Genomics and Intellectual Disability: what psychiatrists need to know

Dr Frances Elmslie
Consultant Clinical Geneticist
SE Genomic Medicine Service Alliance

8th May 2026

NHS South East Genomic Medicine Service

1

Summary

- Uses of genomics in mental health services
- Why a diagnosis matters
- Background to genomics
- Methods of interrogating the genome
- The Genomic Medicine Service in England

NHS South East Genomic Medicine Service

2

Potential Applications of Genomics in ID and Mental Health services

- Diagnostic testing – use of different technologies to make a diagnosis
- Pharmacogenomics – use of genomic testing to inform prescribing *(we are almost here)*
- Polygenic risk scores – testing multiple variants to assess risk, often integrated with other risk factors (eg BMI, ethnicity) to create an Integrated Risk Score *(we are not here yet…)*

NHS South East Genomic Medicine Service

3

Why is a diagnosis important?

- A genomic diagnosis can give individuals an explanation, likely prognosis and can avoid other unnecessary investigations
- Allows screening/monitoring for other symptoms
- Can help with access to education/support/care
- May allow access to specific therapies, research, clinical trials
- Will enable genetics professionals to give advice about risks to other family members

NHS South East Genomic Medicine Service

4

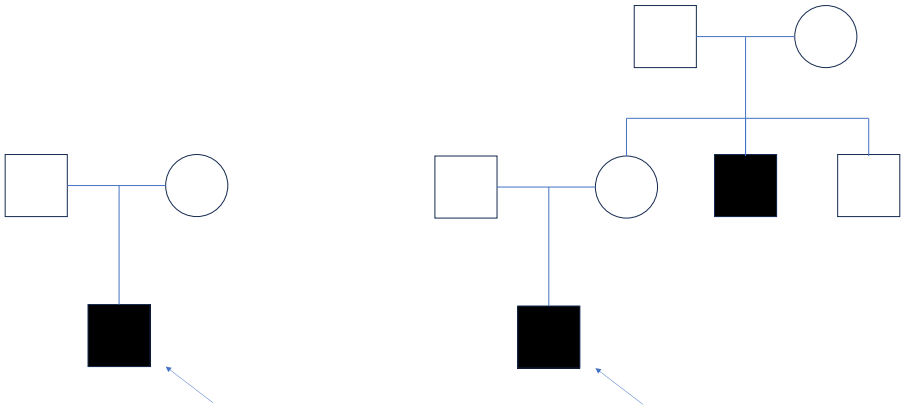
Factors influencing a diagnosis

- Severity of developmental delay/intellectual disability
- Presence of comorbidities eg epilepsy, physical characteristics
- Absence of family history
- Earlier age of presentation

NHS South East Genomic Medicine Service

5

The importance of the family history



NHS South East Genomic Medicine Service

6

Genetics vs. Genomics

Genetics is the study of heredity, focussing on specific genes that code for functional molecules

Genomics is the study of an organism's complete set of genetic information

The **genome** is the complete genetic information of an organism (usually a human or a pathogen in healthcare)

NHS South East Genomic Medicine Service

7

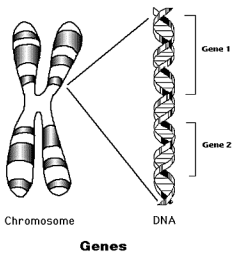
What can go wrong?

NHS South East Genomic Medicine Service

46 Chromosomes

23 pairs

22 pairs of autosomes,
1 pair sex chromosomes



Molecular Genetic abnormalities

~20,000 genes

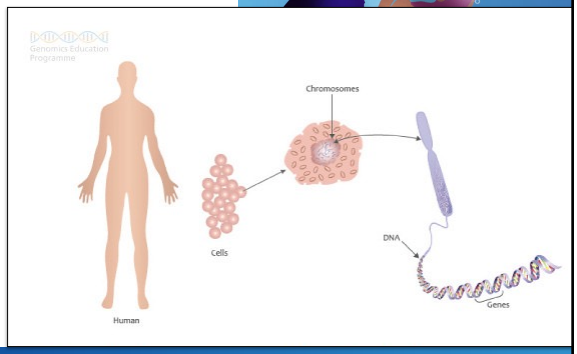
8

Variation in the human genome

The genome consists of **3 billion** base pairs of DNA

Only **0.1%** different from any other person's

This equates to **3 million** differences in the DNA sequence



NHS South East Genomic Medicine Service

9

Variant calling

Scientists identify gene variants by comparing the patient's genome to a reference genome

