

## Chromosome Breakage Disorders Gene Panel

### Contact details:

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### Sample Required:

Adult: 3-4mls blood in EDTA

Paediatric: at least 1ml EDTA (preferably >2ml)

### DNA: 2µg total

Samples should be accompanied by a FULLY completed request form (available at [www.nbt.nhs.uk/genetics](http://www.nbt.nhs.uk/genetics) or from the laboratory).

Please include details of test, family history, address and POSTCODE, NHS number, referring clinician and unit/hospital.

### Consent and DNA Storage:

Genetic testing requires consent. It is the responsibility of the referring clinician to ensure that appropriate consent has been obtained.

This is a gene panel test using next generation sequencing. It contains genes associated with chromosome breakage disorders and their differential diagnoses. Included in the test are cancer susceptibility genes including *BRCA2*. There is therefore a possibility of incidental findings. Results obtained may have implications for the wider family. Results may also include variants of unknown clinical significance requiring further family studies to determine their significance. The interpretation provided is based on the available information at the date of issue; it may change if further evidence becomes available.

DNA is stored from all patients unless consent for this is specifically denied. Stored samples may be used anonymously for quality assurance and development purposes for this assay.

### Clinical Background and Genetics

- Chromosome breakage disorders are a group of rare genetic conditions inherited in an autosomal recessive or X linked inheritance pattern.
- Patients with these disorders show increased predisposition to solid and haematological malignancies have a high incidence of other congenital abnormalities such as microcephaly and radial ray defects.
- The disorders are characterised by defects in DNA repair mechanisms, cell cycle control or genomic instability.
- The service is designed to support the specialist cytogenetic chromosome breakage service offered by Bristol Genetics Laboratory, further details of which are available on the laboratory [website](#).
- The panel test includes genes known to be associated with chromosome breakage disorders, premature chromosome separation and premature centromeric separation.
- Due to the clinical overlap and complexity in diagnosis the gene panel contains genes for several key differential diagnoses e.g. radial ray abnormality syndromes.
- A full list of genes and disorders included in the panel is on page 2.

### Service offered

- 63 genes are sequenced using a custom designed Agilent SureSelect Target Enrichment method; sequencing is performed on an Illumina MiSeq. Analysis is performed using an open source in-house developed pipeline (alignment: BWA; alignment modification and variant calling: GATK; variant annotation: Annovar).
- All variants reported are confirmed by Sanger sequencing
- MLPA analysis for *FANCA* is also available.

### Referrals

- Diagnostic referrals are accepted from Consultant Clinical Geneticists, Consultant Paediatricians and Consultant Oncologists.
- It is essential that the referring clinician provides the clinical information and consent required in the pre-test pro forma (page 3) or relevant clinical letter of referral.

### Quality

- BGL participates in the appropriate technical EQA schemes for Sanger and next generation sequencing.

### Target reporting Time (2016/2017)

- Gene panel testing 16 weeks
- Cascade tests 14 days

- Please contact the laboratory for up-to-date prices and more information on this test.
- For clinical advice please contact Dr Ruth Newbury-Ecob, Clinical Genetics, St. Michael's Hospital, Bristol, Tel: 0117 342 5653

## Chromosome Breakage Disorders NGS Gene Panel Proforma

Patient Name:		Consultant Name:	
Patient postcode:		Hospital Address:	
Date of Birth:			
Sex:			
NHS Number			
Hospital Number:			

