectrum disorder
  - Hypotonia
  - Squint
  - Normal growth parameters
  - Mild dysmorphisms
  - eg. hypoplastic nasal bridge, short nose with long philtrum, prominent antihelices etc.

- **Candidate genes**
  - SUPT16H — Subunit of FACT Chromatin binding and remodelling
  - CHD8 — Epigenetic regulation of transcription
  - NDRG2 — Neurite outgrowth

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Zahir F et al. Novel deletions of 14q11.2 associated with mental retardation and similar minor anomalies in three children. J Med Genet 2007 May 2007 epub

DECIPHER v5.0

Search DECIPHER: Enter search here...

Home | About | Documents | Forms | Help | Syndromes | My patients

Logged in as **Nigel Paul Carter** | log out

Patients » ASMP » ASMP000126

Patient ASMP000126

Print Report

Overview | Aberrations (1) | Phenotypes (5) | Citations (1) | Karyotype

1 to 1 of 1 aberrations

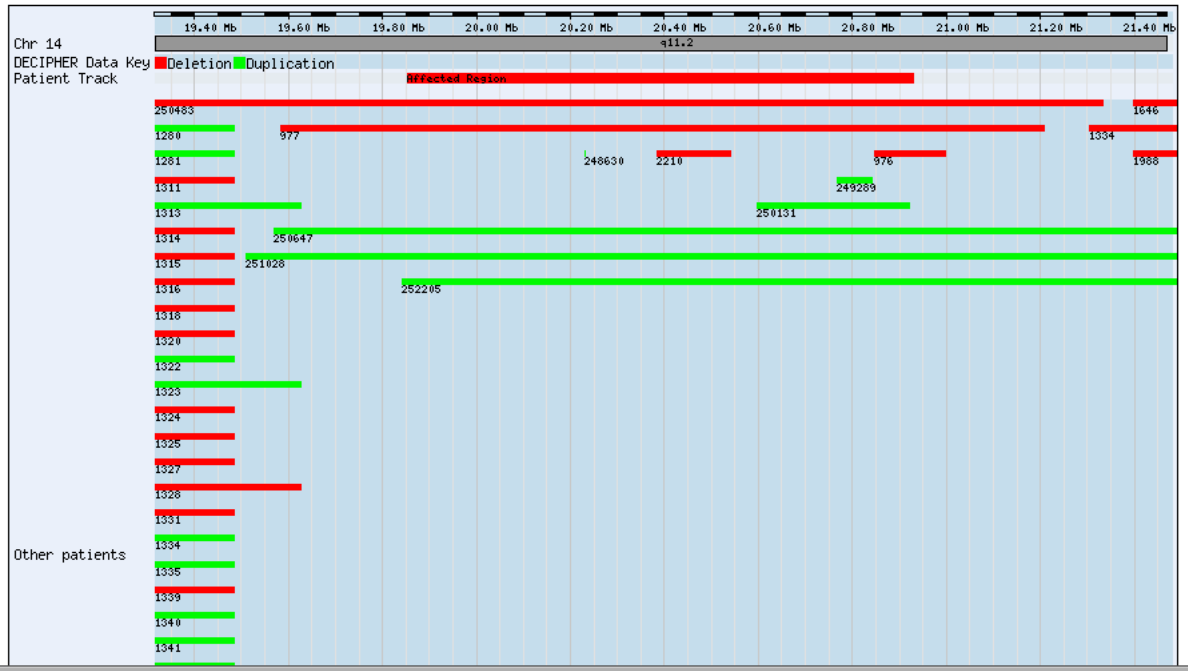
Filter...

