

Felbamate induced persistent thrombocytopenia in a patient found to have a novel SMC1A variant

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Abstract

Objective: Cornelia de Lange Syndrome (CdLS) is a developmental disorder affecting several body systems including an elevated risk of thrombocytopenia. Definitive diagnosis is determined by genetic tests. Mutations in the seven known genes associate with CdLS; SMC1A gene mutations associate with a mild form. Drug interactions are reported in children with CdLS, especially during sedation. To our knowledge, felbamate induced thrombocytopenia is unreported in patients with CdLS.

Methods: We describe a patient with an epileptic encephalopathy who failed other anticonvulsant medication and developed thrombocytopenia following initiating felbamate. The patient's prior metabolic work up did not reveal any contraindication to starting treatment. We performed a Whole Exome Sequencing (WES) to evaluate the cause of epilepsy.

Results: We report a female patient with epileptic encephalopathy (with seizure onset at age 13 months) that failed other anticonvulsant medication. Initial genetic work up was unremarkable. Patient began felbamate treatment at 4 years of age and subsequently developed persistent thrombocytopenia. No prior metabolic testing indicated a risk for thrombocytopenia; platelet levels were normal prior to starting felbamate, with the exception of one prior episode of transient thrombocytopenia with respiratory illness. We then performed WES and identified a likely pathogenic de novo SMC1A variant, c.3652_3663del (p.Phe1218_Thr1221del). Based on her presentation with infantile epileptic encephalopathy, a diagnosis of CdLS was made.

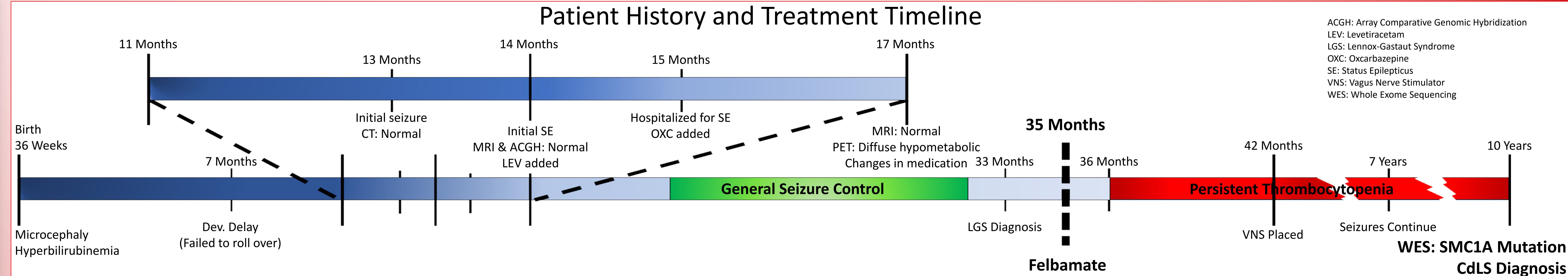
Conclusion: This patient had a mild CdLS phenotype that went undiagnosed despite infantile epileptic encephalopathy until WES following acquired persistent thrombocytopenia. Symonds has described this same presentation, including clusters of seizures with febrile illness which this patient also had, in patients with SMC1A mutations. We suggest that WES may provide vital information in cases of undiagnosed epileptic encephalopathy and advocate WES prior to starting treatments with potential life threatening side effects, such as felbamate, in patients for whom other epilepsy genetic testing has been unrevealing. We would also suggest avoiding the use of felbamate in patients diagnosed with CdLS, especially with SMC1A mutations.

