Role of *CACNG2* variants in human pathology

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Background

CACNG2 encodes a synaptic trafficking protein (TARPγ2/Stargazin) that **binds to AMPA receptors** (AMPARs), which are transmembrane ion channels gated by neurotransmitter **glutamate** binding

CACNG2 variants were previously reported only twice in humans :

- in a patient with non syndromic intellectual disability, carrying a *de novo* missense variant p.(Val143Leu)
- in a patient with seizures, carrying a c.295+1G>C variant, predicted to affect splicing

By co-immunoprecipitation, the authors demonstrated that the missense variant decreases the ability for CACNG2 to bind to AMPAR subunits, and subsequently reduces glutamatergic transmission

Methods

After diagnosing a new patient with a *de novo CACNG2* variant, we launched an **international collaboration** through the GeneMatcher platform to identify additional **patients with *CACNG2* variants**

Clinical, genetic, imaging and EEG data were collected

Results

We identified **9 patients** with a *CACNG2* variant, ranging from 3 to 28 years old

6/9 showed **intellectual disability**, mostly mild

4/9 with **autism spectrum disorders**

4/9 with **seizures** (including 1 atypical rolandic, 2 drug-resistant)

3/9 with **attention deficit hyperactivity disorders**

2/9 with mild dysmorphic features

Brain MRI did not show any brain malformation

All variants were **missense** except 3 (2 intronic, 1 frameshift)

5 ***de novo***, and 1 inherited among available data

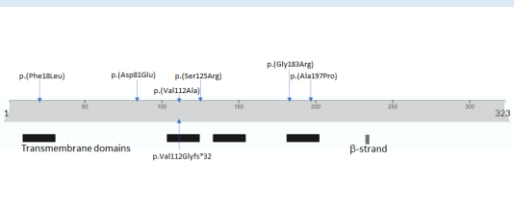

Figure 1 :
Schematic representation of the location of the missense and frameshift variants of the patients of the cohort
Proteic domains are represented by rectangles

Table 1 : Genetic and clinical data of the 9 patients with a *CACNG2* variant

Patient	*CACNG2* variant						Clinical data						
	Genetic coordinates NM_006078.5		Family segregation	CADD score	REVEL score	ACMG classification	Gender	Current age years	Intellectual deficit	Autism spectrum disorders	Behavior troubles	Seizures	Dysmorphic features
P1	c.243T>A	p.(Asp81Glu)	NA	22.4	0.678	3	M	11	Y, mild	Y	Y, ADHD	N	N
P2	c.295+1G>C		*de novo*	33	NA	5	F	5	N	N	N	Y, atypical rolandic	N
P3	c.589G>C	p.(Ala197Pro)	*de novo*	27.8	0.89	4	F	7	Y, mild	N	Y, ADHD	Y, drug-resistant	N
P4	c.375C>G	p.(Ser125Arg)	*de novo*	24.3	0.793	4	F	28	N	N		Y, drug-resistant	N
P5	c.547G>A	p.(Gly183Arg)	*de novo*	32	0.906	4	M	4.5	Y, mild	Y	Y	N	Y, long palpebral fissures, thin vermillion of the upper lip
P6	c.335_351del	p.Val112Glyfs*32	*de novo*	NA	NA	4	F	5.5	Y, mild	N	Y, ADHD	N	Y, thin vermillion of the upper lip, long eyelashes
P7	c.436+1G>A		inherited	33	NA	4	M	15	Y, mild	Y	Y	N	N
P8	c.335T>C	p.(Val112Ala)	NA	23.3	0.677	3	M	3.5	Y	Y	Y	N	N
P9	c.54C>A mosaic	p.(Phe18Leu)	NA	24.1	0.734	3	M	11	N	N		Y	N

Conclusion

We report the clinical and genetic features of an **international cohort of patients with *CACNG2* variants**

The next step will consist in the evaluation of functional consequences of the variants and electrophysiological-clinical correlation

No conflict of interest to disclose.

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