Correlation between age of onset and genotype with systemic symptomatology in Aicardi Goutières Syndrome

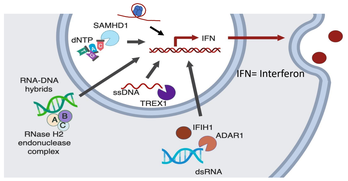
Amanda Jan[1], Nicolson Modesti[2], Isabella Barcellos[2], David Isaacs[2], Sarah Woidill[2], Ani Dixit[2], Russell D'Aiello[2], Zaida Flores[2], Francesco Gavazzi[2], Kayla Muirhead[2], Bridget Slattery[2], Omar Sherbini[2], Justine Shults[3], Ariel Vincent[2], Adeline Vanderver[2], Laura Adang[2]

1 School of Medicine, University of California Davis, Sacramento, CA, USA
2 Division of Neurology, Children's Hospital of Philadelphia, Philadelphia, PA, USA
3 Department of Statistics, University of Pennsylvania, Philadelphia, PA, USA

Background

Aicardi Goutières Syndrome (AGS) is a heritable interferonopathy that results in variable neurologic disability and systemic complications[1]. Key variables (e.g. genotype and age at onset) only partially correlate with neurologic function, which can range from isolated spastic paraparesis to profound global developmental delay. **AGS Subtypes by Genotype:**

- *TREX1* (AGS1)
- *RNASEH2A* (AGS2)
- *RNASEH2B* (AGS3)
- *RNASEH2C* (AGS4)
- *SAMHD1* (AGS5)
- *ADAR1* (AGS6)
- *IFIH1* (AGS7)
- *LSM11* (AGS8)
- *RNU7-1* (AGS9)



Potential systemic complications of AGS

Neurologic:
Global developmental delay with regression
Encephalopathy
Tone abnormalities, including spastic paraparesis
Seizures
Strokes and Moyamoya
Myositis

Ophthalmic:
Glaucoma
Retinopathy
Cortical visual impairment

Respiratory:
Central apnea
Sleep disturbance
Pulmonary hypertension
Recurrent pneumonia

Dermatologic:
Chilblains
Other inflammatory skin complications

Cardiac:
Cardiac hypertrophy
Cardiac valve issues

Gastrointestinal & urologic:
Hepatosplenomegaly
Poor GI motility with constipation
Failure to thrive
Neurogenic bladder with recurrent urinary tract infections
Inflammatory bowel disease

Orthopedic:
Delayed bone age
Hip dysplasia & scoliosis
Arthropathy/arthritis

Renal:
Lupus-like nephropathy
Hypertension

Hematologic:
Anemia
Leukopenia
Thromobocytopenia
Neutropenia

Endocrinologic:
Growth failure
Diabetes
Hypothyroidism

Methodology and cohort description

Data were collected from existing medical records stored in the Myelin Disorders Biorepository Project database. Time to Event curves were created for each systemic event. Genotypes for each event were analyzed separately if there were at least 5 patients of that genotype with the event. RNASEH2A, B, and C were categorized as one genotype. Data were analyzed using Graphpad Prism 9.

Cohort description:

- 186 patients' medical records were reviewed
- The most common AGS-causing mutation in our cohort was RNASEH2B (27.96%). The least common was RNASEH2C (1.61%)
- No patients had LSM11-related AGS at the time of review
- The mean age of AGS presentation was oldest in IFIH1 at 0.81 years and youngest in TREX1 at 0.12 years
- The average time between onset of symptoms and diagnosis was longest for SAMHD1 at 5.38 years and shortest for RNASEH2C at 0.4 years.
- Aside from irritability and lethargy, the most common inflammatory complications were:
  - **Liver Dysfunction** - TREX1, RNASEH2B, ADAR1, IFIH1, and RNU7-1
  - **Anemia -** RNASEH2A and RNASEH2C
  - **Chilblains** - SAMHD1