CATTTGCCGTAGGTAATC

Reference Genome

Single nucleotide deletion

CTTAGCCGGTAGGT

Patient's Genome

Substitution **Insertion** **Larger deletion**

NHS South East Genomic Medicine Service

10

Technologies to interrogate the genome

Tests to identify copy number variation:

- Karyotype
- Qf-PCR
- Cell free DNA (NIPT/ct DNA)
- FISH
- Array-CGH
- SNP array
- MLPA

Tests to identify genetic variation:

- Sanger sequencing -
  - Single gene analysis
- Next generation sequencing
  - Panel tests
  - Whole exome – panel based/agnostic
  - Whole genome - panel based/agnostic

Epigenetic tests:

- Methylation studies eg PWS
- Methylation signatures
- Genome-wide methylation analysis

RNA – based tests:

- Splicing studies
- RNA sequencing

NHS South East Genomic Medicine Service

11

NHS South East Genomic Medicine Service

Technologies to interrogate the genome

COPY NUMBER VARIATION

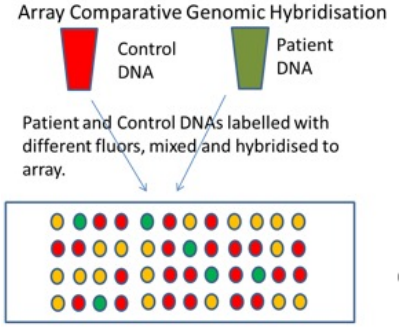
@SEgenomics

12

2005 Array-CGH

NHS South East Genomic Medicine Service

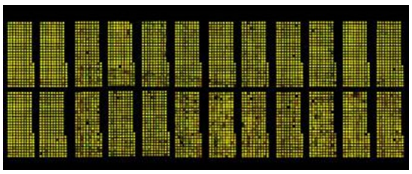
Array Comparative Genomic Hybridisation

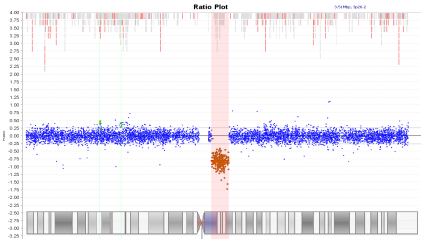


- 1:1 ratio of green:red – normal copy number
- 1.5:1 ratio of green:red - duplication
- 0.5:1 ratio of green:red - deletion

Computer analysis of the ratio of the intensity of the two fluors provides copy number information

Based on oligonucleotides





Now replaced by SNP array – 1M SNPs/array

First line test in person with multiple congenital anomalies, dysmorphism and/or developmental delay/intellectual disability

Identifies copy number variation NOT structural variation

13

Microdeletion syndromes

• Velocardiofacial (DiGeorge, Shprintzen)	chromosome 22q11
• Wolf-Hirschhorn	chromosome 4p16
• Williams	chromosome 7q11
• Smith-Magenis	chromosome 17p11
• Angelman	chromosome15q11-13(mat)
• Prader-Willi	chromosome 15q11-13 (pat)

Common CNVs – issues of penetrance, consider value of cascade testing eg 15q11.2 deletion, 16p11.2 del/dup and guidelines for prenatal testing

