# An Epigenomic ID for a better Diagnosis

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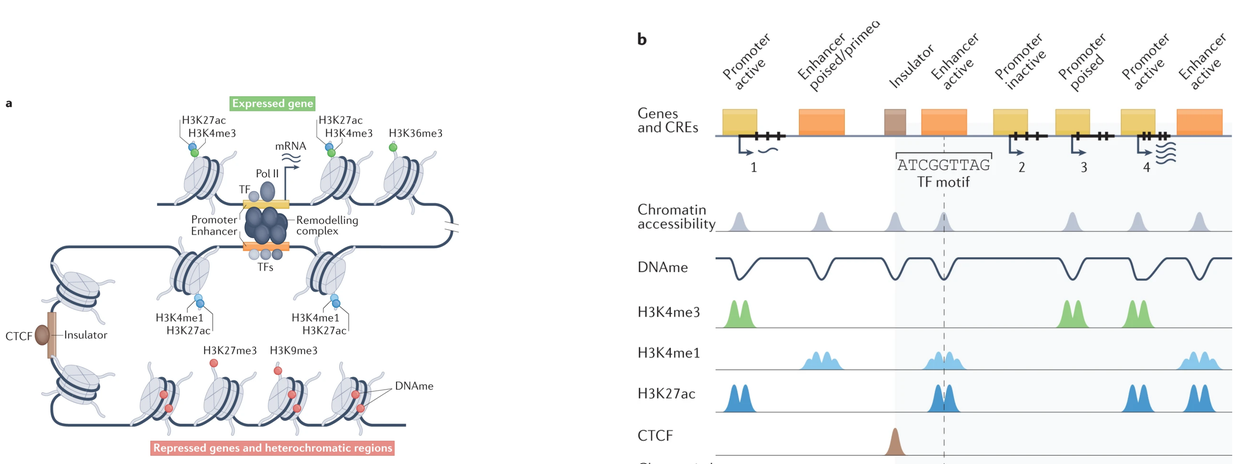
## ABSTRACT

Recent breakthroughs in sequencing technology have ushered in a new era of patient diagnosis. However, a significant number of cases continue to evade resolution due to elusive mutations and regulatory sequences. This project is dedicated to expediting diagnostics by constructing Epigenetic Identification (Epigenetic ID) maps for diseases, with a specific focus on growth-related disorders commonly associated with epigenetic regulator mutations.

We will rigorously analyze 41 lymphoblastoid cell lines and patient/control DNA samples using cutting-edge techniques, including ChIP-Seq, ATAC-Seq, and Illumina EPIC arrays for methylome analysis, meticulously profiling five key epigenetic markers. These efforts will culminate in the development of Epigenetic IDs for nine growth-related pathologies across two distinct patient cohorts. This ambitious initiative promises to yield profound insights into the underlying epigenetic mechanisms, fostering the creation of functional hypotheses and innovative diagnostic methodologies.

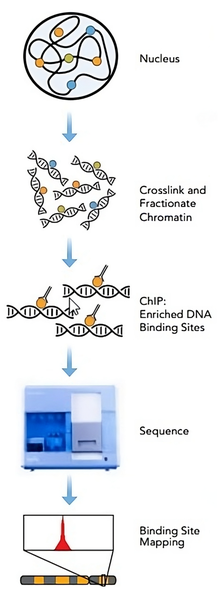
This project represents a significant advancement in medical diagnostics, offering a comprehensive approach to the understanding, diagnosis, and management of complex pathologies. It will refine our grasp of disease-related epigenetic mechanisms and potentially pave the way for further research. Epigenetic IDs hold the promise of reshaping our approach to diseases, ultimately benefiting patients and the broader healthcare community.

