Kleefstra Syndrome
ICD-10-CM Code Request

ICD10 Coordination and Maintenance Committee

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Disclosures

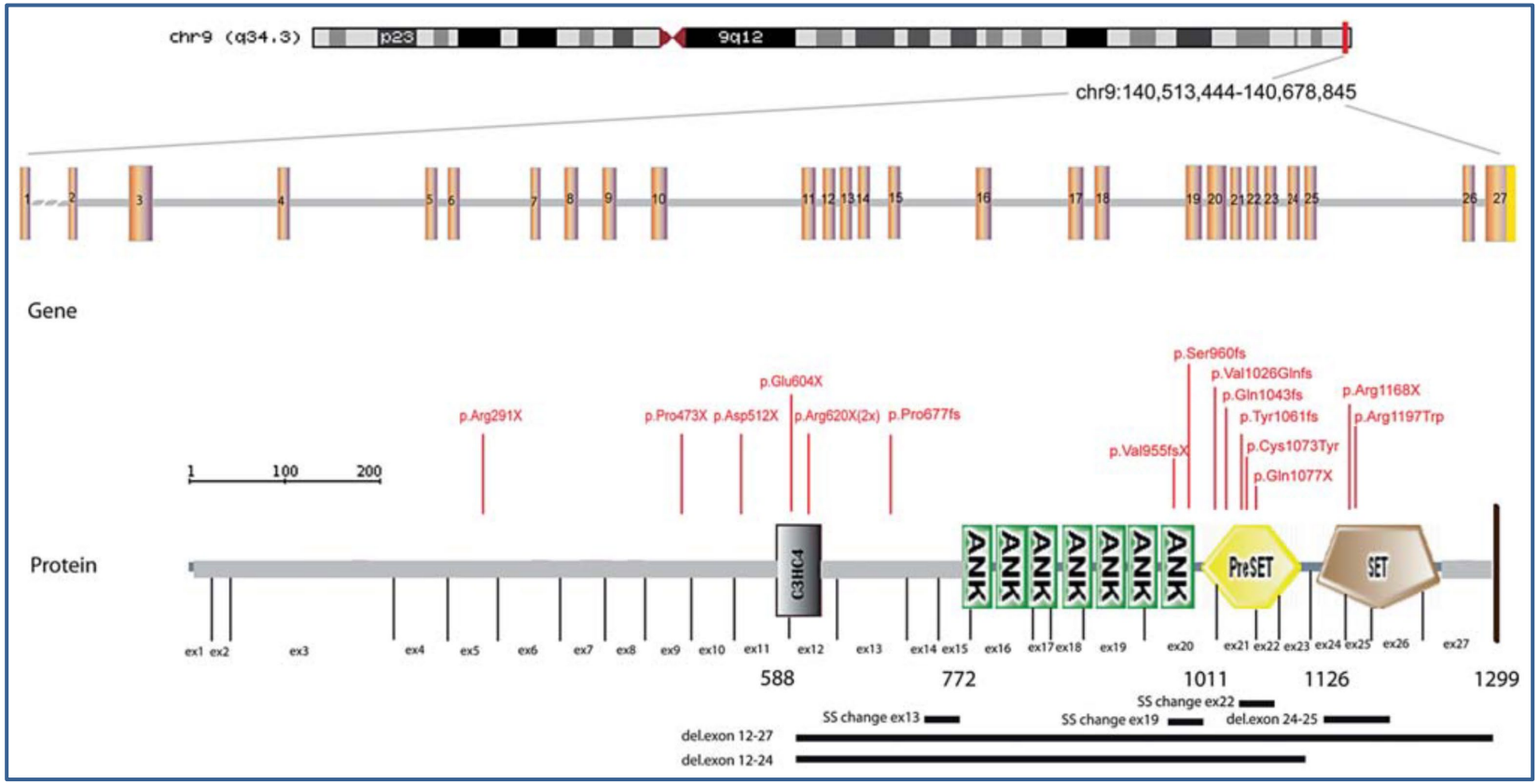
I have received consulting fees from:
GLG
Guidepoint (which connected to a client, Fortress Biotech)
Novartis
ExpertConnect
Orchard Therapeutics
Stoke Therapeutics

Kleefstra Syndrome is a Precisely Defined Genetic Disorder

- Kleefstra Syndrome (KS) is *always* caused by a loss function in *one copy* of the gene EHMT1 on Chr9
- Loss of EHMT1 can be due to a deletion (~50% of patients) or a pathogenic mutation (~50% of patients)
- KS is almost always due to a spontaneous (*de novo)* mutation, and is therefore equally distributed in all ethnic groups and regions