NHS South East Genomic Medicine Service

14

NHS South East Genomic Medicine Service

Technologies to interrogate the genome

GENE VARIATION

@SEgenomics

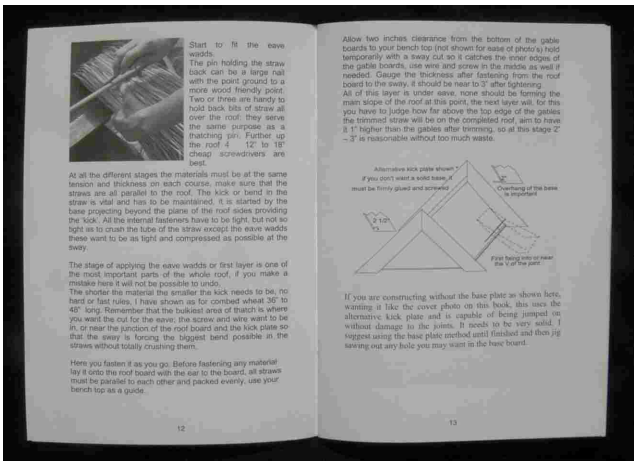
15

NHS South East Genomic Medicine Service

The Genome

16

Single gene disorders



17

Types of sequencing

- Genetic sequencing techniques ‘read’ the sequence of bases in a length of DNA
- Different tests examine different amounts of the genome and each is used for different indications:
  - Targeted variant test ✓
  - Single gene test ✓
  - Panel test (multiple genes) ✓
  - Whole exome sequencing ✓ Prenatal setting only
  - Whole genome sequencing ✓

18

Variant classification

Pathogenic (causative) >99% likelihood

Likely Pathogenic >90% likelihood

Clinically Actionable

Variant of Uncertain Significance (VUS) 10-90% likelihood

Likely benign (up to 10% likelihood)

Benign (non-causative) <1% likelihood

Not reported

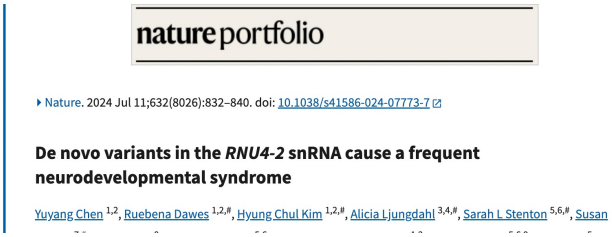
It is recommended that variants of uncertain significance (VUS) will usually only be reported if additional investigations (e.g. biochemical testing or co-segregation studies) could provide sufficient additional evidence to reclassify the variant as likely pathogenic- *Guidelines for Rare Disease Genomic Testing, Interpretation and Reporting, NHS England Genomics Unit*

NHS South East Genomic Medicine Service

19

The dark genome

- Chen *et al.* 2024 (Nature)
- Landmark study identifying *RNU4-2* as a syndromic NDD gene
- Global collaboration (13 countries)
- 115 patients
- 12 variants identified within a highly constrained 18bp region
- ***0.68% of genetically undiagnosed NDD probands in NGRL***


nature portfolio

Nature. 2024 Jul 11;632(8026):832–840. doi: 10.1038/s41586-024-07773-7

De novo variants in the *RNU4-2* snRNA cause a frequent neurodevelopmental syndrome

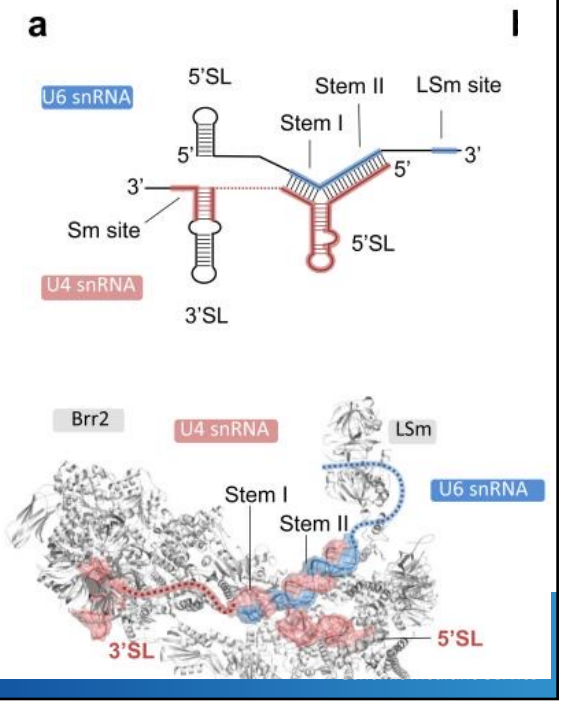
Yuyang Chen [1,2], Ruebena Dawes [1,2,#], Hyung Chul Kim [1,2,#], Alicia Ljungdahl [3,4,#], Sarah L Stenton [5,6,#], Susan