Cornelia de Lange Syndrome (CdLS)

Phenotype	Genetics
Classic CdLS Phenotype	The spectrum of CdLS phenotypes have been found to associate with mutations in genes involved with chromatin regulation. Cohesin complex tethers the two sister chromatins. It is a regulator of chromosome function, including segregation, regulation of gene expression, and maintenance of chromatin structure. Seven gene mutations have been identified within CdLS spectrum: NIPBL, SMC1A, SMC3, RAD21, BRD4, HDAC8, ANKRD11.(1)
CdLS Phenotype associated with SMC1A	1. Mildly concave nasal ridge 2. Lacks other cardinal features

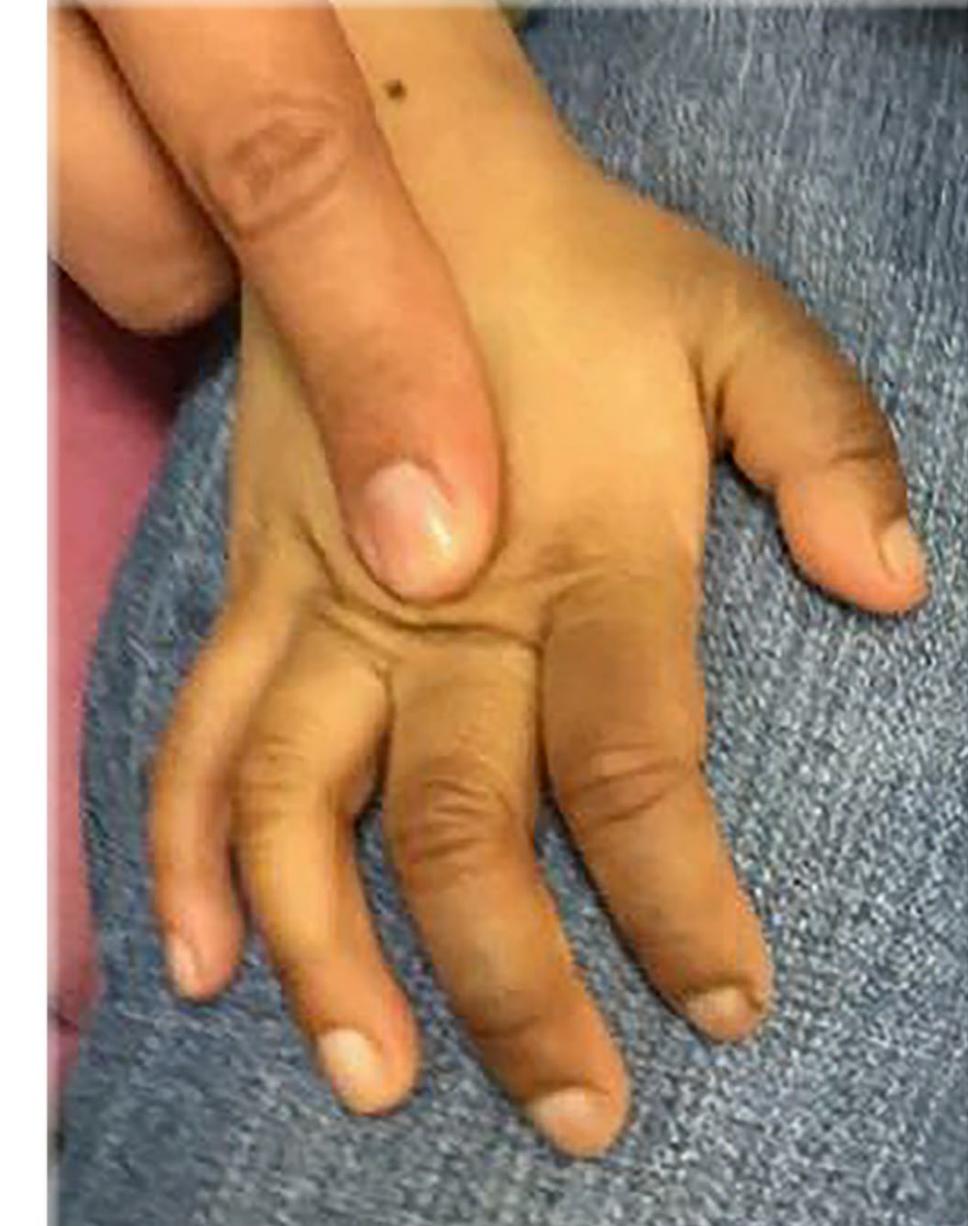
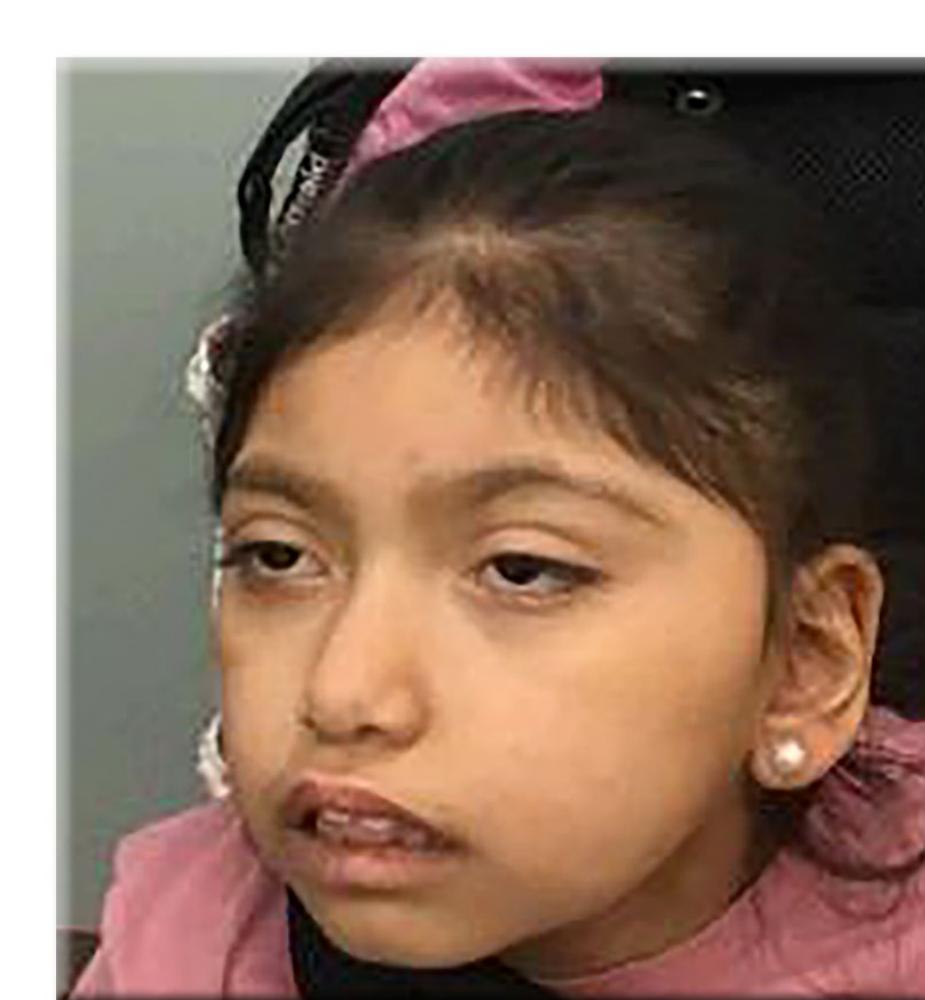
SMC1A Gene

