Bristol Genetics Laboratory is a UKAS accredited medical laboratory No.9307.

Paediatric Cardiomyopathy

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Sample Required
See Sample requirements page at www.nbt.nhs.uk/genetics for full details

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

Please include details of the test required, family history, address and POSTCODE, NHS number, referring clinician and centre.

Consent and Storage:
All genetic testing requires consent. **It is the responsibility of the referring clinician to ensure that appropriate consent has been obtained.**

DNA is stored from **ALL** patients undergoing DNA testing, unless consent for this is specifically denied.

Stored material from all referrals may be retained for quality assurance purposes and may be used anonymously for the development of new tests for the disorder in question.

Clinical Background and Genetics

- Paediatric cardiomyopathy is defined as a disease of the myocardium associated with cardiac dysfunction and/or abnormal cardiac structure.
- This is a heterogeneous group of disorders with a strong genetic component (more than in adults) and includes metabolic, sarcomeric, cytoskeletal protein, neuromuscular and syndromic disorders.
- There are a number of different forms of cardiomyopathy including DCM, HCM, RCM, ARVC/D, LVNC and unclassified, and these can be seen in combination.
- The prognosis for paediatric patients is poor; it is a major cause of cardiac mortality and the leading cause of cardiac transplantation in children (Kindel *et al* (2012) J Card Fail 18:396).
- The differential diagnosis in children is different to that in adults mainly due to the contribution of metabolic disease and dysmorphic syndromes. Few are associated with a single distinct form of cardiomyopathy, demonstrating the heterogeneity of this disorder.
- Digenic inheritance is becoming more widely reported, the involvement of more than one variant in different genes is suggested to increase severity and result in earlier age of onset (Rampersaud *et al* (2011) Prog Pediatr Cardiol 31:39).

Service Offered

- 71* genes undergo panel testing using a custom Clinical Exome target enrichment kit and sequenced using a NextSeq (Illumina) analyser. Analysis is performed using an open source in-house pipeline (alignment: BWA; alignment modification and variant calling: GATK). ExomeDepth algorithm (Plagnol et al, Bioinformatics (2012) 28 (21): 2747) has been validated for CNV calling.

***Genes included:**

ABCC9; ACADVL; ACTC1; ACTN2; ANKRD1; BAG3; BRAF; CPT2; CRYAB; CSRP3; CTF1; DES; DMD; DNAJC19; DSC2; DSG2; DSP; DTNA; EMD; EYA4; FHL1; FKTN; GBE1; GLA; HRAS; ILK; JUP; KRAS; LAMA4; LAMP2; LDB3; LMNA; MAP2K1; MAP2K2; MMACHC; MUT; MYBPC3; MYH6; MYH7; MYL2; MYL3; MYPN; NEBL; NEXN; PCCA; PCCB; PDLIM3; PKP2; PLN; PNPLA2; PRKAG2; PTPN11; RBM20;RYR2; SCN5A; SGCD; SLC22A5; SLC25A20; STK4; TAZ; TCAP; TGFB3; TMEM43; TMPO; TNNC1; TNNI3; TNNT2; TPM1; TTN; TTR; VCL.

- Familial tests for known variants are undertaken using Sanger sequencing. **Predictive tests must be referred from Clinical Genetics.**

Referrals

- Referrals can be accepted nationally from consultants from appropriate disciplines such as clinical geneticists, paediatric cardiologists and paediatric metabolic consultants. **However, it is recommended that discussion in an inherited cardiac conditions MDT is undertaken prior to referral.**

Target reporting Times

Diagnostic screen of 71 genes:	84 calendar days
Familial testing (Including predictives unless urgent):	42 days (by Sanger sequencing)
Urgent:	4-6 weeks on a case by case basis

Please contact the laboratory for up to date prices

Quality

•BGL participates in the following external quality assurance schemes: GenQA arrhythmia and cardiomyopathy; pathogenicity of sequence variants; variant validation and NGS (germline) schemes along with the EMQN DNA Sanger sequencing.

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North Bristol NHS Trust

Paediatric cardiomyopathy NGS panel pre-test proforma:

Paediatric cardiomyopathy can be caused by pathogenic changes in at least one of many genes. The Bristol Genetics laboratory has validated a diagnostic next generation sequencing panel assay of 71 implicated genes (see tables below for details). Testing each of these genes separately would be a lengthy and costly process, however simultaneous testing of the included genes would provide a cost-effective and more rapid genetic test.