NHS South East Genomic Medicine Service

20

The spliceosome

- *RNU4-2* is one of several genes encoding the U4 small nuclear RNA (U4 snRNA)
- A critical component of the U4/U6.U5 tri-snRNP complex of the major spliceosome



21

Variant analysis

- Single base insertions
  - ➢n.64_65insT (n=89)
  - ➢n.77_78insT (n=6)
- Single nucleotide variants → similar, albeit more moderate phenotypes
- Parental origin analysed in 54 *RNU4-2* variants → ALL maternal

NHS South East Genomic Medicine Service

22

RNU4-2 NDD clinical features

Characteristic	Percentage (%)
Global developmental delay (moderate- severe)	100
Intellectual disability	100
Delayed ambulation (average 3.4yr)	83
Hypotonia	87
Speech anomalies (mostly non-verbal)	94
Seizures (median onset 3 years)	77
Microcephaly	77
Behavioural issues	67
Autism spectrum disorder	48

NHS South East Genomic Medicine Service

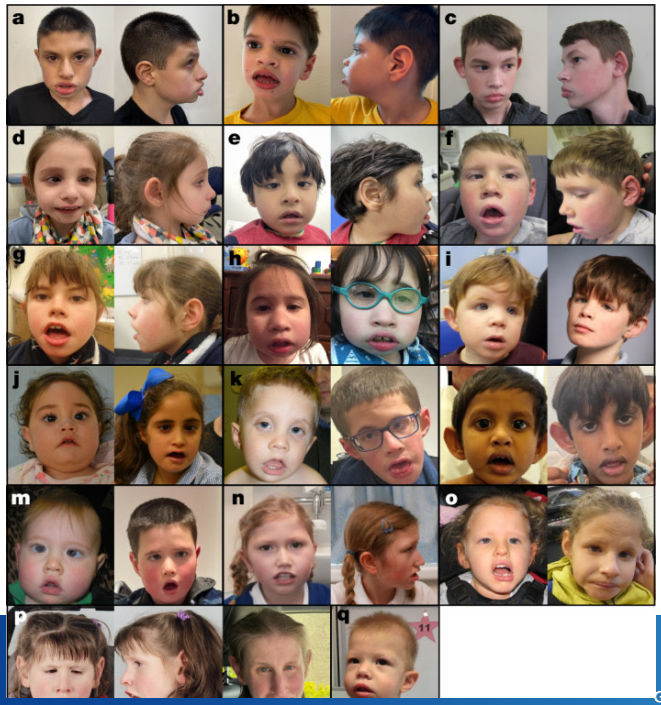
23

Characteristics	Percentage (%)
Hearing loss	22
Visual issues (e.g., optic nerve hypoplasia, nystagmus, strabismus)	79
ENDOCRINE/ SKELETAL	
Short stature	76
Hypothyroidism, pituitary issues, GH deficiency	44
Osteopenia, recurrent fractures, scoliosis	64
GASTROINTESTINAL	
Constipation	66
Reflux	49
Feeding difficulties	76

NHS South East Genomic Medicine Service

24

Facial features



NHS South East Genomic Medicine Service

25

PARENTING

My son Charlie — and the breakthrough that changed our lives

James Coney and his wife, Sarah, struggled not knowing why their 12-year-old was born with a severe learning disability. In their darkest moments, they blamed themselves. Then, out of the blue, came a video call and an answer

James Coney with his son Charlie
LAURA PANNACK FOR THE SUNDAY TIMES MAGAZINE

James Coney, News Projects Editor
Sunday March 02 2025, 12.00am, The Sunday Times

Article | Open access | Published: 30 March 2026

Biallelic variants in *RNU2-2* cause a remarkably frequent developmental and epileptic encephalopathy

