Epigenomics of Rare Disorders (EpiGenRare)

Rare Disease Research UK
Epigenomics of Rare Disorders - EpiGenRare

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Background and aims

Epigenetic diseases, including chromatinopathies and multilocus imprinting disorders (MLIDs), remain difficult to discover, diagnose, understand, and treat. Although individually rare, more than 100 epigenetic disorders have been identified, affecting an estimated 1 in 500–1000 individuals. The EpiGenRare Node (Epigenomics of Rare Disorders) aims to lead and coordinate UK research into epigenetic rare diseases by providing research expertise, analytical pipelines, and access to state-of-the-art resources to address key challenges via five work packages:

WP1. Decipher genome–epigenome relationships in rare epigenetic conditions.
WP2. Understand therapeutic convergence in chromatinopathies to identify shared treatments.
WP3. Develop human stem cell models for high-throughput drug screening.
WP4. Build a network of patients, researchers, and clinicians for rare epigenetic conditions.
WP5. Deliver real patient benefit through a comprehensive PPIE programme.

Upcoming Events
Scan QR code above for more details

EpiGenRare Session at ESHG
13-16 June 2026
Gothenburg, SE

ESHG European Society of Human Genetics

WP1: Understanding genome-epigenome relationships

Understanding how genetic variants lead to complex epigenetic alterations in imprinting disorders remains challenging. This project aims to integrate genomic and DNA-methylation data from a large patient cohort to develop diagnostic epigenetic signatures.

Key Progress:
- Identified an association between the extent of MLID and underlying genetic causes (1).
- Conducted comprehensive DNA methylation profiling and exome/genome sequencing in approximately 120 individuals with imprinting disorders.
- Novel gene discovery for an autosomal recessive form of MLID: Ubiquitin-like, containing PHD and RING finger domains 1 protein (UHRF1) (Figure 1).

Next Steps:
- Determine whether specific DNA methylation patterns can predict genetic causes and clinical outcomes.
- Define the role of UHRF1 in epigenetic regulation and disease mechanisms.

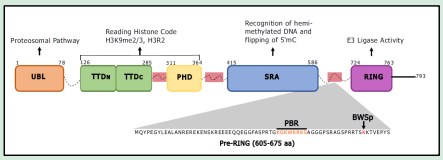
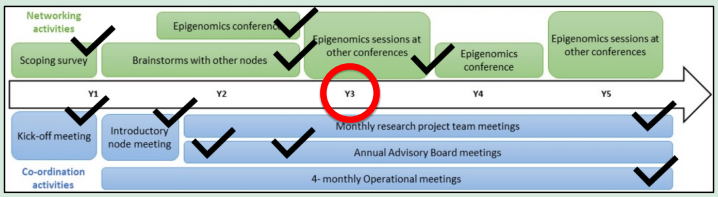


Figure 1. Location of functional domains in UHRF protein.

WP4: Networking activities

All networking objectives have been achieved.



The EpiGenRare Node has established a strong global network through:
- Successful kick off meeting, annual conferences, two symposia at external major conferences and two Scientific Advisory Board (SAB) meetings.
- Many invited international talks and workshops at major meetings and institutions.
- Expanding its reach to over 70 members and affiliates with strong links to existing infrastructure such as BRCs, other RDRUK Nodes, and industrial partners, e.g. ORYZON (Figure 2).

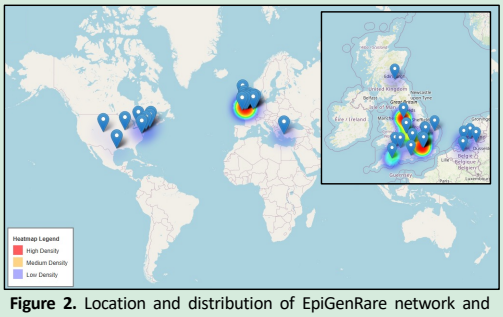


Figure 2. Location and distribution of EpiGenRare network and images from the 1st EpiGenRare Conference 2025.

WP2: Therapeutic convergence in chromatinopathies

A key challenge is that developing individual therapies for each rare chromatinopathy is impractical due to their rarity and heterogeneity. This project aims to test whether different disorders with shared epigenetic mechanisms converge on common molecular pathways and could therefore respond to the same targeted treatment (Figure 3).

Key Progress:
- Treated Kabuki and CHARGE syndrome mouse models with ORY-2001 with ORYZON.
- Comparative multi-omics in progress.
- Conducting multi-omics with the Kabuki Syndrome Foundation, focusing on hippocampus.

Next Steps:
- Characterise a new Kabuki syndrome GEMM mouse model, incorporating neuroimaging studies.
- Comparative neuroimaging planned for the CHARGE syndrome model.