EHMT1 Gene Structure on Chr 9

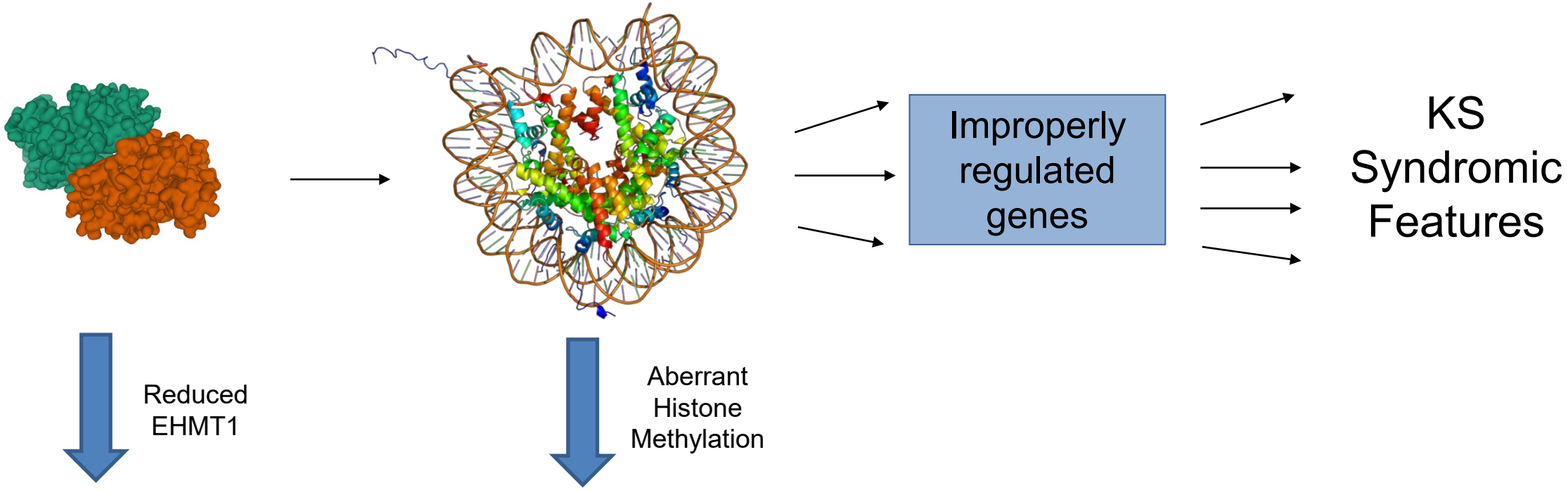
EHMT1 Protein Architecture With Documented Pathogenic Mutations and Microdeletions



From Willemsen et al., Mol Syndromology 2011;2:202–212

Kleefstra Syndrome is a Disorder of Epigenetic Regulation

- EHMT1 is an epigenetic regulator, which methylates histones to control opening and closing of chromatin
- Loss of EHMT1 leads to dysregulation of multiple downstream genes due to aberrant chromatin regulation



KS Presents a Unique Clinical Phenotype in Patients

KS Phenotype May Include

Neurological

- Intellectual disability (universal)
- Limited or absent speech capabilities
- Global developmental delay
- Autism
- Seizures (~40%)
- Sleep disorders
- Hypotonia

Physical

- Mild facial dysmorphism
- Risk for hearing impairment
- Risk for visual impairment
- Risk for congenital malformations (heart, kidney)
- GI disturbance (constipation)

Psychological

- Risk of psychosis in teenage years
- Risk of regression (i.e. loss of skills + personality) in teenage years

A Diagnosis of KS Can Be Made Definitively

Requires:
1) Pathogenic or likely pathogenic mutation in EHMT1 *OR* Deletion of EHMT1
2) Correlated clinical symptoms