Adam Jackson, Alexander J. M. Blakes, Bader Alhaddad, Olivia J. Henry, Angelica M. Delgado-Vega, Elizabeth Wall, Ola Abdelhadi, Shakti Agrawal, Khadijah Bakur, Edward Blair, Angela F. Brady, Helen Brittain, Kate E. Chandler, Natasha Clarke, Miriana Danelli, Nicholas Drinkall, Irene Duba, Frances Elmslie, Jamie Ellingford, Lisa J. Ewans, Andrew P. Fennell, Gabriella Gazdagh, Simon P. Heller, Anna Hammarsjö, ... Siddharth Banka + Show authors

Nature Genetics **58**, 798–809 (2026) | Cite this article

Brief Communication | Open access | Published: 29 May 2025

Analysis of R-loop forming regions identifies *RNU2-2* and *RNU5B-1* as neurodevelopmental disorder genes

Adam Jackson, Nishi Thaker, Alexander Blakes, Gillian Rice, Sam Griffiths-Jones, Meena Balasubramanian, Jennifer Campbell, Nora Shannon, Jungmin Choi, Juhyeon Hong, David Hunt, Anna de Burca, Soo Yeon Kim, Taekeun Kim, Seungbok Lee, Melody Redman, Rocio Rius, Cas Simons, Tiong Yang Tan, Jamie Ellingford, Raymond T. O'Keefe, Jong Hee Chae & Siddharth Banka

Nature Genetics **57**, 1362–1366 (2025) | Cite this article

Review Article | Published: 04 December 2025

Small nuclear RNA genes in Mendelian disorders

Stylianos E. Antonarakis

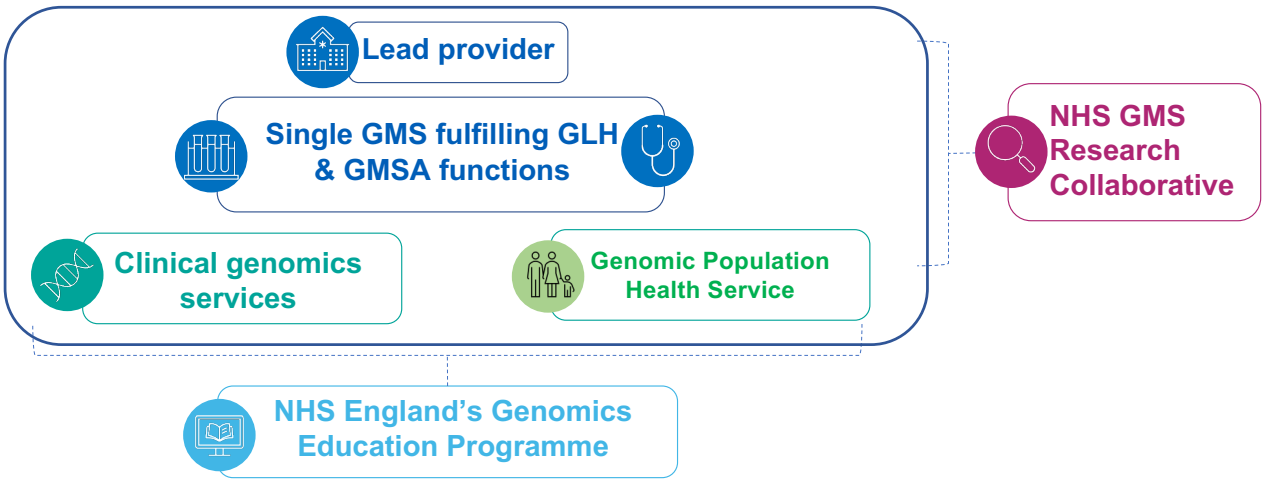
Nature Genetics **58**, 28–38 (2026) | Cite this article

https://www.thetimes.com/life-style/parenting/article/our-son-charlie-has-a-severe-learning-disability-we-finally-know-why-cr92ch2gq

NHS South East Genomic Medicine Service

26

England's Genomic Medicine Service



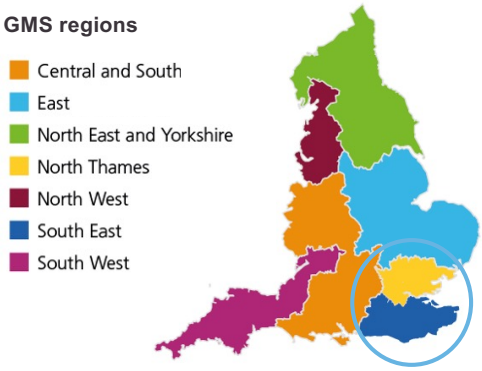
Courtesy of NHS England's Genomics Education Programme