SMC1A encodes structural maintenance of chromosomes protein 1a, a central component of the cohesion complex. It is an X-linked non-inactivated gene that has also been described in females with epileptic encephalopathy and cluster seizures with a similar phenotype to PCDH19, an X-linked mutation affecting protocadherin 19. (2) Transient thrombocytopenia occurs in CdLS patients with a higher incidence than the general population. Intermittent surveillance with annual platelet counts is likely adequate unless patients are taking medications known to cause thrombocytopenia, such as valproic acid. (3)



ACGH: Array Comparative Genomic Hybridization
LEV: Levetiracetam
LGS: Lennox-Gastaut Syndrome
OXC: Oxcarbazepine
SE: Status Epilepticus
VNS: Vagus Nerve Stimulator
WES: Whole Exome Sequencing

Patient Characteristics

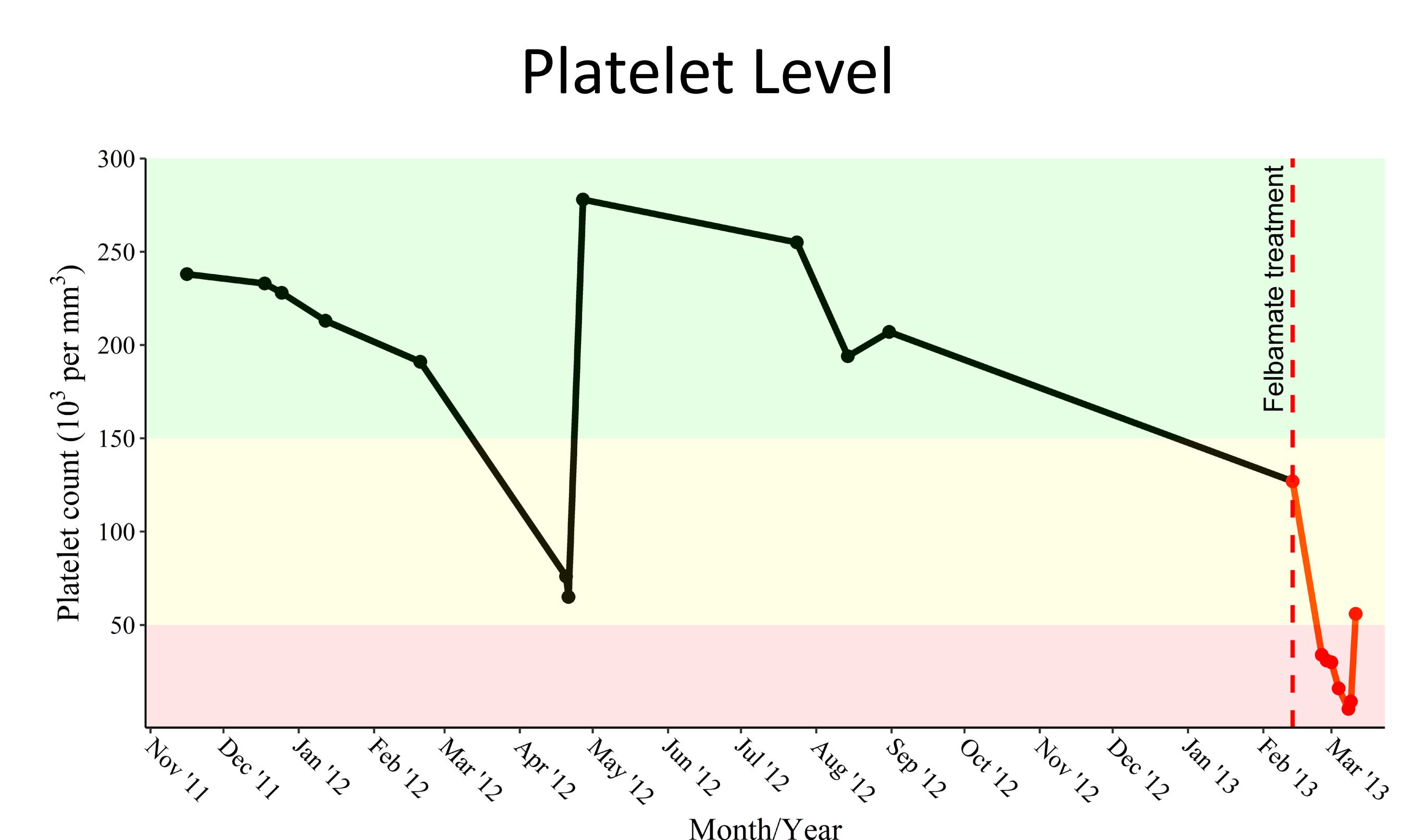


- Synophrys
- curved eyebrows
- long lashes.
- Lacks the upturned nose or thin upper lip usually seen in CdLS
- Small hand and thin fingers in relation to body

Images used with consent of the patient's family.