Patient name:		Referring consultant*:
DOB:	Gender:	Department and hospital:
Postcode:		
NHS number:		Hospital number/CG number:
Ethnic origin:		Date requested:

*** Please note that all referrals should be discussed at an ICC MDT prior to referral**

Indications for testing:

Suspected diagnosis:

Disorder	Tick as appropriate
DCM – dilated cardiomyopathy	
HCM – hypertrophic cardiomyopathy	
LVNC - Left ventricular non-compaction	
ARVC – Arrhythmogenic right ventricular cardiomyopathy	
RDM/RCM –restrictive cardiomyopathy	
Mixed features of above	

Clinical features:

Criteria	Indicate if this patient meets each criteria (Yes/No/Not known)
Sudden cardiac death	
Congestive heart failure	
Syncope	
Palpitations	
Septal hypertrophy	
LV thickening	
Cardiomegaly	
LV dilatation	
LV systolic impairment	
ECG (electrocardiography) results:	

Echocardiography results:	
Ejection fraction < 50%?	
Serum creatine kinase results:	
Other features e.g. dysmorphism, valvular heart defect, any facial features of Noonan, CFC (cardio-facio-cutaneous), Costello or LEOPARD syndromes.	
Neuromuscular features	
Metabolic features	
Other investigations carried out including array CGH	
Histology if available	

Family history of cardiomyopathy (please give details below including relationship and if any consanguinity in the family) including any genetic testing:

Please give any further clinical details including any possible suspected diagnoses:

Counselling and consent:

<u>It has been assumed that, in submitting a sample and request for testing, that the referring clinician has counselled the patient appropriately that:</u>

- multiple genes will be targeted and analysed in the proband.
- the test may or may not find the cause of the condition.

- **the test may find changes in included genes associated with either predisposition, syndromic or metabolic disorders (see tables below).**
- that any genetic changes detected will fall into one of the following categories:

  1. Known genetic variants compatible with the patient's phenotype.

  2. Novel genetic variants, which may be clinically relevant but which may require further investigation including family studies.

  3. Novel genetic variants that may be related to the phenotype but which we are unable to interpret the clinical significance of at present.

  4. That the results obtained may have implications for relatives of the proband.

Please note this NGS panel test includes genes associated with either predisposition, syndromic or metabolic disorders (see tables below) these genes can be excluded from this test upon request:

Gene	OMIM number	Associated phenotype/ OMIM standard name of condition and symbol	Mode of inheritance
ABCC9	601439	a)Cardiomyopathy, dilated 10 b)Atrial Fibrillation 12 c)Cantu Syndrome	AD; sporadic
ACADVL	609575	VL chain acyl-CoA dehydrogenase deficiency	AR
ACTC1	102540	a)Cardiomyopathy, dilated 12 b)Cardiomyopathy, familial hypertrophic 11 c)Atrial septal defects 5 d)Left ventricular noncompaction 4	AD
ACTN2	102573	Cardiomyopathy, dilated, 1AA	AD
ANKRD1	609599	Cardiomyopathy, dilated	AD
BAG3	603883	a) Cardiomyopathy, dilated, 1HH b) Myopathy, myofibrillar, 6	AD
BRAF	164757	a) Adenocarcinoma of lung, somatic b) Cardiofaciocutaneous syndrome 1 c) Colorectal cancer, somatic d) LEOPARD syndrome 3 e) Melanoma, malignant, somatic f) Nonsmall cell lung cancer, somatic g) Noonan syndrome 7	AD/Sporadic
CPT2	600435	?DCM	AD
CRYAB	600650	a)CPT deficiency, hepatic, type II b)CPT II deficiency, lethal neonatal c)Myopathy due to CPT II deficiency d)Encephalopathy, acute, infection-induced, 4, susceptibility to	AR
CSRP3	123590	a)Cardiomyopathy, dilated, 1II b)Cataract 16, multiple types c)Myopathy, myofibrillar, 2 d)Myopathy, myofibrillar, fatal infantile hypertrophy, alpha-B crystallin-related	AD
CTF1	600824	a)Cardiomyopathy, dilated, 1M b)Cardiomyopathy, familial hypertrophic, 12	AD
DES	125660	a) ?Muscular dystrophy, limb-girdle, type 2R b)Cardiomyopathy, dilated, 1I c)Myopathy, myofibrillar, 1	a)AR b)AD c) AD, AR,