NHS South East Genomic Medicine Service

27

England's Genomic Medicine Service

- 7 NHSE Genomic Laboratory Hubs (GLHs) and 7 Genomic Medicine Alliances (GMSAs)
- In transition to 7 GMSs
- All hubs operate to common **national guidelines and standards**, improve **equity of access** to genomic testing
- All deliver genomic testing from the **National Genomic Test Directory**



NHS South East Genomic Medicine Service

28

How to request genomic tests…

NHS South East Genomic Medicine Service

29

Points to consider:

- Is the test urgent/will affect immediate management? Consider R14 and consult clinical genetics
- Is there a definite clinical diagnosis/familial diagnosis – ie is a targeted test possible?
- Cost billed directly to NHSE (must meet eligibility criteria)
- Gene panels/technology subject to change as knowledge increases

National Genomic Test Directory

Testing Criteria for Rare and Inherited Disease

Version 9
8 April 2026

NHS South East Genomic Medicine Service

30

Part III. Developmental disorders

R26 Likely common aneuploidy....34
R27 Paediatric disorders....35
R28 Congenital malformation and dysmorphism syndromes – microarray only....37
R47 Angelman syndrome....38
R48 Prader-Willi syndrome....39
R69 Hypotonic infant....40
R312 Parental sequencing for lethal autosomal recessive disorders....41

Eligibility criteria

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Paediatric neurology
- Paediatrics
- Community Paediatrics
- Psychiatry

Who can request?

R27 Paediatric disorders

Testing Criteria

- Congenital malformations and/or dysmorphism highly suggestive of an underlying monogenic disorder where targeted genetic testing is not possible.
- Unexplained moderate/severe/profound global developmental delay or unexplained moderate/severe/profound intellectual disability, and where clinical features are highly suggestive of an underlying monogenic disorder requiring sequencing and targeted genetic testing is not possible.
- Craniofacial dysmorphism in combination with additional issues with health or development suggestive of a single genomic explanation, e.g. intellectual disability, congenital malformation, organ dysfunction.
- Syndromic overgrowth or overgrowth in combination with intellectual disability or developmental delay.
- Adults with congenital malformation and dysmorphism syndromes, however the clinical utility of testing should be made clear on the request form e.g. to inform a clinical management decision or reproductive choice.
- Fetus from a demised/non-continued pregnancy, with multiple major structural abnormalities detected on fetal ultrasound or post-mortem examination and where a monogenic malformation disorder is considered highly likely
- Unexplained epilepsy with clinical suspicion of a monogenic cause including onset under 2 years, OR clinical features suggestive of specific genetic epilepsy, for example Dravet syndrome.

Exclusion criteria

- Isolated Congenital Heart Disease and other isolated congenital malformations where the likelihood of a monogenic disorder is low are not eligible for testing under this indication.
- Isolated craniofacial dysmorphism is not an indication for testing; exceptions to this can only be made following multidisciplinary discussion with clinical genetics.

R28 microarray testing is not a requirement prior to R27 being initiated in patients with a possible monogenic cause of a syndromic paediatric disorder in whom there are no recognisable features of a specific chromosome disorder (eg 22q11 deletion syndrome).

Overlapping indications

- R14 Acutely unwell infants with a likely monogenic disorder test should be used instead where relevant where a rapid result is required and in children with onset under the age of 12 months with unexplained epilepsy.
- R412 Fetal anomalies with a likely genetic cause – non urgent can be used in a fetus where insufficient DNA is available for R27

Specialist Service Group

- Core

What technology?