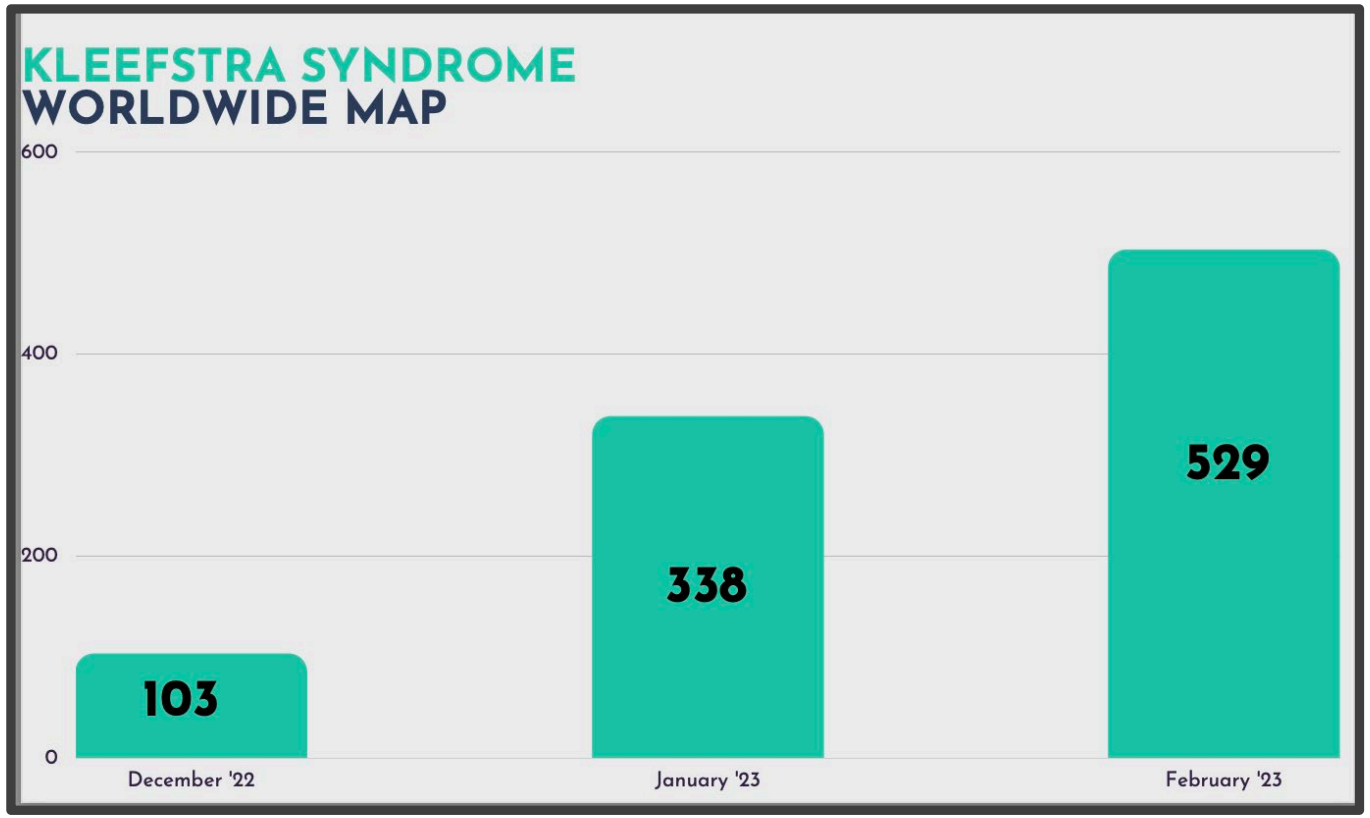
In cases of a VUS in EHMT1, the *EpiSign* commercial test is available, which confirms a KS diagnosis based on distinctive aberrant methylation patterns present in the disorder

Kleefstra Syndrome Prevalence

- Estimated prevalence of KS is 1:25K-35K people[1], similar to prevalence of other conditions that have received ICD-10-CM codes
- Underdiagnosis and underreporting is a huge challenge

Provision of an ICD-10-CM would:

- Assist in efforts to locate patients
- Help confirm the prevalence rate among patients with NDDs as they are newly diagnosed



The KS World Map Project:

- Allows KS families with a diagnosis to voluntarily report
- Has grown rapidly since launch in late 2022
- >200 patients registered in the US and rising

[1]Estimate generated through unbiased NDD genome sequencing studies, and cross-correlated with population-scale studies in the Netherlands by Dr. Kleefstra

A Specific Code for KS is Required to Support Appropriate Clinical Management

Management includes:

Neurological Management

- Early intervention (speech therapy, occupational therapy, etc)
- Autism therapy (Applied Behavior Analysis)
- Careful monitoring for seizures and immediate pharmacological intervention if needed

Physical Management

- Hearing assessments
- Visual assessments
- Heart and kidney ultrasounds

Psychological

- Monitoring for psychosis/severe sleep disturbance and rapid intervention with Olanzapine if needed

