NIHR | BioResource

CRD. Chromatin Disorders

NIHR BioResource – Rare Diseases study project

Lead Investigators: Dr. Cristina Dias & Dr. Siddharth Banka

V1 23/10/2020

Summary

Several genetic disorders caused by variants in genes encoding various components of the chromatin regulation machinery have been identified in the recent years. Most of these 'Chromatin disorders' (CDs) result in varying combinations of neurodevelopmental disorders (NDD), intellectual disability (ID), malformations of internal organs, abnormal growth and problems with other body systems. ID and NDDs such as Autism Spectrum Disorder (ASD), have significant and life-long impact on affected individuals, families and communities. CDs are now recognized to be among the most common causes of NDD and malformations. However, our knowledge of the mechanistic basis of CDs, their phenotypic spectrum and broader health implications is limited. There is a need to expand our understanding to improve their diagnosis, management and therapy.

As part of the Chromatin Disorders ('CRD') project, the overall aims are to:

1. Uncover the spectrum of genetic variants and associated clinical features
2. Identify biomarkers for diagnosis and prognosis
3. Conduct longitudinal natural history studies in a large cohort of children and adults
4. Define stratified anticipatory guidance
5. Generate a tissue resource for basic science studies into the biology of the syndromes

Recruitment Criteria

Inclusion

- Pathogenic or likely pathogenic variant(s) (ACMG class 5 or 4) in a CD-associated gene
- Variant of unknown significance in CD associated gene with a suggestive phenotype

See Table 1.

Exclusion

- None

References/Tables

[1]Table 1: Disorders of chromatin regulation

Gene (HGNC Approved Symbol)	Gene OMIM#	Condition	Condition OMIM#
ACTL6A	604958	IDD	PMID:28649782
ACTL6B	612458	Epileptic encephalopathy, early infantile, 76	618468
ACTL6B	612458	IDD with severe speech and ambulation defects	618470
ADNP	611386	Autosomal dominant MR 28; Helsmoortel-van der aa syn.	615873
ARID1A	603024	Autosomal dominant MR 14; Coffin-Siris Syn. 2	614607
ANKRD11	611192	KBG Syndrome	148050
ARID1B	614556	Autosomal dominant MR 12; Coffin-Siris Syn. 1	135900
ARID2	609539	IDD (Coffin-Siris type phenotype)	609539
ASH1L	607999	Autosomal dominant MR 52	617796
BAZ2B	605683	NDD with DD, ID and ASD	*PMID:31999386*
BCL11A	606557	IDD with persistence of fetal hemoglobin; Dias-Logan Syn.	617101
BPTF	601819	NDD with dysmorphic facies & distal limb anomalies	617755
CDC6	602627	Meier-Gorlin Syn. 5	613805
CHD2	602119	Epileptic encephalopathy, childhood-onset	615369
CHD3	602120	Apraxia of speech; Snijders Blok-Campeau Syn.	618205
CHD4	603277	Sifrim-Hitz-Weiss Syn.	617159
CHD7	608892	CHARGE Syn.**	214800
CHD7	608892	Hypogonadotropic hypogonadism 5 with or without anosmia	612370
CHD8	610528	Autism, susceptibility to, AUTS18	615032
CREBBP	600140	Rubinstein–Taybi Syn. 1	180849
CREBBP	600140	Menke-Hennekam Syn. 1	618332
DMAP1	605077	Cerebellar Ataxia Deafness and Narcolepsy, AD	*PMID:28600779*
DPF2	601671	Coffin-Siris Syn. 7	618027
EED	605984	Cohen-Gibson overgrowth Syn.	617561
EHMT1	607001	Kleefstra Syn. 1	610253
EP300	602700	Rubinstein–Taybi Syn. 2	613684
EP300	602700	Menke-Hennekam Syn. 2	618333
EZH2	601573	Weaver Syn.	277590
HDAC8	300269	Cornelia de Lange Syn. 5	300882
KANSL1	612452	Koolen De Vries Syn.	610443
KAT5	601409	NDD with sleep disturbance, cerebellar atrophy, & facial dysmorphisms	*PMID:32822602*
KAT6A	601408	Autosomal dominant MR 32	616268
KAT6B	605880	Genitopatellar Syn.	606170
KAT6B	605880	Say Barber Biesecker Young Simpson Syn.	603736
KDM1A	609132	Cleft palate, psychomotor retardation, & distinctive facial features	616728
KDM3B	609373	IDD, short stature, facial dysmorphism; Diets-Jongmans Syn,	618846
KDM5B	605393	Autosomal recessive MR 65	618109
KDM5C	314690	*(JARID1C)* Claes–Jensen Syn.	300534
KDM6A	300128	Kabuki Syn. 2	300867
KDM6B	611577	NDD with coarse facies & mild distal skeletal abnormalities	618505
KMT2A	159555	Wiedemann-Steiner Syn.	605130
KMT2B	606834	Childhood-onset dystonia 28	617284
KMT2C	606833	Kleefstra Syn. 2	617768
KMT2D	602113	Kabuki Syn. 1	147920
KMT2E	608444	O'Donnell-Luria-Rodan Syn.	618512
KMT2F	611052	*(SETD1A)* Epilepsy, early-onset, with or without DD	618832
KMT2F	611052	*(SETD1A)* NDD with speech impairment & dysmorphic facies	619056
KMT2G	611055	*(SETD1B)* IDD with seizures and language delay	619000
KMT5B	610881	*(SUV420H1)* Autosomal dominant MR 51	617788
MSL3	300609	X-linked syndromic MR 36	301032

NSD1	606681	Sotos Syn. 1	117550
PCGF2	600346	Turnpenny-Fry Syn.	618371
PHF6	300414	Borjeson-Forssman-Lehmann Syn.	301900
PHF8	300560	Siderius X-Linked Mental Retardation Syn.	300263
PRMT7	610087	Short stature, brachydactyly, IDD, and seizures	617157
SETD2	612778	Luscan-Lumish Syn.	616831
SETD5	615743	Autosomal dominant mental retardation 23	615761
SMARCA1	300012	Coffin-Siris-like IDD with Severe Cortical Atrophy	*PMID:26539891*
SMARCA2	600014	Nicolaides Baraitser Syn.; Coffin-Siris Syn.	601358
SMARCA2	600014	Blepharophimosis intellectual disability Syn.	*PMID:32694869*
SMARCA4	603254	Autosomal dominant MR 16;Coffin-Siris Syn. 4	614609
SMARCB1	601607	Autosomal dominant MR 15; Coffin-Siris Syn. 3	614608
SMARCC2	601734	Coffin-Siris Syn. 8	618362
SMARCD1	601735	Syndromic Neurodevelopmental Disorder; Coffin-Siris Syn. 11	618779
SMARCE1	603111	Coffin-Siris Syn. 5	616938
SRCAP	611421	Floating-Harbor	136140
SUZ12	606245	Imagawa-Matsumoto Syn.	618786

ASD: Autism Spectrum Disorder; DD: developmental delay; IDD: Intellectual Developmental Disorder/Intellectual Disability; MR: Mental Retardation; NDD: Neurodevelopmental disorder. * As mutations in new chromatin associated genes are identified, this list will be updated. However, if clinicians identify a patient with a mutation in a CD gene not yet listed, please contact the study leads or study coordinating centre rarediseases@bioresource.nihr.ac.uk . **Patients with CHARGE Syndrome should be recruited to the CHG project, as part of the BioResource – Rare Diseases study. Where an OMIM# has not yet been attributed a reference is indicated (Pubmed ID).