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R27.3	Paediatric disorders	Trio or singleton	Exon level CNVs, Small variants, STRs	Panel of genes or loci	Paediatric disorders (486)	WGS

NHS South East Genomic Medicine Service

31

R68 Huntington disease

Testing Criteria

Clinical features that indicate a likely diagnosis of Huntington disease

- Specialties other than those listed in Requesting Specialties may request tests in certain settings following discussion with their local laboratory-clinical team

Overlapping indications

- R56 Adult onset dystonia, chorea or related movement disorder or other relevant broader test should be used where clinical features are not strongly suggestive of Huntington disease

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Neurology
- Psychiatry

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R68.1	HTT STR testing	Singleton	STRs	Single gene(s)	HTT STR	STR testing

NHS South East Genomic Medicine Service

R458 Young onset or familial dementia

Testing Criteria

Unexplained dementia where acquired causes (e.g. stroke, tumour) have been excluded AND

a. Age at onset <55 years, OR
b. First or second degree relative with MND/ALS OR
c. Neurological features suggestive of a monogenic disorder where cognitive impairment is part of a wider phenotype, OR
d. Family history highly suggestive of a monogenic cause for dementia for example one or more first or second degree relatives with dementia onset <65y where the type of dementia is the same as the proband. **NOTE a family history of dementia of uncertain or mixed type where onset is predominantly over 65y is unlikely to represent a monogenic disorder.**

Where in Pathway

At presentation following assessment by a Neurologist

Requesting Specialties

- Clinical Genetics
- Neurology
- Psychiatry

Specialist Service Group

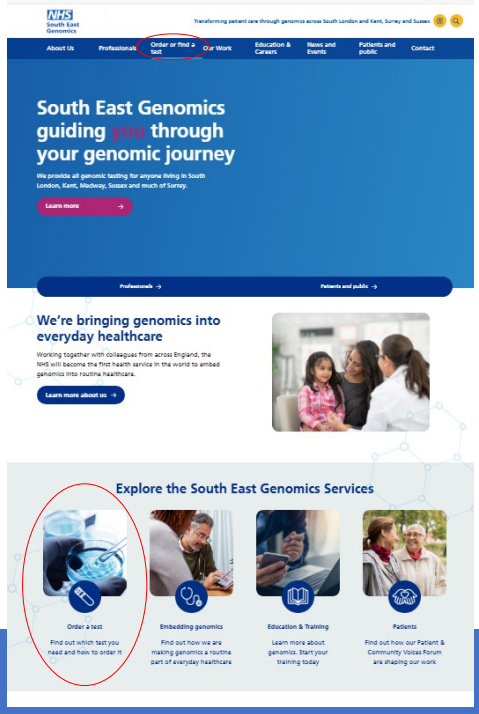
- Neurology

Associated Tests

From April 2026: The gene content of the Adult onset neurological disorders panel includes all genes on Hereditary ataxia with onset in adulthood (R54), Adult onset dystonia, chorea or related movement disorder (R56) Adult onset neurodegenerative disorders (previously R58, now R458, R459, R460 & R461), Adult onset hereditary spastic paraplegia (R60)

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R458.1	Young onset or familial dementia	Trio or singleton	Exon level CNVs, Small variants, STRs	Panel of genes or loci	Adult onset neurological disorders (1669)	WGS

32



NHS South East Genomic Medicine Service

33

Role of clinical genetics -

clinical geneticists and genetic counsellors

- Provide a pre- or postnatal clinical opinion in individuals with ID +/- a syndromic presentation
  Facilitate urgent testing (R14)
- Counsel regarding risks to individuals & family members, organise prenatal testing, refer for PGT, refer for surveillance
- Support clinical scientists in the interpretation of variants through expert phenotyping
- Support mainstream clinicians to request appropriate genomic testing and referral through MDTs and A&G
- Organise or refer for investigations, therapies, surveillance. Signpost families to sources of support eg charities
- Recruit to research studies including clinical trials