		d)Scapuloperoneal syndrome, neurogenic, Kaeser type	sporadic d)AD, sporadic
DMD	300377	a)Becker muscular dystrophy b)Cardiomyopathy, dilated, 3B c)Duchenne muscular dystrophy	X-linked
DNAJC19	608977	3-methylglutaconic aciduria, type V	AR
DSC2	125645	a)Arrhythmogenic right ventricular dysplasia 11 b)Arrhythmogenic right ventricular dysplasia 11 with mild palmoplantar keratoderma and woolly hair	a) AD (incomplete pentrance) b)AR
DSG2	125671	a)Arrhythmogenic right ventricular dysplasia 10 b)Cardiomyopathy, dilated, 1BB	a)AD; ?digenic b)AD; AR
DSP	125647	a)Arrhythmogenic right ventricular dysplasia 8 b)Dilated cardiomyopathy with woolly hair and keratoderma c)Epidermolysis bullosa, lethal acantholytic d)Keratosis palmoplantaris striata II e)Skin fragility-woolly hair syndrome	a)?AD b)AR d/e) AD
DTNA	601239	Left ventricular noncompaction 1, with or without congenital heart defects	AD
EMD	300384	Emery-Dreifuss muscular dystrophy 1, X-linked	X-linked
EYA4	603550	a)Cardiomyopathy, dilated, 1J b)Deafness, autosomal dominant 10	AD
FHL1	300163	a)Emery-Dreifuss muscular dystrophy 6, X-linked b)Myopathy, reducing body, X-linked, childhood-onset c)Myopathy, reducing body, X-linked, severe early-onset d)Myopathy, X-linked, with postural muscle atrophy e)Scapuloperoneal myopathy, X-linked dominant	X-linked
FKTN	607440	a)Cardiomyopathy, dilated, 1X b)Muscular dystrophy-dystroglycanopathy (congenital with brain and eye anomalies), type A, 4 c)Muscular dystrophy-dystroglycanopathy (congenital without mental retardation), type B, 4 d)Muscular dystrophy-dystroglycanopathy (limb-girdle), type C, 4	AR
GBE1	607839	a)Glycogen storage disease IV b)Polyglucosan body disease, adult form	AR
GLA	300644	a)Fabry disease b)Fabry disease, cardiac variant	X-linked
HRAS	190020	a)Congenital myopathy with excess of muscle spindles b)Costello syndrome c) Schimmelpenning-Feuerstein-Mims syndrome, somatic mosaic d) Bladder cancer, somatic e) Nevus sebaceous, somatic f) Thyroid carcinoma, follicular, somatic	a & b) AD/somatic mosaicism
ILK	602366	Not available	?AD/sporadic
JUP	173325	a)Arrhythmogenic right ventricular dysplasia 12 b)Naxos disease	a)AD b)AR
KRAS	190070	a)Cardiofaciocutaneous syndrome 2 b) Noonan syndrome 3 c) Bladder cancer, somatic d) Breast cancer, somatic e) Gastric cancer, somatic f) Leukaemia, acute myelogenous g) Lung cancer, somatic h) Pancreatic carcinoma, somatic i) SFM syndrome, somatic mosaic	a & b) AD/sporadic
LAMA4	600133	Cardiomyopathy, dilated, 1JJ	AD

LAMP2	309060	Danon disease	X-linked
LDB3/ZASP	605906	a)Cardiomyopathy, dilated 1C b)Left ventricular noncompaction 3, with or without dilated cardiomyopathy c)Myopathy, myofibrillar, 4	AD
LMNA	150330	a) Cardiomyopathy, dilated, 1A b) Charcot-Marie-Tooth disease, type 2B1 c) Emery-Dreifuss muscular dystrophy 2, AD d) Emery-Dreifuss muscular dystrophy 3, AR e) Heart-hand syndrome, Slovenian type f) Hutchinson-Gilford progeria g) Lipodystrophy, familial partial, 2 h) Malouf syndrome i) Mandibuloacral dysplasia j) Muscular dystrophy, congenital k) Muscular dystrophy, limb-girdle, type 1B l) Restrictive dermopathy, lethal	a)AD b)AR c)AD d)AR e)AD f)AD g)AD h)AD i)AR j)AD or sporadic k)AD l)?sporadic
MAP2K1	176872	Cardiofaciocutaneous syndrome 3	Sporadic
MAP2K2	601263	Cardiofaciocutaneous syndrome 4	Sporadic
MMACHC	609831	Methylmalonic aciduria and homocystinuria, cblC type	AR
MUT	609058	Methylmalonic aciduria, mut(0) type	AR
MYBPC3	600958	a)Cardiomyopathy, dilated, 1MM b) Cardiomyopathy, familial hypertrophic, 4 c) Left ventricular noncompaction 10	a) & c) AD b) AD or AR
MYH6	160710	a)Atrial septal defect 3 b)Cardiomyopathy, dilated, 1EE c)Cardiomyopathy, familial hypertrophic, 14 d){Sick sinus syndrome 3}	a)AD b)AD or sporadic c)AD
MYH7	160760	a)Cardiomyopathy, dilated, 1S b)Cardiomyopathy, familial hypertrophic, 1 c)Laing distal myopathy d)Left ventricular noncompaction 5 e)Myopathy, myosin storage f)Scapuloperoneal syndrome, myopathic type	a) & d) AD b) sporadic, AD or AR c)AD e)AD f)AD A number of cases of digenic inheritance
MYL2	160781	Cardiomyopathy, familial hypertrophic, 10	AD or sporadic
MYL3	160790	Cardiomyopathy, familial hypertrophic, 8	AD or AR
MYPN	608517	a)Cardiomyopathy, dilated, 1KK b)Cardiomyopathy, familial restrictive 4 c)Cardiomyopathy, familial hypertrophic, 22	AD or sporadic
NEBL	605491	?Cardiomyopathy, dilated	?Sporadic
NEXN	613121	a)Cardiomyopathy, dilated, 1CC b)Cardiomyopathy, familial hypertrophic, 20	AD
PCCA	232000	Propionicacidemia	AR
PCCB	232050	Propionicacidemia	AR
PDLIM3	605889	?Possibly cardiomyopathy, dilated	Unknown
PKP2	602861	Arrhythmogenic right ventricular dysplasia 9	AD (possibly AR and digenic inheritance)
PLN	172405	a)Cardiomyopathy, dilated, 1P	AD