Fanconi Anaemia				
FANCA	FANCB	FANCC	BRCA2	FANCD2
FANCE	FANCF	FANCG	FANCI	BRIP1
FANCL	PALB2	RAD51C	SLX4	XRCC2
Ataxia Telangiectasia (& AT-Like)				
ATM		MRE11A		
Ataxia with oculomotor apraxia and hypoalbuminemia				
APTX				
Xeroderma Pigmentosum				
XPA	XPC	ERCC1	ERCC3	ERCC4
DDB2	ERCC5	POLH		
Trichothiodystrophy				
ERCC2	MPLKIP	ERCC3	GTF2H5	
Cockayne syndrome				
ERCC6		ERCC8		
Autosomal Recessive Primary Microcephaly				
MCPH1	CDK5RAP2	ASPM	STIL	WDR62
CASC5	CENPJ	CEP135		
Seckel Syndrome				
ATR	RBBP8	CEP152	CENPJ	
Meier-Gorlin Syndrome				
ORC1	ORC4	ORC6	CDT1	CDC6
Cerebro Oculo Facio Skeletal syndrome				
ERCC1	ERCC2	ERCC6		
Baller-Gerold/Rothmund Thomson/RAPADILINO				
RECQL4				
Natural killer cell and glucocorticoid deficiency with DNA repair defect				
MCM4				

Nijmegen breakage syndrome (& NBS-like)	
NBN	RAD50
Werner syndrome	
WRN	
Warsaw breakage syndrome	
DDX11	
Roberts /SC phocomelia syndrome	
ESCO2	
Bloom Syndrome	
BLM	
Immunodeficiency-centromeric instability-facial anomalies syndrome	
DNMT3B	
Duane-Radial Ray & IVIC Syndrome	
SALL4	
Townes-Brocks Syndrome	
SALL1	
Holt-Oram Syndrome	
TBX5	
Ulnar-mammary syndrome	
TBX3	
TAR Syndrome	
RBM8A	
LIG4 Syndrome	
LIG4	
N Syndrome	
POLA1	

Indications for testing:

Criteria	Tick if this patient meets criteria
Unexplained pre- and postnatal growth deficiency or failure to thrive and small stature in association with immune deficiency or cancer	
Progressive cerebellar ataxia in young children	
Physical features consistent with a chromosome breakage disorder e.g. limb malformations, microcephaly, growth retardation	
Recurrent infections or immunodeficiency in association with microcephaly	
History of leukaemia, lymphoma or solid tumour at an earlier than expected age, particularly in association with other features of chromosome breakage disorder	
Increased sister chromatid exchange as detected cytogenetically, chromosomal instability or increased cellular sensitivity to ionizing radiation	
Unexpected toxicity to chemotherapy or radiation therapy	
Borderline increased chromosome breakage with DEB exposure.	

Please indicate suspected clinical diagnosis:

Disorder	Tick
Ataxia Telangiectasia	
Ataxia, early-onset, with oculomotor apraxia and hypoalbuminemia	
Ataxia-telangiectasia-like disorder	
Baller-Gerold syndrome	
Bloom Syndrome	
Cerebrooculofacioskeletal syndrome 1	
Cerebrooculofacioskeletal syndrome 2	
Cockayne syndrome	
Cutaneous telangiectasia and cancer syndrome, familial	
De Sanctis-Cacchione syndrome	
Fanconi Anaemia	
Jawad syndrome	
LIG4 syndrome	
Meier-Gorlin syndrome	
N syndrome	
Natural killer cell and glucocorticoid deficiency with DNA repair defect	
Nijmegen breakage syndrome	
Nijmegen breakage syndrome-like disorder	
Primary autosomal recessive Microcephaly	
RAPADILINO syndrome	

Roberts syndrome/ SC phocomelia syndrome	
Rothmund-Thomson syndrome	
Seckel syndrome	
Trichothiodystrophy	
UV-sensitive syndrome 2	
Warsaw breakage syndrome	
Werner syndrome	
Xeroderma Pigmentosum	
XFE Progeroid syndrome	

Please detail the clinical features of this patient, including relevant haematology results:

Please note this NGS panel test includes cancer predisposition genes including *BRCA2*. Analysis may reveal information regarding cancer susceptibility that may have implications for this patient and other family members. It is laboratory policy to report all clinically relevant findings. Please sign below to indicate that informed consent has been obtained prior to testing. Testing will not be undertaken if this form is not signed by the referring clinician.

Signed \_\_\_\_\_  
 Print \_\_\_\_\_  
 Position \_\_\_\_\_