	Chr	Start(bp)	End(bp)	Interval (Mb)	Mean Ratio	Classification	UCSC/e!	Edit/Del
⊙	14	19853959	20930827	1.08	-1	de novo		

10 per page

add aberration

Graph | HGNC (35) | OMIM (12) | Imprinted (0) | known (42) | novel (7) | Overlap (15)



Display a menu

LETTERS

nature genetics

Microdeletion encompassing *MAPT* at chromosome 17q21.3 is associated with developmental delay and learning disability

Charles Shaw-Smith[1,8], Alan M Pittman[2,8], Lionel Willatt[3,8], Howard Martin[4], Lisa Rickman[1], Susan Gribble[5], Rebecca Curley[5], Sally Cumming[4], Carolyn Dunn[3], Dimitrios Kalaitzopoulos[5], Keith Porter[5], Elena Prigmore[5], Ana C V Krepischi-Santos[6], Monica C Varela[7], Celia P Koiffmann[7], Andrew J Lees[2], Carla Rosenberg[6], Helen V Firth[1], Rohan de Silva[2] & Nigel P Carter[5]

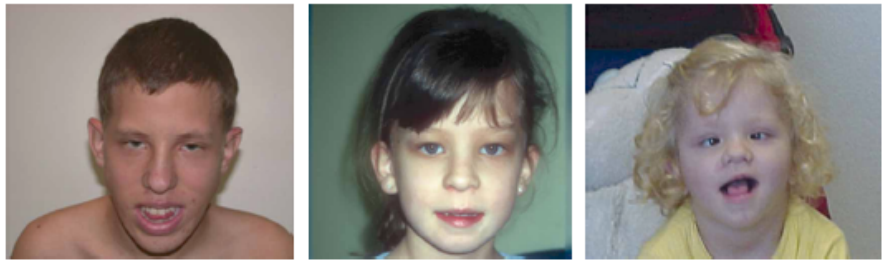
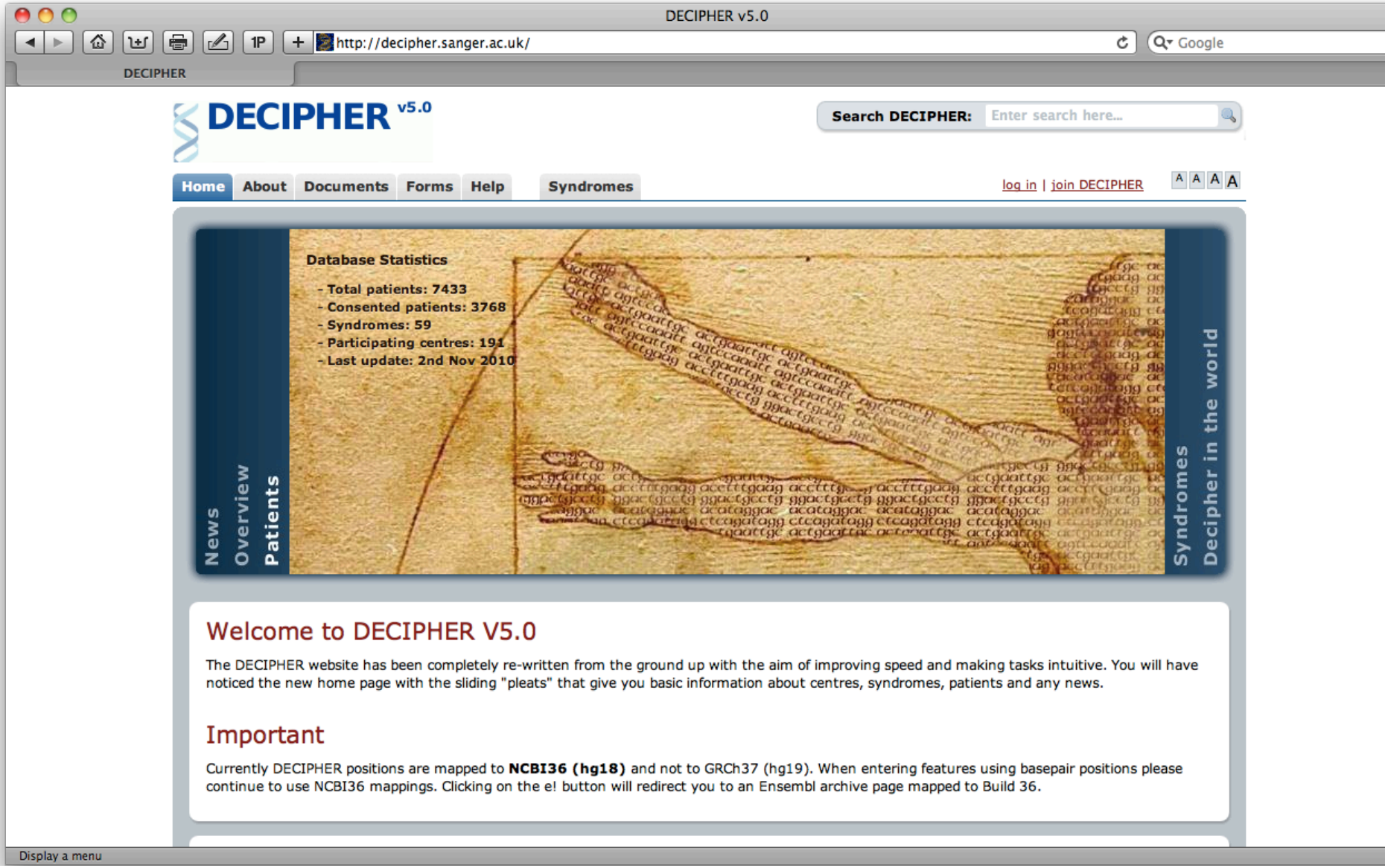
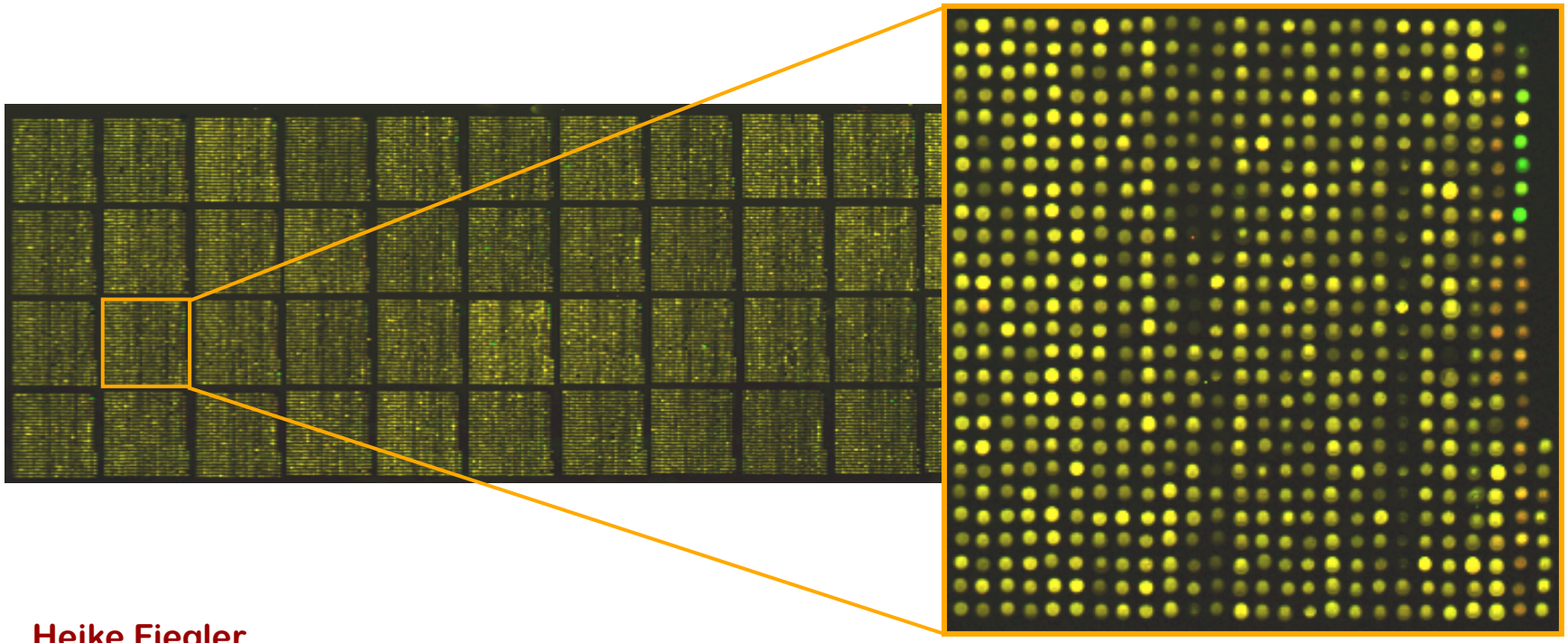