## BACKGROUND

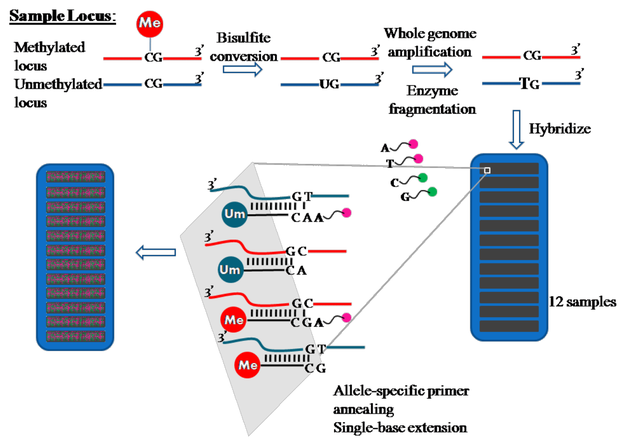



Epigenetic modifications and their effects on gene expression

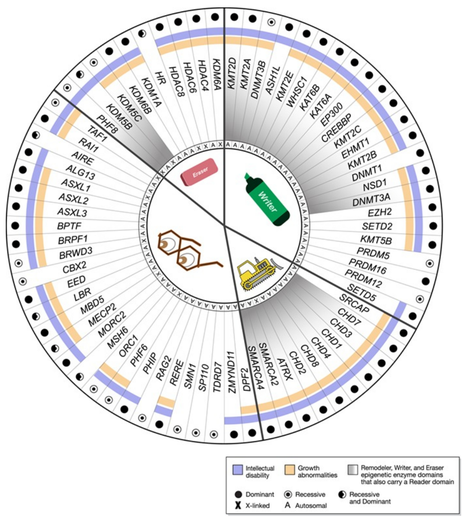
## METHODOLOGY




Chip seq protocol



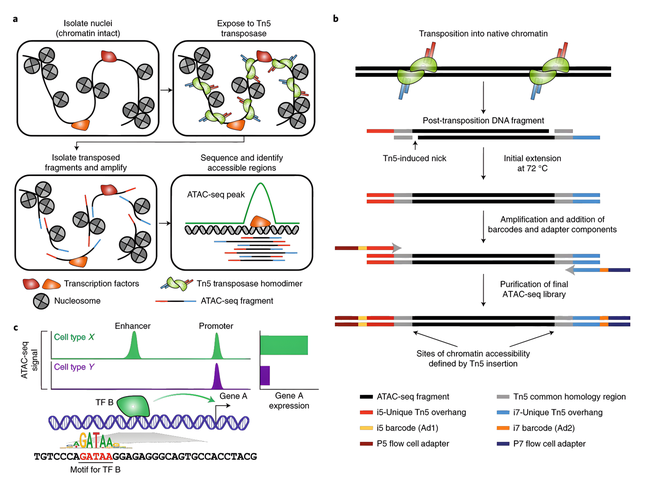

Methylome Illumina EPIC arrays




| ORPHAcode | Disease | Clinical signs |
|---|---|---|
| ORPHA:2554 | Meier-Gorlin syndrome | Very short stature, Patella aplasia/hypoplasia, small ears, microcephaly, Cryptorchidism |
| ORPHA:138 | Charge syndrome | Cup-shaped ears, coloboma, delayed puberty, hearing loss, short stature, Choanal atresia, heart defects |
| ORPHA:404440 | Intellectual disability-facial dysmorphism syndrome due to SETD5 haploinsufficiency | Intellectual disability, hypotonia, feeding difficulties, dysmorphic features, autism, growth retardation |
| To come | Heyn-Sproul-Jackson syndrome | Short stature, Microcephaly, Impaired intellectual development, Short broad phalanges |
| ORPHA:821 | Sotos syndrome | Tall stature, macrocephaly, variable intellectual impairment |
| ORPHA:404443 | Tatton-Brown-Rahman syndrome | Tall stature, Large head circumference, Narrow palpebral fissures, Hypermobile joints, Intellectual disability, mild to moderate |
| ORPHA: 599082 | Snijders Blok-Campeau syndrome | Intellectual impairment, macrocephaly, dysmorphic facies |
| OMIM# 615032 | Intellectual developmental disorder with autism and macrocephaly | Autism, macrocephaly, tall stature, distinct facial features |
| ORPHA:847 | Alpha-thalassemia-X-linked intellectual disability syndrome | intellectual disability, facial dysmorphism, genital abnormalities, alpha thalassemia, Ambiguous genitalia, autism |