NHS South East Genomic Medicine Service

34

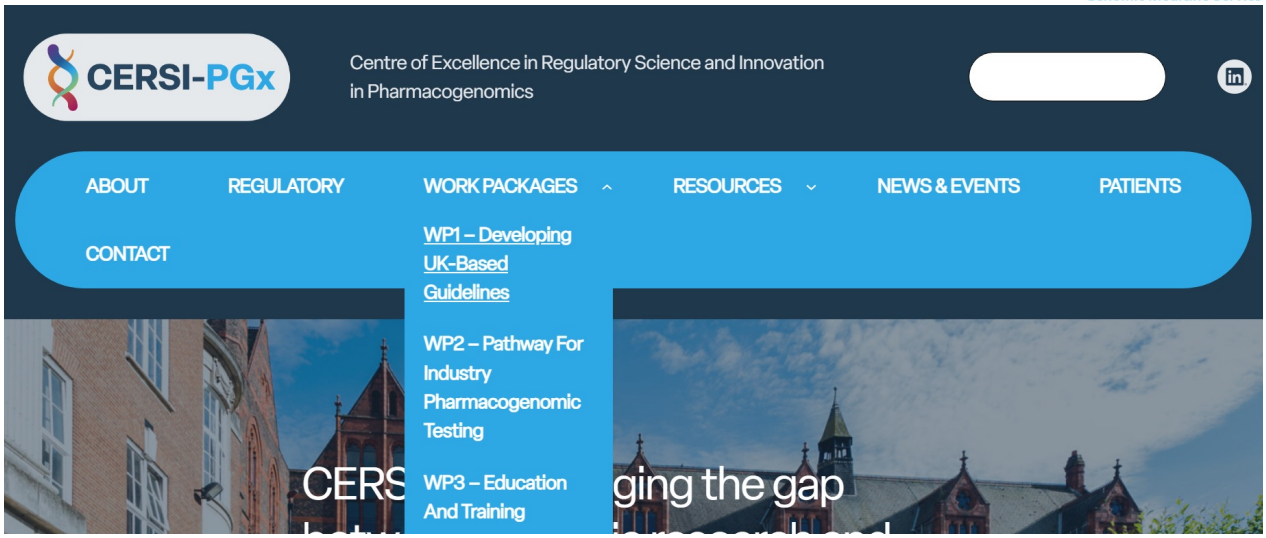
Pharmacogenomics in psychiatry

- Pharmacogenomics uses genetic information to improve safety and effectiveness, reduce adverse drug reactions and improve patient outcomes
- Ambition to pre-emptively test for pharmacogenomic targets
  - PROGRESS study in UK is examining feasibility and acceptability of testing through primary care

NHS South East Genomic Medicine Service

35

NHS South East Genomic Medicine Service



36

Received: 11 March 2026 | Accepted: 24 March 2026
DOI: 10.1002/bcp.70559

NHS South East Genomic Medicine Service

GUIDELINES

BJCP BRITISH PHARMACOLOGICAL SOCIETY

HLA genotype testing for carbamazepine, oxcarbazepine and eslicarbazepine: A guideline developed by the UK Centre of Excellence in Regulatory Science and Innovation in Pharmacogenomics (CERSI-PGx)

Lucy Galloway[1,2] | Cinzia Dello Russo[3,4] | Nicholas Bass[5] | Elvira Bramon[5,6] | Helen Cross[7,8] | Natalie Curley[9] | Sarah Curran[10] | Helen Davies[11] | Jana De Villiers[12] | William Evans[13,14,15] | Bernhard Frank[16] | Alice Groves[17] | Judith Hayward[18,19,20] | Jon Higham[21] | Dyfrig A. Hughes[22] | Shwe Sin Kyaw[22] | Anthony G. Marson[3,16] | Ailsa McLellan[23] | Seth Mensah[24] | Francis O'Neill[25] | Jane Sargison[26] | Sanjay M. Sisodiya[27,28] | Jill Swan[29] | Joanna M. Zakrewska[30] | Munir Pirmohamed[3,31]

37

Other examples in psychiatry

- CYP2C19 and SSRIs
  - Poor metabolisers show increased plasma levels and increased side effects
  - Ultrametabolisers show decreased response
- ACKR1/DARC
  - ACKR1/DARC polymorphism causes benign neutropenia – known as ADAN
  - Clozapine is associated with c.4% risk of neutropenia and prescription requires regular blood monitoring
  - If ADAN is undiagnosed patients may be denied access to clozapine
  - Guidelines for testing currently in development

NHS South East Genomic Medicine Service

38

39