The Kleefstra Syndrome Clinical Guidelines Project

- A consortium of universities and hospitals is currently developing rigorous guidelines for appropriate management of KS
- Multiple institutions across North America, Europe, and Australia
- Domains of focus include neurology, psychiatry, sleep, behavior, GI, cardiology, nephrology, and genetics
- Draft of publication expected in early 2024

Kleefstra Syndrome is Currently Not Coded in a Consistent Way

Absent a unique code for KS, multiple codes may be entered for the manifestations of the disorder, e.g.:

- ID (F79)
- Autism (F84.0)
- Hypotonia (P94.2)
- Epilepsy (G40)

These are non-specific:

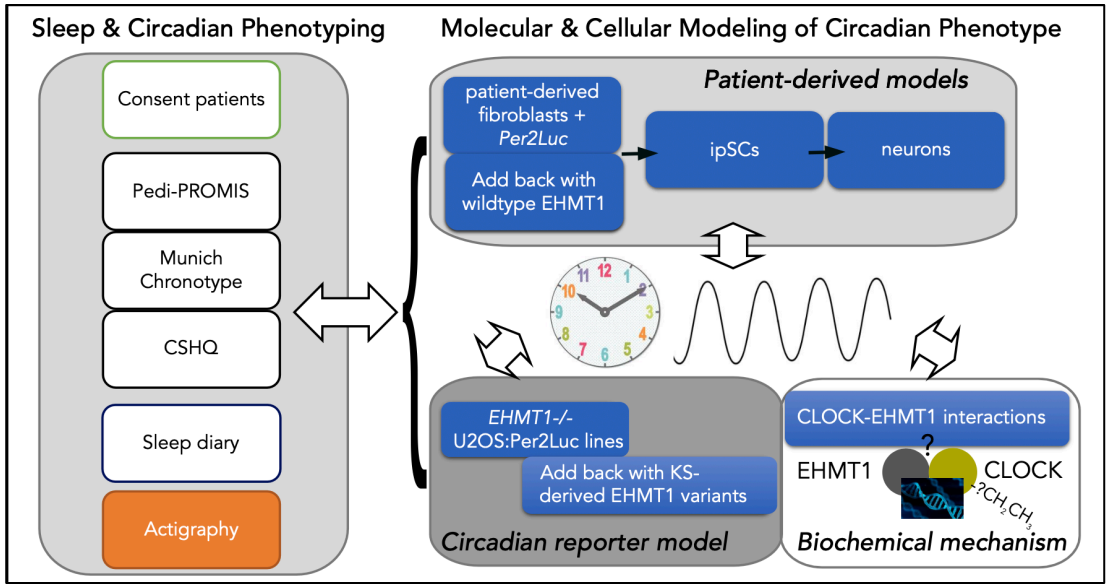
- Can apply to literally hundreds/thousands of different genetic conditions
- Do not indicate a path to other manifestations that should be evaluated/managed appropriately

The Current Codes uses for Kleefstra Syndrome are not Specific Enough

With the current system:

- We cannot precisely define the disorder
- We cannot corroborate prevalence estimates (chicken-and-egg problem)
- We cannot easily track patients to better understand morbidity/mortality
- We cannot easily find cohorts for clinical studies (e.g. sleep study at Boston Children's Hospital)
- We cannot easily prepare for future clinical drug trials by establishing number and location of available patients
- We cannot easily track patients to ensure they are receiving the appropriate interventions

The Boston Children's Hospital Translational KS Sleep Study



Multiple Pre-Clinical Drug Development Programs for KS are Ongoing

- These interventions are biochemically specific to KS
- An ICD-10-CM code will support these programs when they reach the clinical stage, and encourage additional drug developers to work on the disorder

Approach	Rationale	Number of Programs
Drug Repurposing Screens	Screen small molecules in model systems for phenotypic improvement	At least 2
Anti-Sense Oligonucleotide (ASO)	Use an ASO to increase EHMT1 levels from the intact *EHMT1* gene copy	At least 1
Gene Therapy	Use a gene therapy vector to deliver the additional missing copy of the *EHMT1* gene	At least 1

Summary

- Kleefstra Syndrome is a unique disorder with a unique set of required interventions and potential treatments
- KS requires its own to code to support appropriate clinical management
- KS requires its own code to improve research and treatment development

The North American Kleefstra Syndrome Family Conference

June 2022

Outside Chicago, IL

75 Families