Kleefstra Syndrome: Association with Congenital Heart Disease and Arrhythmias

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Kleefstra Syndrome

• Rare genetic disorder caused by a sub-telomeric deletion in chromosome 9 (9q34.3) or by a rare variant in EHMT1, leading to haploinsufficiency of EHMT1

• Often diagnosed in early childhood

• Characterized by the core phenotype of hypotonia, developmental delay/intellectual disability and distinct facial features

• Also been associated with neuromuscular and skeletal abnormalities, delayed or impaired speech, seizures, as well as behavioral and sleep abnormalities

• Congenital heart defects are frequently reported in KS patients (10%-50%)

• Structural defects such as atrial septal defects (ASD) and ventricular septal defects (VSD), aortic coarctation, bicuspid aortic valve, pulmonary valve stenosis, persistent foramen ovale, patent ductus arteriosus, conotruncal cardiac defects including tetralogy of Fallot and transposition of great vessels.

• Isolated case reports of aberrant muscle bundle in the left ventricle, hypoplastic left heart and pulmonary hypertension

EHMT1

- **EHMT1** (Euchromatic Histone Lysine Methyltransferase 1) gene modulates several other genes that regulate cardiomyocyte cell-cycle and maturation from a neonatal to adult state via post-translational histone modifications and DNA methylation.
- Animal studies have linked EHMT1 to congenital malformation of the atrioventricular septum
- Suppression of **EHTM1** gene expression (microRNA or medication induced) linked to pathological hypertrophy and preferential proliferation of neonatal (immature) cardiac cells.
- iPSC-derived neural cells from an 11-year-old patient with developmental delay showed altered morphology and cholinergic dysfunction.

**Current Recommendations for Cardiac workup**

- Baseline EKG recommended once after Kleefstra Syndrome diagnosis established. Many but not all patients get cardiac imaging including echocardiography upon diagnosis.
- No routine surveillance (rhythm monitoring or imaging) recommended currently
Our Case: Inspiration

- 27-year-old man with a diagnosis of Kleefstra syndrome and AFib w/ RVR first diagnosed at age 23 who presented with fatigue and palpitations.
- Exhibited KS-associated features including hypotonia, hypernasal speech, truncal obesity, developmental delay, and hearing loss.
- He had no baseline structural or congenital heart disease on Echo or Cardiac MRI
- Thyroid function and electrolytes were normal
- No other known risk factors for arrhythmia other than sleep apnea
- Despite medical treatment with beta-blockers and sotalol, there was a 20% AFib burden with a transient drop in EF to 45%.
- PVI performed successfully (first known): triggers in RIPV and LIPV that initiated AF.
- No further AFib after 16 months.
- Two additional young patients with KS with arrhythmias were also identified.
  1) Diagnosed AF incidentally at age 25 during a visit to the dentist without structural disease on echocardiography at Boston Children’s/Harvard
  2) Unstable AT in a 17 year old admitted for pneumonia to Johns Hopkins.
  3) Neither of these patients had structural heart disease on cardiac imaging (echocardiography). These patients were medically managed with metoprolol, atenolol, and amiodarone.
Stanford Patient: Ambulatory Rhythm Monitoring

Ambulatory Rhythm Monitoring Summary for 9 days:
Mostly Sinus Rhythm.
Atrial Fibrillation: 20% Burden, longest: 11 hours 45 minutes with HR: 42-190
Atrial Ectopy (PACs): 13,913 singles, 863 couplets, 151 triplets
Ventricular Ectopy (PVCs): 2,204 singles. No couplets or triplets.
Systematic review of CHD and Arrhythmias in Kleefstra Syndrome:

Radboudumc and GenIDA Registries
Registries: Radboudumc and GenIDA

• The Radboudumc registry
  • All patients referred to Radboud University Medical Center in the Netherlands
  • Clinically confirmed to have KS and consented to the use of their de-identified health records (50 patients)
  • Medical records were reviewed by designated medical personnel to extract information regarding demographic characteristics, results of genetic testing and medical history including congenital heart disease and arrhythmias.