Results

- Patient was premature with microcephaly and developmental delay with initial seizure at 13 months.
- Patient characteristics do not match classic CdLS.
- Transient thrombocytopenia.
- Persistent thrombocytopenia following felbamate.
- Novel PHE1218 to Thr1221 deletion in SMC1A gene.
- Diagnosed with Cornelia de Lange Syndrome following finding of SMC1A variant by WES.



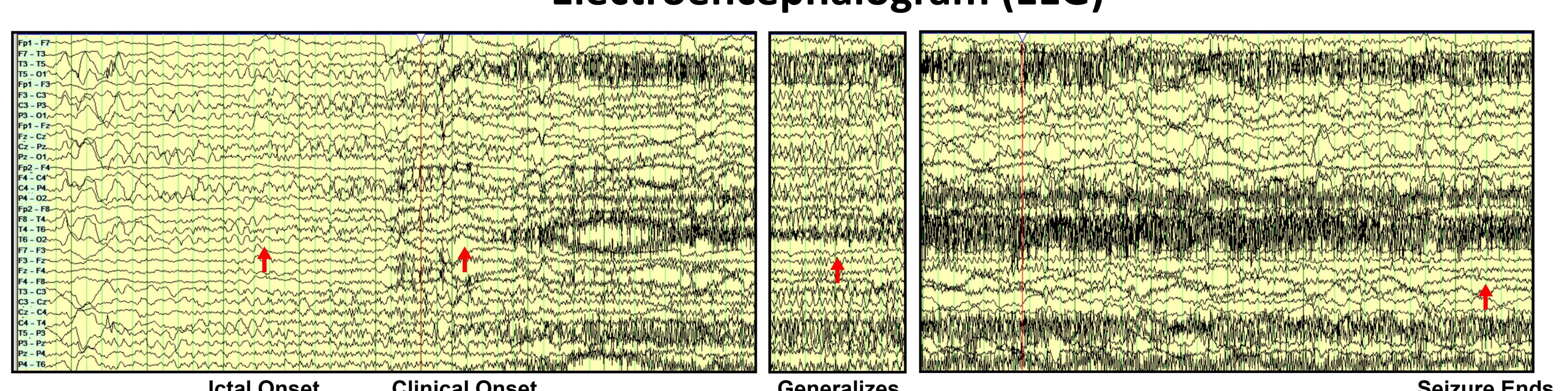
- Transient thrombocytopenia occurred at April 2012
- Platelet count quickly recovered
- Patient received Felbamate at Nov. 13, 2013
- Within 2 weeks following felbamate, developed persistent thrombocytopenia
- 6 years out, the patient is still thrombocytopenic

Conclusions

- Would have withheld felbamate with CdLS diagnosis.
- Suggests the use of WES/genomic sequencing for all cases of intractable epileptic encephalopathy.



Electroencephalogram (EEG)



- Focal seizure with tonic features.
- Onset is poorly localized.
- Note diffuse, paroxysmal, low voltage fast activity that persists as long as clinical signs of seizure are seen.