Figure 1 Clinical photographs of affected individuals. Craniofacial dysmorphic features are presented for each case in **Table 1**. We obtained informed consent to publish the photographs above.


DECIPHER v5.0
http://decipher.sanger.ac.uk/
Google
DECIPHER
DECIPHER v5.0
Search DECIPHER:
Enter search here...
Home
About
Documents
Forms
Help
Syndromes
log in | join DECIPHER
Database Statistics
- Total patients: 7433
- Consented patients: 3768
- Syndromes: 59
- Participating centres: 191
- Last update: 2nd Nov 2010
News
Overview
Patients
Syndromes
Decipher in the world
Welcome to DECIPHER V5.0
The DECIPHER website has been completely re-written from the ground up with the aim of improving speed and making tasks intuitive. You will have noticed the new home page with the sliding "pleats" that give you basic information about centres, syndromes, patients and any news.
Important
Currently DECIPHER positions are mapped to NCBI36 (hg18) and not to GRCh37 (hg19). When entering features using basepair positions please continue to use NCBI36 mappings. Clicking on the e! button will redirect you to an Ensembl archive page mapped to Build 36.
Display a menu

The Sanger Institute
Whole Genome Tiling Path Array

27,000 clones covering the whole human genome



Heike Fiegler

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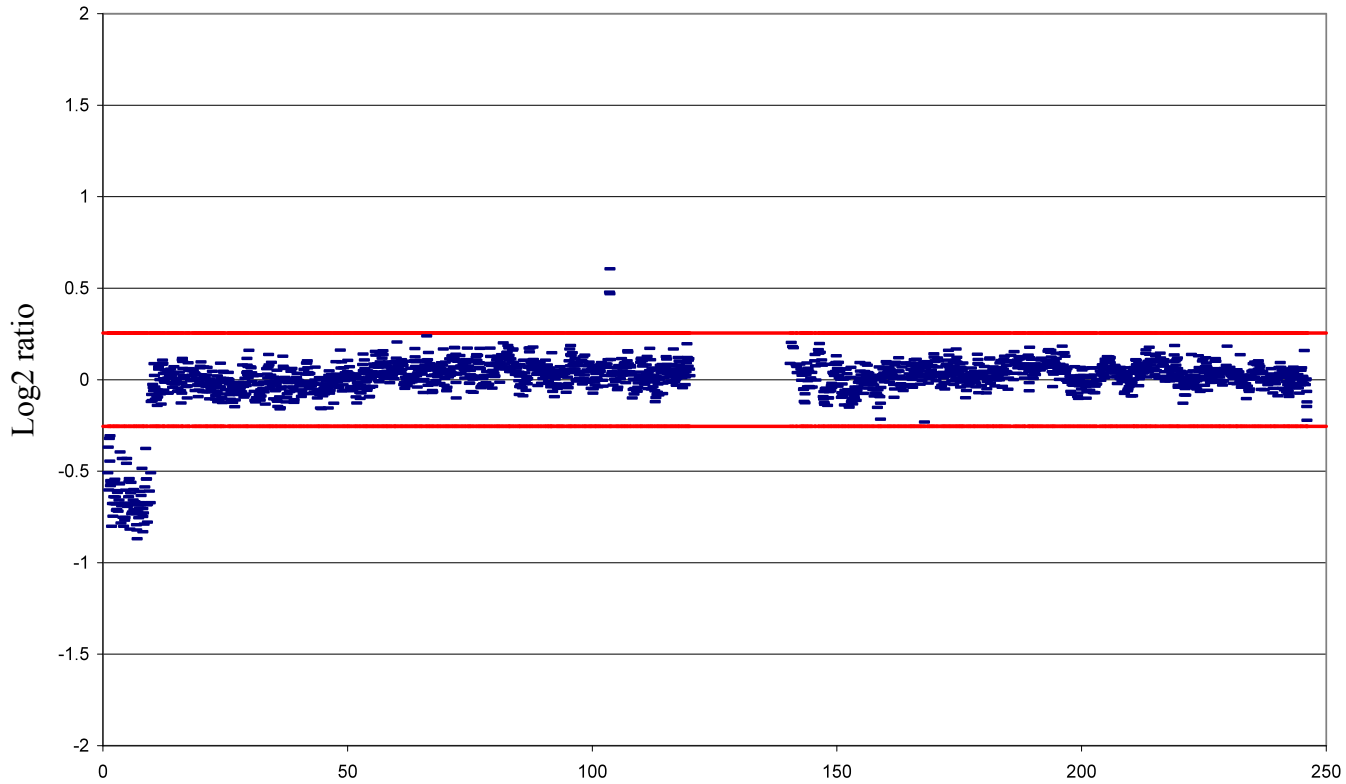
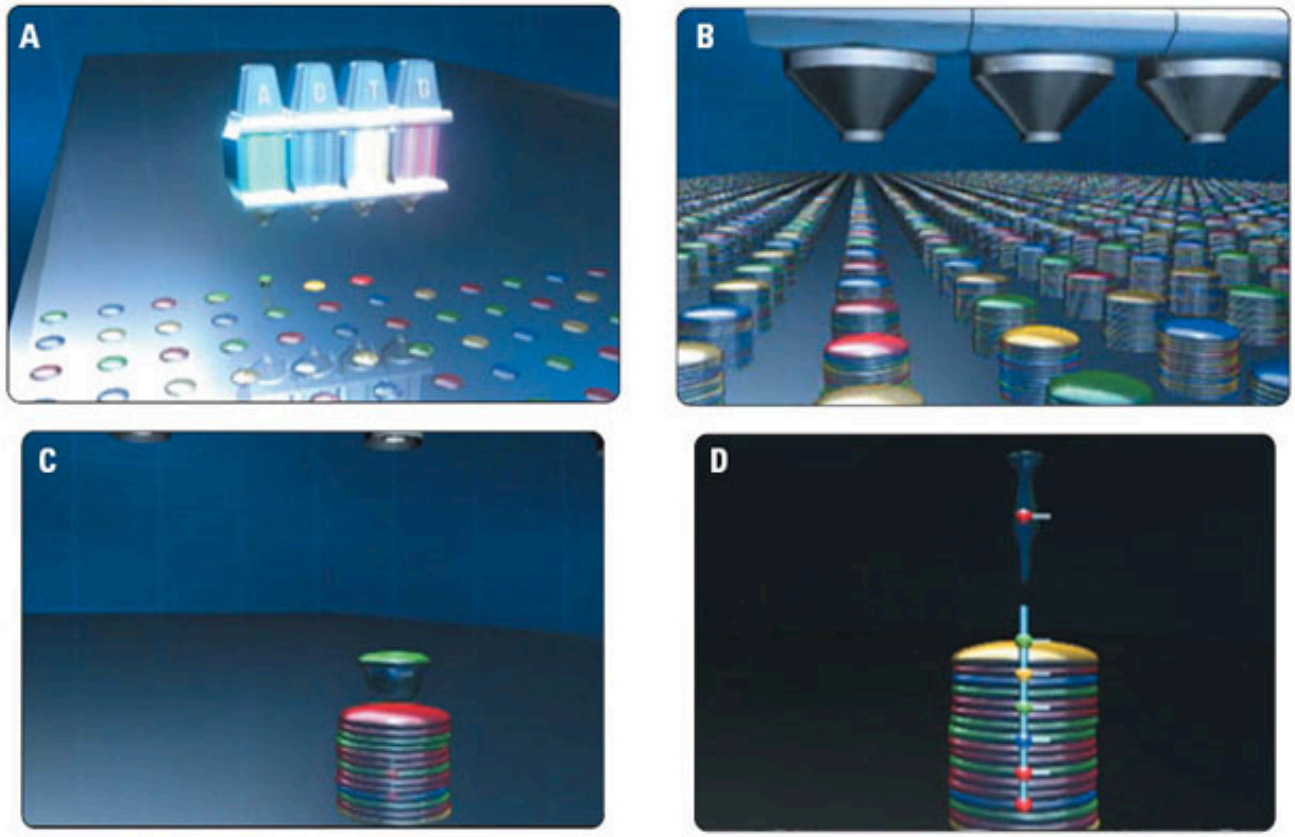
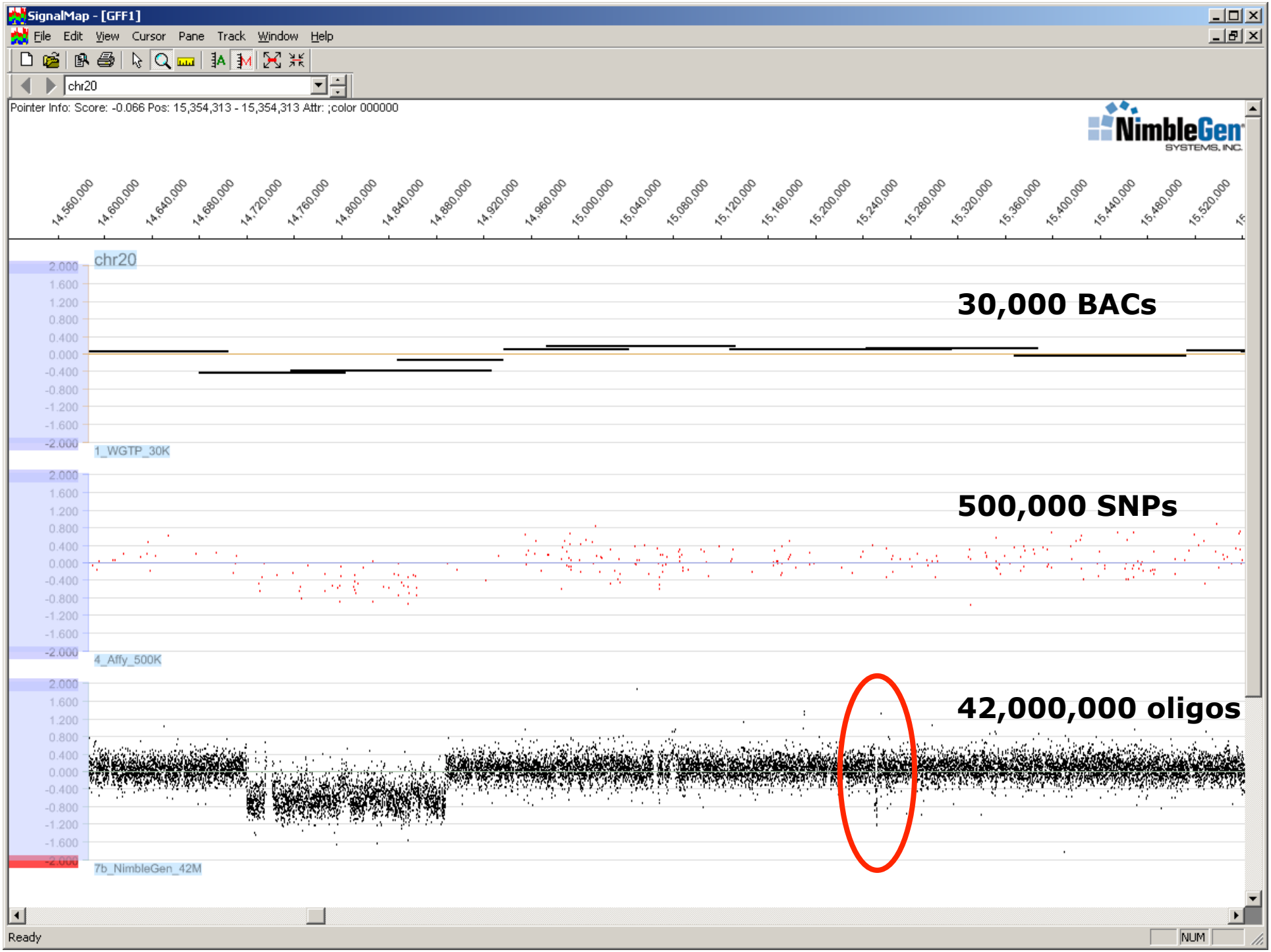
Deletion on Chromosome 1