• GenIDA registry
  • “participatory” by patients and families online
  • available in 7 languages
  • Aimed at compiling the genotype and phenotype information of multiple neurodevelopmental disorders worldwide (1500 patients) of which Kleefstra Syndrome is one (163 patients)

https://genida.unistra.fr/

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>48</td>
</tr>
<tr>
<td>UK</td>
<td>18</td>
</tr>
<tr>
<td>France</td>
<td>17</td>
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<tr>
<td>Germany</td>
<td>15</td>
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<td>Spain</td>
<td>10</td>
</tr>
<tr>
<td>Australia</td>
<td>5</td>
</tr>
<tr>
<td>Netherlands</td>
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</tr>
<tr>
<td>Canada</td>
<td>4</td>
</tr>
<tr>
<td>Switzerland</td>
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<tr>
<td>Brazil</td>
<td>3</td>
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<tr>
<td>Italy</td>
<td>3</td>
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<tr>
<td>Colombia</td>
<td>3</td>
</tr>
<tr>
<td>Slovenia</td>
<td>2</td>
</tr>
<tr>
<td>Denmark</td>
<td>2</td>
</tr>
<tr>
<td>Portugal</td>
<td>2</td>
</tr>
<tr>
<td>Hungary</td>
<td>2</td>
</tr>
<tr>
<td>Japan</td>
<td>1</td>
</tr>
<tr>
<td>Egypt</td>
<td>1</td>
</tr>
<tr>
<td>Luxembourg</td>
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<tr>
<td>Ireland</td>
<td>1</td>
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<tr>
<td>Albania</td>
<td>1</td>
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<tr>
<td>India</td>
<td>1</td>
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<tr>
<td>Belgium</td>
<td>1</td>
</tr>
<tr>
<td>South Africa</td>
<td>1</td>
</tr>
<tr>
<td>New Zealand</td>
<td>1</td>
</tr>
<tr>
<td>Norway</td>
<td>1</td>
</tr>
<tr>
<td>Greece</td>
<td>1</td>
</tr>
<tr>
<td>Israel</td>
<td>1</td>
</tr>
</tbody>
</table>

GenIDA registry countries
## Congenital Heart Disease in KS: Registries

<table>
<thead>
<tr>
<th>Kleefstra syndrome</th>
<th>Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Radboudumc</td>
</tr>
<tr>
<td>Total included patients</td>
<td>50</td>
</tr>
<tr>
<td>Age at last examination in years: Median (IQR)</td>
<td>13.5 (13)</td>
</tr>
<tr>
<td>Gender (Male/Female)</td>
<td>M: 38%, F: 62%</td>
</tr>
<tr>
<td>Abnormality of the cardiovascular system</td>
<td>20 (40%)</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>None reported</td>
</tr>
<tr>
<td>Abnormal ventricular septum morphology</td>
<td>6 (12%)</td>
</tr>
<tr>
<td>Atrial septal defect</td>
<td>7 (14%)</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Patent foramen ovale</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td>N/A</td>
</tr>
<tr>
<td>Pulmonary valve stenosis</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Bicuspid aortic valve/aortic valve stenosis</td>
<td>None reported</td>
</tr>
<tr>
<td>Mitral or tricuspid valve prolapse/insufficiency</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Abnormality of the greater vasculature</td>
<td>None reported</td>
</tr>
<tr>
<td>Source</td>
<td>Cardiac Arrhythmia</td>
</tr>
<tr>
<td>------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>Radboudumc</td>
<td>Paroxysmal Atrial Fibrillation</td>
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<tr>
<td></td>
<td></td>
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<tr>
<td>Radboudumc</td>
<td>SVT (Supraventricular Tachycardia)</td>
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<td></td>
<td></td>
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<tr>
<td>Radboudumc</td>
<td>Paroxysmal SVT (Accelerated Nodal Rhythm)</td>
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<tr>
<td>Radboudumc</td>
<td>Non-sustained Ventricular Tachycardia</td>
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<tr>
<td>GenIDA</td>
<td>Bursts of Atrial Fibrillation</td>
</tr>
<tr>
<td>GenIDA</td>
<td>Chronic Atrial Ectopic Tachycardia</td>
</tr>
<tr>
<td>Stanford</td>
<td>Paroxysmal Atrial Fibrillation, Atrial Flutter, PVCs, NSVT</td>
</tr>
<tr>
<td>Harvard</td>
<td>Paroxysmal Atrial Fibrillation</td>
</tr>
<tr>
<td>Johns Hopkins</td>
<td>Unstable SVT (Atrial Tachycardia)</td>
</tr>
</tbody>
</table>

