

# KLS Research Update

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# KLS Research

## Introduction

- Challenge - KLS is a rare, ‘orphan disease’
- 15 years ago, sparse research being conducted
- Mostly single ‘case reports’, little scientific value
- KLS is an unusual medical disorder:
  - Understanding the cause KLS will lead to better treatment for the benefit of patients and lead to new insights in sleep, behavior & neurobiology

# Orphan Drugs

Summit 2011

Copenhagen, Denmark, 14<sup>th</sup> - 16<sup>th</sup> September 2011



It is estimated that 6%-10% of the world's population will suffer from a rare disease at one point in life and almost 1 in every 5 personally knows of an individual suffering from a rare disease. Finding a cure or better treatment for such patients is fundamental not only to their lives but also to society as a whole.

... there is a great potential to improve the work amongst all stakeholders: patient organizations, governmental authorities, health technology assessment organizations, payers, drug developers and patients' access to such drugs.

# Building a Research Program

- KLS Foundation mission ... to support scientific research, to find effective treatment & ultimately a cure for KLS



- Bring leading KLS researchers together
  - 2006 (Utah) – APSS Annual Sleep Conference - 1<sup>st</sup> KLS Symposium
  - 2011 (California) – KLS Foundation Conference
  - 2015 (S. Korea) - World Congress on Sleep Medicine KLS Symposium

# KLS Research - where to start?

- Some clinical observables:
  - All medical tests within normal ranges
  - Typically starts in adolescence with the first episode following an illness, trauma or other stress event
  - Episodes are cyclical, lasting from a week to months
  - Frequency of episodes vary from monthly to years in between
- There is no known test for KLS
- There is no known cure or consistent treatment

# KLS Medical Research - Challenges

- Etiology ('cause of illness') unknown
- All medical tests within normal ranges
- Nature of illness (episodic, attenuates over time)
- Small patient population, obtaining clinical samples
- Accurate diagnosis
- Funding

# KLS Research some working hypotheses

Genetic?

- Ethnic prevalence, Multiplex cases

Viral?

- Viral-like prodrome, Cyclical nature

Immune mediated?

- Presentation, HLA

Neuro-anatomical?

- Brain Imaging data, Onset

Hormonal?

- Sporadic clinical findings

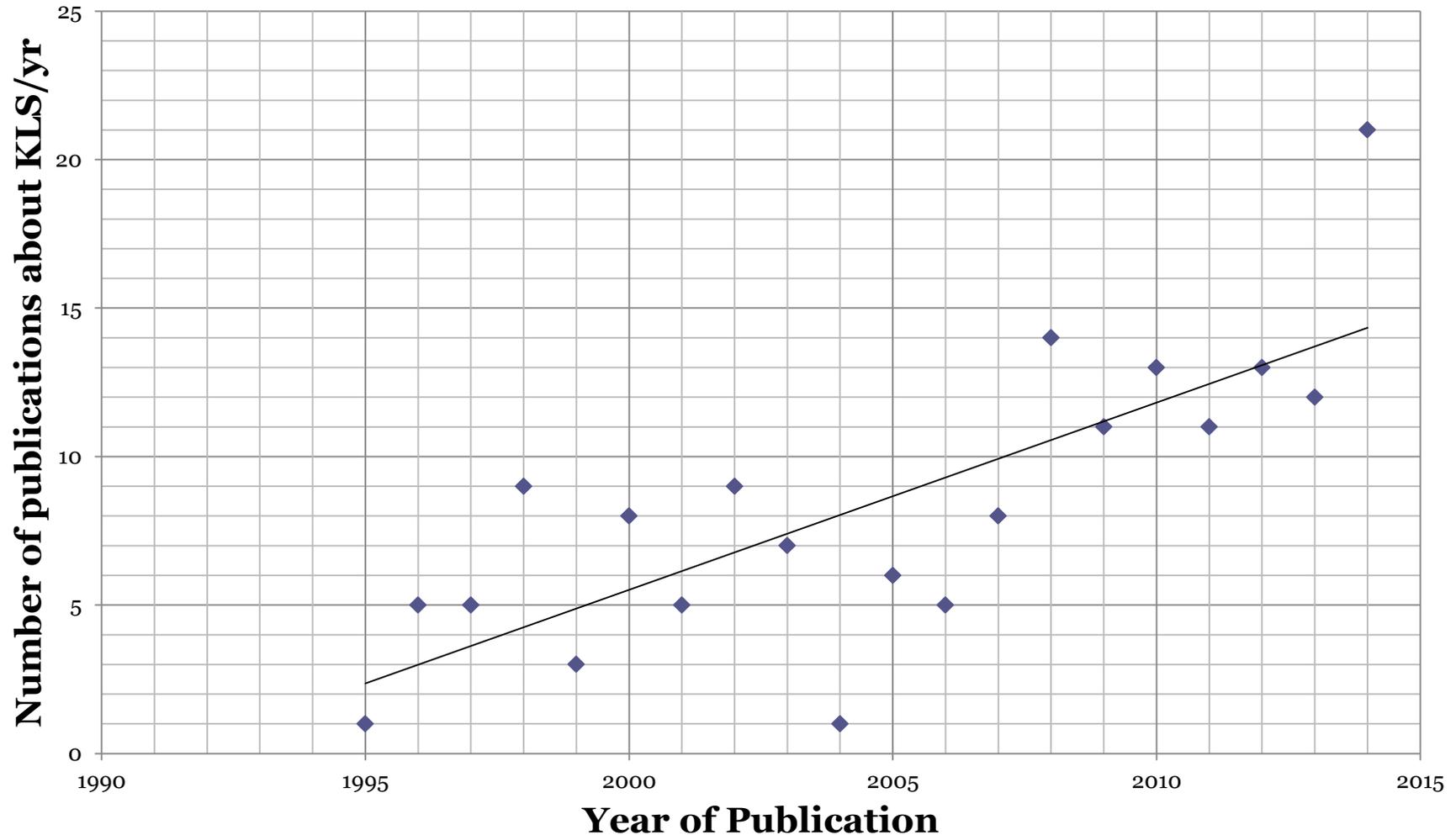
Environmental?