Richard Redon

Oligonucleotide Arrays




SignalMap - [GFF1]
File Edit View Cursor Pane Track Window Help
chr20
Pointer Info: Score: -0.066 Pos: 15,354,313 - 15,354,313 Attr: ;color 000000
NimbleGen SYSTEMS, INC.
14,560,000 14,600,000 14,640,000 14,680,000 14,720,000 14,760,000 14,800,000 14,840,000 14,880,000 14,920,000 14,960,000 15,000,000 15,040,000 15,080,000 15,120,000 15,160,000 15,200,000 15,240,000 15,280,000 15,320,000 15,360,000 15,400,000 15,440,000 15,480,000 15,520,000
chr20
2.000 1.600 1.200 0.800 0.400 0.000 -0.400 -0.800 -1.200 -1.600 -2.000
1_WGTP_30K
30,000 BACs
4_Affy_500K
500,000 SNPs
7b_NimbleGen_42M
42,000,000 oligos
Ready
NUM

Deciphering Developmental Disorders

'To advance clinical genetic practice for children with developmental disorders by the systematic application of the latest microarray and sequencing methods while addressing the new ethical challenges raised'

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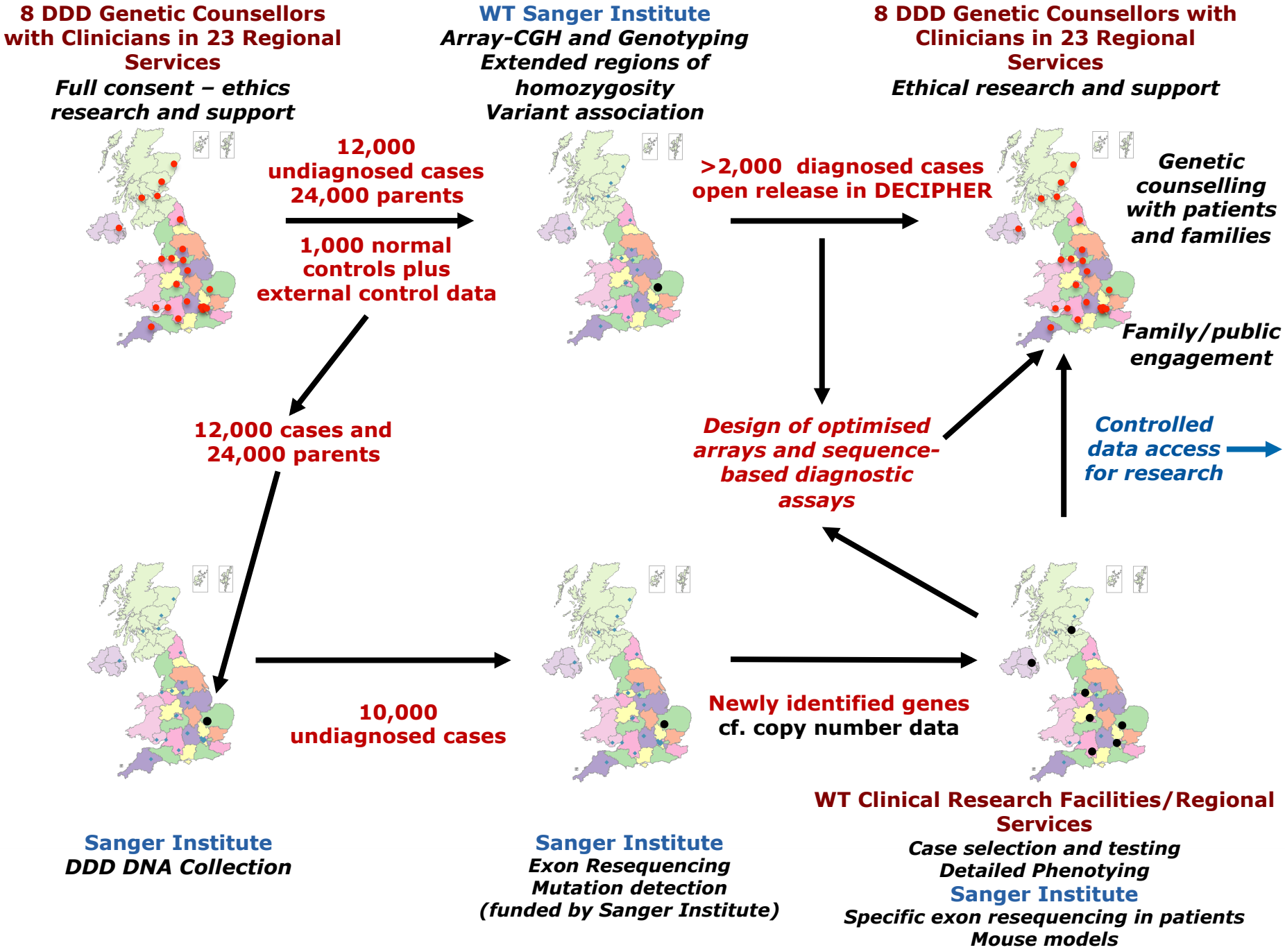
Health Innovation Challenge Fund