* patient also harbored heterozygous PRKAG2, c.1571T>G (p.Ile524Arg) variant of uncertain significance
Limitations

• Rare condition with limited available information

• Registry Data is based primarily on health records at a single institution, and patient and family surveys from patients referred from around the world

• Despite best efforts, many KS patients might not be captured

• Information from these registries is not specifically aimed to target cardiac concerns

• In the GenIDA registry, self-reported conditions were not validated with medical record review

• All patients did not get imaging or rhythm monitoring

• Selection bias of specific cases chosen for case reports of patients with atrial tachyarrhythmias
  • Still proves occurrence of a very unexpected phenomenon (AF in such young patients)
Conclusion

• Compilation of the two largest known KS registries with this rare genetic disorder (213 patients)
• Reveals a high prevalence of various types of congenital structural heart disease (40%) and early-onset arrhythmias (2-8%).

• Arrhythmias were noted to be primarily atrial tachyarrhythmias and included multiple KS patients with young patients incidentally diagnosed with AF.
• First known case of a successful AF ablation (without arrhythmia recurrence at 16 months)
• Arrhythmias noted without congenital or structural heart disease.
• AF and atrial tachycardia were noted in at least four young KS patients (3 AF and 1 AT) without structural heart disease, there is the possibility of a novel epigenetic mechanism for Atrial Fibrillation which needs further study that might help understand this complex arrhythmia in all patients of all ages with or without KS.
• Unique challenges and barriers for patients to communicate their symptomatology within this unique population.
• Need for iPSC-derived cardiac ep studies, and clinical guidelines for monitoring, surveillance and treatment.
• There might be a role for routine and regular EKG and ambulatory rhythm monitoring strategies for these patients especially with several affordable wearable rhythm monitoring technologies.
Thank you

• Questions/Discussions

• Special Thank you:
  Tanja Zdolsek Draksler, Arianne Bouman, Joost Kummeling, Matthew Wheeler, Chloe Reuter,
  Siddharth Srivastava, Jacqueline Harris, Paul Fisher, Paul Wang, Nitish Badhwar

• Tjitske Kleefstra
• Marco Perez

• Acknowledgements: Jennefer Kohler, Colleen Bonnett, Allysonne Smith
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### Structural Heart Disease Type

<table>
<thead>
<tr>
<th>Disease Type</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>None Reported</td>
<td>4</td>
</tr>
<tr>
<td>Pulmonary Stenosis</td>
<td>1</td>
</tr>
<tr>
<td>ASD + Cardiac or Cardiovascular Malformation + Pulmonary Stenosis</td>
<td>1</td>
</tr>
<tr>
<td>ASD + Bicuspid Aortic Valve</td>
<td>1</td>
</tr>
<tr>
<td>Cardiac or Cardiovascular Malformation + Pulmonary Stenosis</td>
<td>1</td>
</tr>
<tr>
<td>Bicuspid Aortic Valve + Cardiac or Cardiovascular Malformation + Pulmonary Stenosis</td>
<td>1</td>
</tr>
</tbody>
</table>

Additional patients coded as “Arrhythmia” in the GenIDA Registry not included in Table 2 showing co-prevalence of “Abnormal EKG” and Structural Heart Disease. There were no further reports/details regarding arrhythmias in these patients except “Abnormal EKG”.