# KLS Research Groups

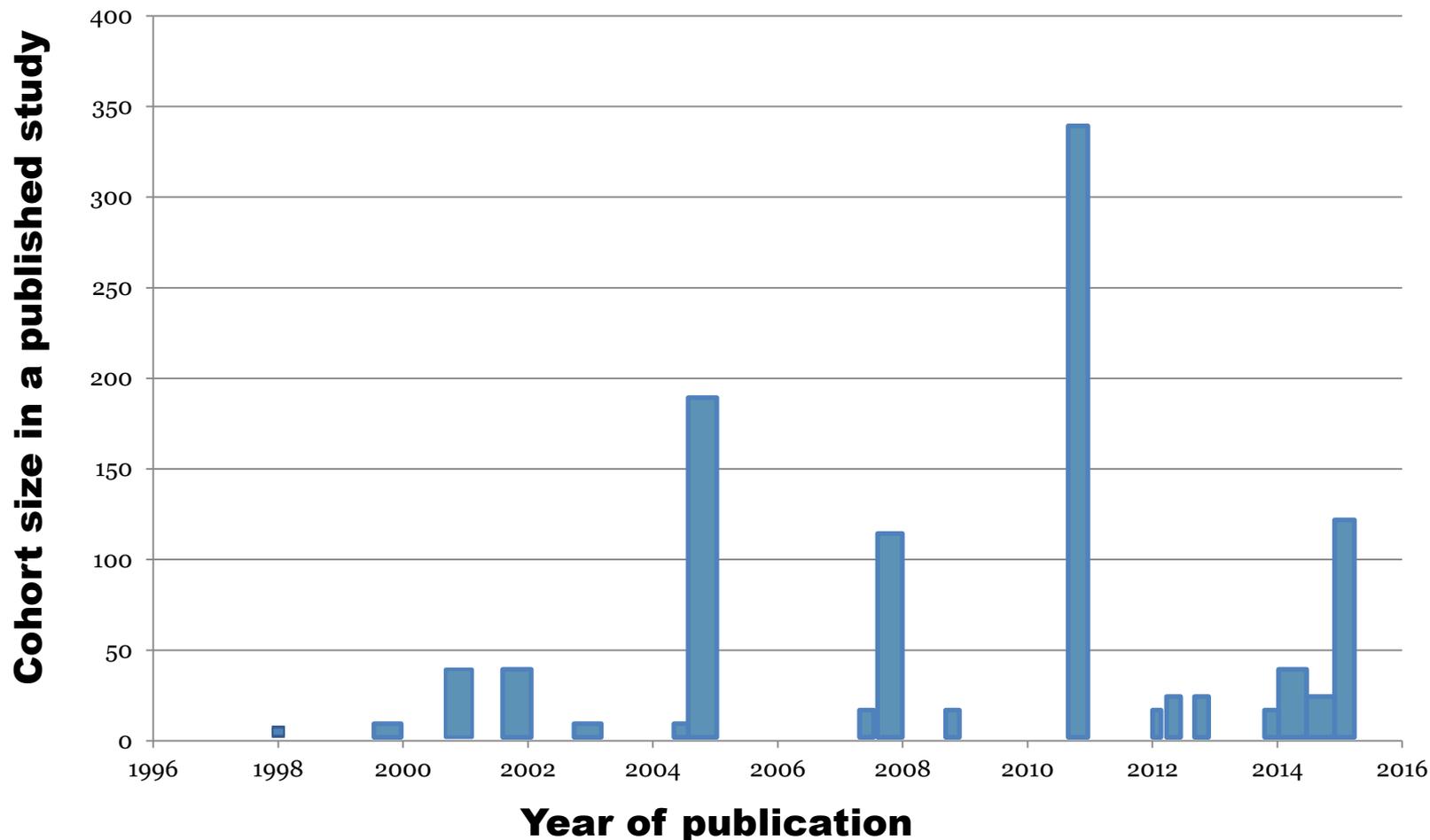
Lead Researcher	Location	Area of KLS Research
Isabelle Arnulf, MD, PhD*	Paris, France	Clinical investigations
Emmanuel Mignot, MD, PhD*	California, USA	Genetics
Yu-Shu Huang, MD	Taiwan, RoC	Long term studies
Han Fang, MD*	China	Hypocretin, clinical studies
Anne-Marie Landtblom, MD, PhD*	Sweden	Neuroanatomical imaging
Yakov Sivan, MD*	Israel	Environmental
Geert Mayer, MD	Germany	Hypocretin, lithium treatments
Charles Chiu, MD, PhD*	California	Viral Infections
Francesca Cañellas Dols, MD*	Spain	Autoimmunity to brain proteins