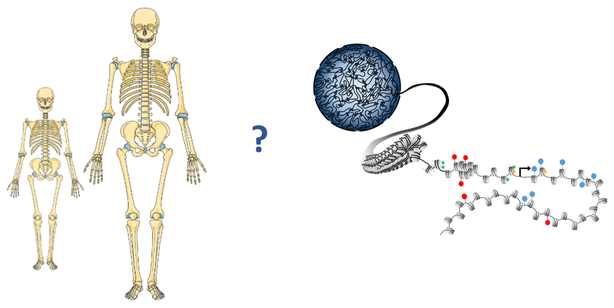
| | Growth | Disease | Genes | # Patients | #LCL |
|---|---|---|---|---|---|
| Cohort 1 | Dwarfism | Meier-Gorlin syndrome | ORC1, ORC4, ORC6, CDC6, CDC45, CDT1 | 3 | 2 |
| | | Charge syndrome | CHD7 | 3 | 1 |
| | | Intellectual disability-facial dysmorphism syndrome due to SETD5 haploinsufficiency | SETD5 | 3 | |
| | | Heyn-Sproul-Jackson syndrome | DNMT3A | 3 | |
| | Overgrowth | Sotos syndrome, Sotos-like syndrome | (NSD1) SETD2 | 3 | 2 |
| | | Tatton-Brown-Rahman syndrome | DNMT3A | 3 | |
| | | Snijders Blok-Campeau syndrome | CHD3 | 3 | |
| | | Intellectual developmental disorder with autism and macrocephaly | CHD8 | 3 | |
| | Not related to growth | Alpha-thalassemia-X-linked intellectual disability syndrome | ATRX | 3 | 2 |
| | Controls | healthy donors | | 6 | 4 |
| Cohort 2 | Dwarfism | Unknown | | 4 | 1 |
| | Overgrowth | Unknown | | 4 | 3 |

Conditions analyzed and epigenetic regulator genes involved



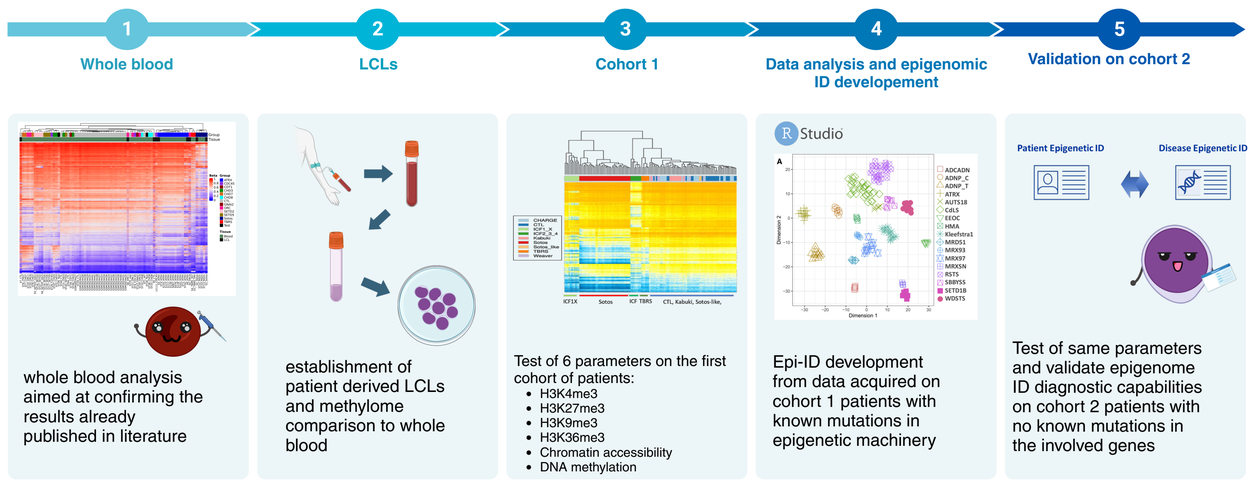

ATAC seq protocol

## QUESTIONS



- **Is there an epigenomic signature for dwarfism vs overgrowth syndromes ?**
- **Is epigenome characterisation (Epi ID) a powerful tool to improve diagnostic yield ?**

## EXPERIMENTAL PLAN

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