wellcome trust NHS

Introduction to Discovering Genomic Variation
November 2010


8 DDD Genetic Counsellors with Clinicians in 23 Regional Services
Full consent – ethics research and support
WT Sanger Institute
Array-CGH and Genotyping
Extended regions of homozygosity
Variant association
8 DDD Genetic Counsellors with Clinicians in 23 Regional Services
Ethical research and support
12,000 undiagnosed cases 24,000 parents
1,000 normal controls plus external control data
>2,000 diagnosed cases open release in DECIPHER
Genetic counselling with patients and families
Family/public engagement
12,000 cases and 24,000 parents
Design of optimised arrays and sequence-based diagnostic assays
Controlled data access for research
10,000 undiagnosed cases
Newly identified genes
cf. copy number data
Sanger Institute
DDD DNA Collection
Sanger Institute
Exon Resequencing
Mutation detection
(funded by Sanger Institute)
WT Clinical Research Facilities/Regional Services
Case selection and testing
Detailed Phenotying
Sanger Institute
Specific exon resequencing in patients
Mouse models

Array Design

- **2 million probe array-CGH (Proband)**
  - **Copy number changes**
    - **5 probes per exon, conserved regions, linc RNAs**
    - **CNVs**
    - **Genome backbone probes – every ~3 kb**
- **> 700+100k SNP genotyping array (Trios)**
  - **SNP association, extended regions LOH**
    - **CNV tagging SNPs**
    - **100k probes filling gaps**

Acknowledgements

DECIPHER Team

Manuel Corpas, Eugene Bragin
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Steven Van Vooren (Data Mining)

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and all DECIPHER Consortium members, patients and families

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DDD

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- **Wet lab - Susan Gribble, Elena Prigmore, Di Rajan, Kirsty Ambridge, Daniel Barrett, Netravathi Krishnappa, Tanya Bayzetinova**
- **+ 1 Statistical Geneticist**
- **Project Manager – Caroline Wright**
- **Social Scientist/Ethicist – Anna Middleton**

- **Sanger Pipelines**
- **DECIPHER Team**