		b)Cardiomyopathy, familial hypertrophic, 18	
PNPLA2	609059	Neutral lipid storage disease with myopathy	AR
PRKAG2	602743	a)Cardiomyopathy, familial hypertrophic 6 b)Glycogen storage disease of heart, lethal congenital c) Wolff-Parkinson-White syndrome	AD Or sporadic (b)
PTPN11	176876	a)LEOPARD syndrome 1 b)Leukaemia, juvenile myelomonocytic c)Metachondromatosis d)Noonan syndrome 1	a) & d) AD or sporadic
RBM20	613171	Cardiomyopathy, dilated, 1DD	AD
RYR2	180902	a)Arrhythmogenic right ventricular dysplasia 2 b) Ventricular tachycardia, catecholaminergic polymorphic, 1	AD
SCN5A	600163	a)Atrial fibrillation, familial, 10 b)Brugada syndrome 1 c)Cardiomyopathy, dilated, 1E d)Heart block, nonprogressive e)Heart block, progressive, type IA f)Long QT syndrome-3 g)Sick sinus syndrome 1 h)Ventricular fibrillation, familial, 1 1){Sudden infant death syndrome, susceptibility to}	a)AD b)AD c)AD d & e)AD f)AD &digenic inheritance g)AR h)AD i)AD
SGCD	601411	a)Cardiomyopathy, dilated, 1L b)Muscular dystrophy, limb-girdle, type 2F	a)AD & sporadic b)AR & digenic inheritance
SLC22A5	603377	Carnitine deficiency, systemic primary	AR
SLC25A20	613698	Carnitine-acylcarnitine translocase deficiency	AR
STK4	604965	T-cell immunodeficiency, recurrent infections, autoimmunity, and cardiac malformations	AR
TAZ	300394	Barth Syndrome	X-linked
TCAP	604488	a)Cardiomyopathy, dilated, 1N b)Muscular dystrophy, limb-girdle, type 2G	a)?AD or sporadic b)AR
TGFB3	190230	a)?Rienhoff syndrome b)Arrhythmogenic right ventricular dysplasia 1	a)AD or sporadic b)AD
TMEM43	612048	a)Arrhythmogenic right ventricular dysplasia 5 b)Emery-Dreifuss muscular dystrophy 7, AD	a)AD b)AD
TMPO	188380	Cardiomyopathy, dilated, 1T	AD
TNNC1	191040	a)Cardiomyopathy, dilated, 1Z b) Cardiomyopathy, familial hypertrophic, 13	a)AD b)?AD or sporadic
TNNI3	191044	a)Cardiomyopathy, dilated, 1FF b)Cardiomyopathy, dilated, 2A c)Cardiomyopathy, familial hypertrophic, 7 d)Cardiomyopathy, familial restrictive	a)AD b)AR c)AD or sporadic d)AD
TNNT2	191045	a) Cardiomyopathy, dilated, 1D b)Cardiomyopathy, familial hypertrophic, 2 c)Cardiomyopathy, familial restrictive, 3 d)Left ventricular noncompaction 6	AD
TPM1	191010	a)Cardiomyopathy, dilated, 1Y b)Cardiomyopathy, familial hypertrophic, 3 c) Left ventricular noncompaction 9	AD
TTN	188840	a) Cardiomyopathy, dilated, 1G b) Cardiomyopathy, familial hypertrophic, 9 c) Muscular dystrophy, limb-girdle, type 2J	a) & b)AD c)?AR homozygous

		d) Myopathy, early-onset, with fatal cardiomyopathy e) Myopathy, proximal, with early respiratory muscle involvement f) Tibial muscular dystrophy, tardive	variants d)?AR homozygous deletion e)AD f)AD
TTR	176300	a)Amyloidosis, hereditary, transthyretin-related b)Carpal tunnel syndrome, familial c)Dystransthyretinemic hyperthyroxinemia	AD
VCL	193065	a)Cardiomyopathy, dilated,1 b) Cardiomyopathy, familial hypertrophic, 15	a)?AD/AR b)?AD/sporadic