\* recipient of financial support from KLS Foundation for research

# Medical publications about KLS



# Importance of participation in KLS research



# Medical Reviews on KLS

- Summary medical review articles are valuable for researchers, healthcare providers, KLS families, school/work support needs
- There are now several good review articles on KLS:
  - Arnulf et al. [Kleine-Levin syndrome: a systematic review of 186 cases in the literature](#). Brain (2005)
  - Billiard et al. [Recurrent hypersomnia: a review of 339 cases](#). Sleep Med Rev (2011)
  - Arnulf et al. [Diagnosis, disease course, and management of patients with Kleine-Levin syndrome](#). Lancet Neurology (2012)
  - Miglis & Guilleminault. [Kleine-Levin syndrome: a review](#). Nature & Science of Sleep (2014)

# Synopsis of Recent Studies as reported at 2015 KLS Symposium

<http://wasmcongress.com/s51>

- **Arnulf:** In a group of 140 KLS patients in France, found that 28% of patients had long (>30 day) episodes and confirmed more birth & developmental problems in KLS patients than controls (Arnulf, Annals of Neurology, 2015).
- **Arnulf:** Brain imaging study showed a lower functioning of some regions (cortical, thalamic and hypothalamic areas) during and between episodes (n=41) (Arnulf, Brain, 2014).
- **Arnulf:** Reported a benefit of lithium therapy over 2 years in 70 patients with severe KLS, compared to 49 patients with moderate KLS who were not given drug treatment. Patients treated with lithium spent one month less incapacitated per year than those without lithium (unpublished).

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<http://wasmcongress.com/s51>

- **Mignot:** A genetic study with 600+ KLS samples collected worldwide found a genetic marker in KLS patients compared to controls. This same genetic locus has been reported to be involved in the risk of bipolar disorder.
- **Han:** Reported that appetite was decreased during KLS episodes in more than 54 % of Chinese patients, while hyperphagia was rarer. Analysis of CSF from up to 20 KLS patients during and between episodes demonstrated a trend for hypocretin to decrease from normal to intermediate levels between vs. during episodes. Found that blood pressure & heart rate monitored during 24 hr in KLS patients were consistently lower during than between episodes, suggesting a mild hypotension during episodes.

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- **Huang:** Studied 30 children in Taiwan with KLS (20 followed for 5 years) finding the frequency of episode clearly decreased with time and cognitive function remained unchanged since KLS onset. SPECT brain imaging revealed some changes, notably in the left thalamus during and between episodes. MSLT latencies were shorter during than between KLS episodes. Other studies ruled out any similarity between primary narcolepsy and KLS.
- **Mayer:** Reported the beneficial treatment of 18 patients in Germany with lithium, some of them for more than 10 years, with relapses when stopping.

# KLS - possible genetic marker?

- Many diseases have a subset of affected individuals with a genetic component or pre-disposition
- Initial epidemiological evidence suggests KLS not a genetic disease, however:
  - Higher than expected incidence of KLS in Jewish population
  - 5-10% multiplex families
- Ongoing studies by Mignot (Stanford U), with participation by >600 individuals with KLS over 10 years, has identified possible genetic markers
- Confirmatory studies underway, **more samples needed**

# KLS Research Update Summary

- Over the past 15 years, there has been a growing and networked international KLS research effort
- Despite the research challenges and with ongoing hypotheses about the nature of KLS:
  - There is now a better understanding and medical description of KLS
  - A multi-disciplined research effort is underway to understand the medical cause of KLS
  - Emerging genetic results may provide a leap in KLS scientific studies
- Your participation in research and funding is key

# **KLS Research Opportunity**

for those who have not yet participated

The Stanford Center for Narcolepsy & KLS Research is currently seeking individuals of all ages who have Kleine-Levin Syndrome (KLS) and their immediate family members (when possible) for a study investigating the genetic basis of KLS.

Candidates must be willing to provide:

- a one-time blood sample
- documentation of diagnosis

For more information please visit the website  
<http://med.stanford.edu/narcolepsy/KLS.html>  
or contact the clinical coordinators:

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Maja Cruz	<a href="mailto:macruz@stanford.edu">macruz@stanford.edu</a>	650-721-7552