

# Power and Promise of Precision Medicine

Even among individuals with the same rare genetic diagnosis, their experiences, their treatment responses, and even the underlying cause of their disease can be different. In the case of Glut1 Deficiency, variants in the *SLC2A1* gene result in decreased glucose transport into the brain and impaired brain metabolism. However, the type and location of each variant may have very different impacts on the function of the GLUT1 transporter, the key protein involved. Better understanding the functional implications of each genetic variant can pave the way for more precise, personalized treatments aimed at correcting and restoring glucose transport by targeting the underlying mechanisms involved. The power and promise of this type of precision medicine is evidenced in the journey of Glut1 Deficiency patient Macie Steele.



**Macie Ann Steele**  
born in Orlando, Florida

**1997**

- slight jerks in her arms, legs, and eyes started around first birthday
- coincided with weaning from breastmilk

**1998**

- developed longer absence seizures
- diagnosed with focal epilepsy at 22 months

**1999**

- failed multiple medications
- some with serious side effects
- hundreds of seizures daily

**1999-2001**

- sought out ketogenic diet
- seizures stopped on 1st day of ketosis

**2001**

- seizures returned
- diet adjustments, medications, VNS
- side effects
- Doose Syndrome, LGS

**2003-2008**

**Pro485Leu**  
c.1454 C>T: p.Pro485Leu  
missense variant

CSF glucose 36 mg/dl  
CSF : serum ratio = 45%

**diagnosed with Glut1 Deficiency**

**2008**



- C7 (triheptanoin) trial with Dr. Juan Pascual
- published paper listing her variant

**2014**



- team at MDC interested in specific variant effects on proteins
- no specific gene or disease focus

**2017**



- found Macie's variant of interest in the C7 paper
- reached out to Dr. Pascual to request skin fibroblasts for iPSCs

**2017**



wild type                      Macie

functional effects determined:  
right number of GLUT1 working in the right way,  
but in the wrong place

**2017-2018**



**correctable**

paper published with results - chlorpromazine corrected mislocation and restored function

**2018**

**MDC researcher awarded KlarText Prize**



prizes awarded

**2019**

internet searches

TXNIP? AMPK?  
endocytosis  
protein trafficking

chlorpromazine side effect profile - are there alternatives?  
what helps Glut1 get to the cell surface?

**2019**



**metformin**

**2019**

**protocol:**

- started metformin with slow titration
- weekly labs to closely monitor blood glucose and lactate levels, no issues
- maintenance dose of 1,000 mg twice daily

**2020**

**benefits:**

- reduced seizure frequency
- dystonia/muscle spasms in back disappeared
- more energy and stamina
- exercise induced leg tremors and sudden loss of muscle tone have stopped

## take-aways:

- variants tell stories
- each story may be different
- each story is important

- know your genetic information
- share your genetic information - tell your story so you can be found
- participate in registries and natural history studies
- get involved in research
- contribute samples to biorepository

stopping metformin results in significant increase in seizure activity

metformin remains part of Macie's current treatment plan

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