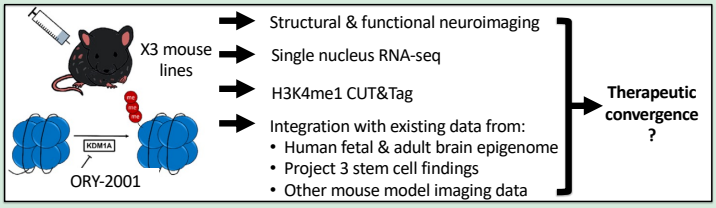


Figure 3. Schematic of therapeutic convergence workflow. Adapted from (Bhatt et. al., 2025) (2).

WP3: High throughput drug screening for therapies

A major obstacle in therapeutic development is the lack of standardised, disease-relevant human cellular models that enable cross-disease comparison and drug screening. This project aims to generate and characterise pluripotent stem cell models across multiple chromatinopathies and establish shared phenotypic readouts suitable for high-throughput therapeutic screening.

Key Progress:
- Published Kabuki syndrome induced pluripotent stem cell (iPSC) neural multi-omic analysis (3).
- Completed high-content imaging pilot at King's College London.
- Generated four RLF iPSC lines.
- Established an inventory of 17 lines covering seven chromatinopathies and matched controls.
- Produced RNA-seq and ATAC-seq datasets from Kabuki syndrome iPSCs, neural progenitors, and immature neurons for comparison with mouse models (Figure 4).

Next Steps:
- Generate and validate two isogenic Kabuki syndrome lines for comparative studies.

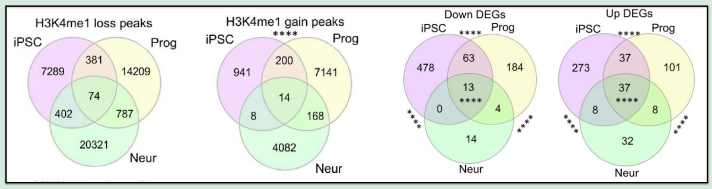


Figure 4. Epigenetic and transcriptomic analyses on iPSCs, neurons and neural progenitors.

WP5: Patient and Public Involvement and Engagement

PPIE is at the heart of the EpiGenRare project. Our major achievements so far are:
- Patient representatives have presented at every EpiGenRare meeting and conference to date.
- Ongoing co-development of management & clinical guidelines for Kabuki & Beckwith-Wiedemann syndromes.
- Ongoing co-development of patient information guides/resources with UNIQUE & Shorthills AI.
- Delivered two educational sessions at family support events.

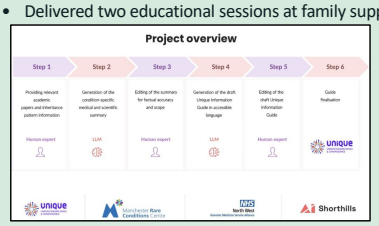


Figure 5. Workflow of the patient information guidelines in collaboration with UNIQUE & Shorthills AI. Image from Kabuki Syndrome Clinical Guidelines Consensus Meeting in Boston.

References

16 MRC-NIHR acknowledged publications (23 EpiGenRare publications in total).

Scan QR code above for full list of publications

(1) Ochoa, E., Zvetkova, I., Liv Lee, S., Takahashi, N., Lan-Leung, B., Hobson, E., Issa, M., Yngvadottir, B., Docquier, F., Rodger, F., Foster-Hall, D., Clark, G., Toribio, A., Martin, E., Bottolo, L., Ferguson-Smith, A. C., Fischle, W., Constancia, M. & Maher, E. R. 2025. Germline variants in UHRF1 are associated with multilocus imprinting disturbance in humans and mice. Proceedings of the National Academy of Sciences, 122, e2505884122.
(2) Bhatt, S. U., Macbean, L., Kramár, E., Pérez-Sisqués, L., Smethurst, P., Robb, J. L., Jindal, N., Fetterly, T. L., Graham, A., Wood, M. A., Gillotin, S., Giese, K. P. & Basson, M. A. 2025. Inhibition of histone lysine demethylase restores learning and memory in aged mice. bioRxiv, 2025.12.22.695858.
(3) Cuvertino, S., Martirosian, E., Bhosale, K., Cheng, P., Garner, T., Donaldson, I. J., Jackson, A., Stevens, A., Sharrocks, A. D., Kimber, S. J. & Banka, S. 2025. Epigenome and transcriptome changes in KMT2D-related Kabuki syndrome Type 1 iPSCs, neuronal progenitors and cortical neurons. PLOS Genetics, 21, e1011608.

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NIHR National Institute for Health and Care Research