Results

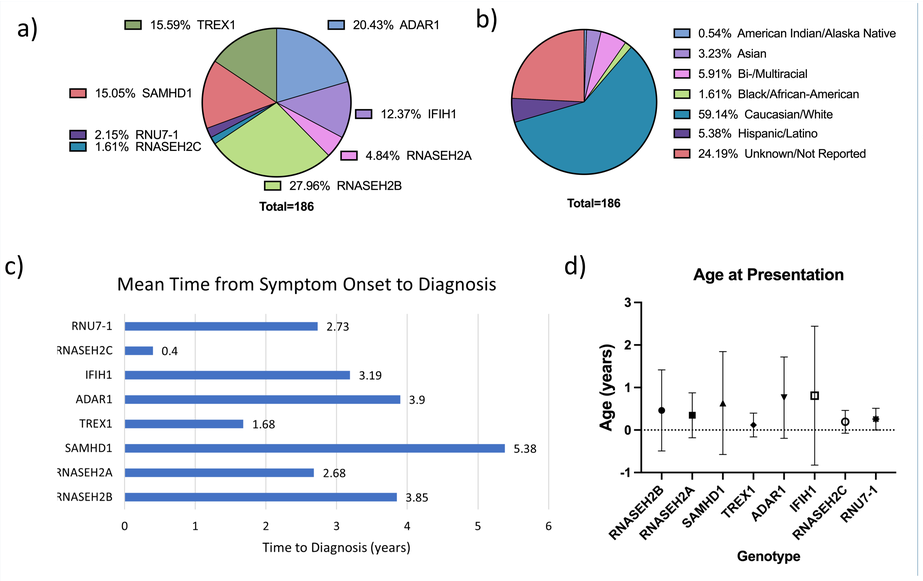


Figure 1: Cohort characteristics: (a) genotypes; (b) race and ethnicity; (c) time to diagnosis from presenting symptom onset; (d) average age at presentation

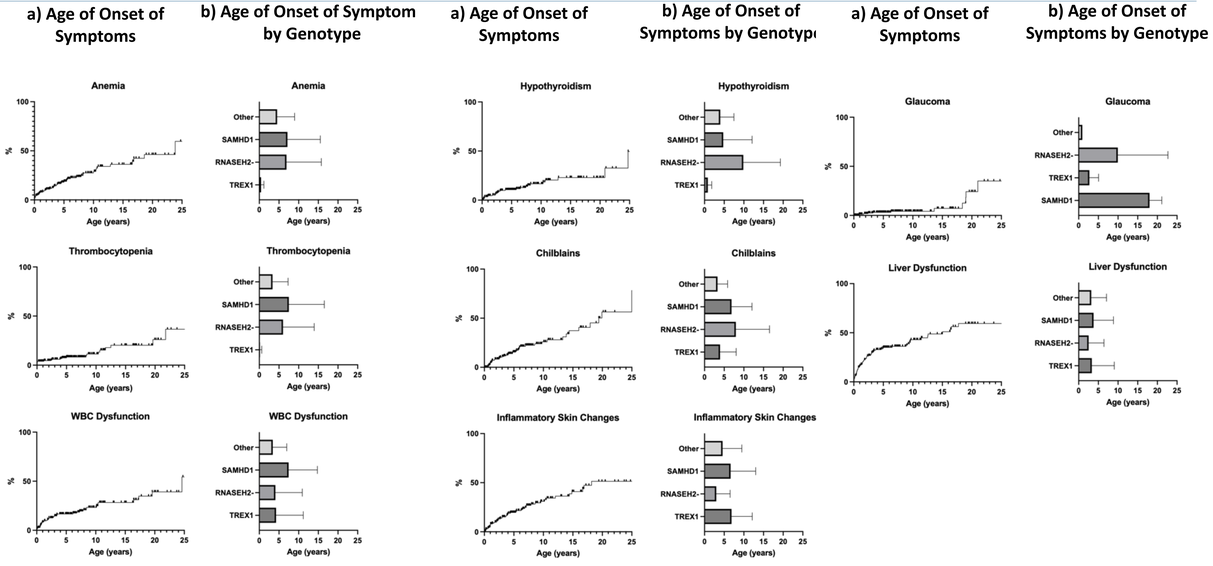


Figure 2: Inflammatory systemic events with (a) age of onset and (b) differences by genotype

Discussion

Our study analyzed the time course of fifteen inflammatory events using medical record data from a well-described cohort of people with AGS. Our data highlight that the frequency and time course of systemic inflammatory events vary among AGS genotypes. Additionally, the incidence of most events plateau at different ages for each symptom. **These data show the importance of tailoring clinical screening guidelines to a patient's age and genotype.**

Limitations and future directions

- There may be human error in data abstraction from medical records
- Data for many events assume that no mention of the event meant the event did not occur
- Variability in the information recorded in the medical record limits data quality and quantity, such as at end of life
- The longer time frame for which we have records on a patient, the more likely it is that we captured a systemic event
- Parent recollection and physician interpretation may cause recall bias
- We relied on patients' clinicians to screen for the relevant systemic complications and to document the results of the screening. Screening and charting practices are inconsistent between providers.

The rate of events is likely higher than estimated here. Further studies are needed to determine the actual prevalence and time course of systemic events in AGS.

References and Funding

References

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2. Uggenti C, Lepelley A, Depp M, et al. cGAS-mediated induction of type I interferon due to inborn errors of histone pre-mRNA processing. Nat Genet. 2020;52(12):1364-1372. doi:10.1038/s41588-020-00737-3

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