**Extra slides**

![AF/AFL Duration Chart](chart)

1. **AF/AFL with Fastest Heart Rate**
   - Average: 99 bpm
   - Range: 40-100 bpm

2. **AF/AFL with Slowest Heart Rate**
   - Average: 45 bpm
   - Range: 42-163 bpm

3. **Longest AF/AFL Episode**
   - Duration: 11 hours 45 minutes
   - Average: 49 bpm
   - Range: 48-100 bpm

Additional details on AF/AFL duration distribution.
Family History
Case: SE

As of 2018

87
no heart prob

82
HTN "blank spells" conscious but unresponsive

no info never knew

83
no heart prob

55
no cardiac issues

58
no known cardiac issues palps - fast 1/year ECG - NML - 2017

58
no known cardiac issues no palps hi chol

55
no cardiac issues

22
no cardiac issues

19
no cardiac issues

31
history of murmur no cardiac issues no palps echo ?ECG elite level athlete runs marathons plays rugby

26
no cardiac issues

22
no cardiac issues college level athlete

As of 2018
Genetic Testing
Case: SE

Prior unrevealing genetic work-up:
• Karyotype (1998)
• Fragile X testing x2
• Prader-Willi/Angelman methylation
• 22q11 FISH (2002)
• Array CGH x2 (2004, 2009)
• Exome sequencing (2012)
• Comprehensive Arrhythmia & Cardiomyopathy (2018)

VUS in PRKAG2
c.1571T>G (p.Ile524Arg)
• PRKAG2 - glycogen storage disorder with Wolff-Parkinson-White and LV hypertrophy.
• p.Ile524Arg: no case data, rare.
UDN Genetic Evaluation
Case: SE

Clinical Genome Sequencing
Research SV analysis
Long Read Genome Sequencing

EHMT1 Tandem Duplication

Slide courtesy of Devon Bonner
UDN Genetic Evaluation – *EHMT1* Tandem Duplication

Case: SE

**Proband lrGS Reads**

**Reference Gene Transcript**

**BLAT**

*SLIDE COURTESY OF DEVON BONNER, CHLOE REUTER*
UDN Genetic Evaluation – *EHMT1* Tandem Duplication

Case: SE

Slide courtesy of Devon Bonner, Chloe Reuter
UDN Genetic Evaluation – *EHMT1* Tandem Duplication

Case: SE

Proband
IrGS
Reads

Reference Gene
Transcript

BLAT

*EHMT1*

Ex1 Ex2 Ex3 Ex4 Ex5 Ex6 Ex7

Duplication -> Frameshift

Slide courtesy of Devon Bonner, Chloe Reuter
**EHMT1 Duplication – Clinical Confirmation & Segregation Analysis**

**Case: SE**

### Genetic Testing

**RESULT: POSITIVE**

One Likely Pathogenic variant identified in EHMT1. EHMT1 is associated with autosomal dominant Kleefstra syndrome.

<table>
<thead>
<tr>
<th>GENE</th>
<th>VARIANT</th>
<th>ZYGOSITY</th>
<th>VARIANT CLASSIFICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>EHMT1</td>
<td>Gain (Exons 3-6)</td>
<td>copy number = 3</td>
<td>Likely Pathogenic</td>
</tr>
</tbody>
</table>

**About this test**
This diagnostic test evaluates 1 gene(s) for variants (genetic changes) that are associated with genetic disorders. Diagnostic genetic testing, when combined with family history and other medical results, may provide information to clarify individual risk, support a clinical diagnosis, and assist with the development of a personalized treatment and management strategy.

### Methylation Analysis

**Greenwood Genetic Center**

**MOLECULAR DIAGNOSTIC LABORATORY**

106 Gregor Mendel Circle
Greenwood, SC 29646
Phone: 800-473-9411
Fax: 864-941-8141
www.ggc.org

**Results:** Abnormal targeted methylation analysis for the epigenetic signature associated with Kleefstra syndrome.