WES: SMC1A Mutation c.3652_3663 del, p.PHE1218_Thr1221 del

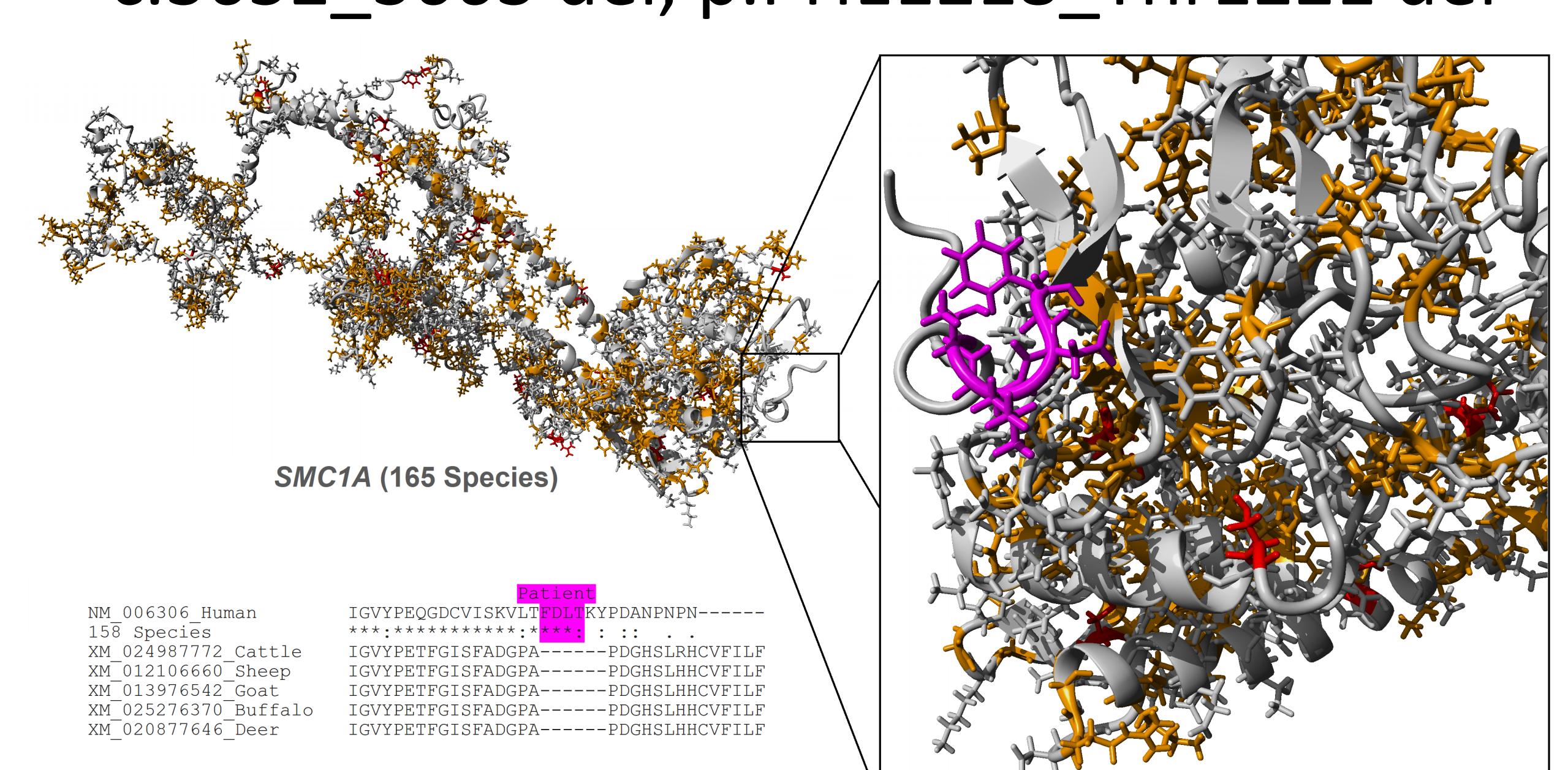


Image created with I-TASSER

- SMC1A is highly conserved
 - Conservation is seen across species
 - Red and Orange indicate highly conserved amino acids.
- Novel deletion of PHE1218 to Thr1221
 - N-Terminal NTPase domain

- References
- Diagnosis and management of Cornelia de Lange syndrome: first international consensus statement, Antoine D. Kline, et al, *Nature Reviews Genetics*, 2018
 - Heterozygous truncation mutations of the SMC1A gene cause a severe early onset epilepsy with cluster seizures in females: Detailed phenotyping of 10 new cases, Joseph D. Symonds, et al, *Epilepsia*, 58(4); 565-575, 2017
 - The Incidence of Thrombocytopenia in Children With Cornelia de Lange Syndrome, Michele P. Lambert, et al, *American Journal of Medical Genetics, Part A* 155:33-37, 2010