Implication of neurotransmitter analysis on the diagnosis of SCN2A-Related disorder: Diagnostic and therapeutic considerations

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Patient data:

14-year-old adopted girl

- Psychomotor delay (HP:0012758)
- Low IQ (HP:0001249)
- Behavioural disorder (HP:0000708)

Clinical course:

- Severe apathy (HP:0000741)
- Bradykinesia (HP:0002067)
- Food refusal (HP:0100738)
- Loss of bladder sphincter control (HP:0000020)
- Sleep disturbances (HP:0002360)

Metabolic work-up

Pterins (CSF)	Results (nmol/L)	Normal range
Neopterin	8	8 – 29
Biopterin	7	8 - 37

Pterins (UR)	Results (mmol/mol creat)	Normal range
Neopterin	0.3	0.2 – 1.5
Biopterin	0.3	0.3 – 3.4
Primapterin	N.D.	< 0.02

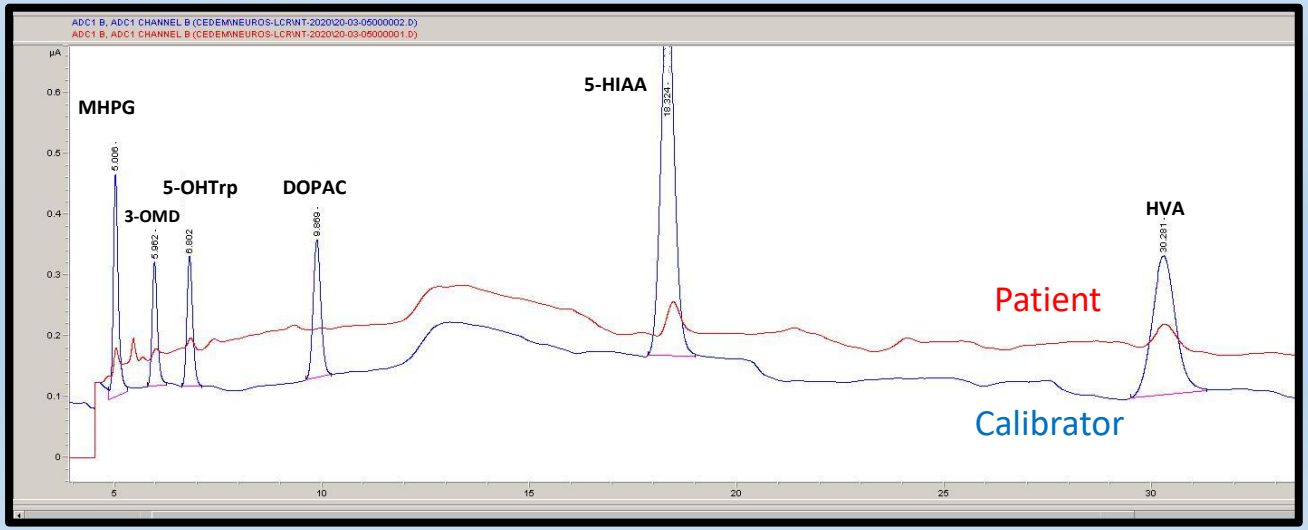
DHPR Activity: Normal

Phenylalanine: Normal

Organic acids: Normal
Acylcarnitines: Normal

Metabolic work-up

Neurotransmitters (CSF)	Results (nmol/L)	Normal range
HVA ↓	90	164 - 560
5-HIAA ↓	47	76 - 210
MHPG	26	23 – 60
3-OMD	11	< 40
5-OHTrp	7	< 15



Metabolic work-up

Differential diagnosis

Possibilities:

- BH_4 synthesis defect (GTP cyclohydrolase I deficiency)
- Dopamine synthesis regulation defect
- Secondary defect

Metabolic work-up

BH_4 synthesis defect (GTP cyclohydrolase I)

BH_4

- Tyrosine hydroxylase (TH)
- Tryptophan-5-hydroxylase (TPH)

→ Byosynthesis of dopamine and serotonine

- Phenylalanine-4-hydroxylase (PAH) → Phenylalanine synthesis

Cofactor defects that do not produce hyperphenylalaninemia

- GTP cyclohydrolase I deficiency
- Sepiapterin reductase deficiency

↔ They can be distinguished by pterin analysis

Metabolic work-up

Dopamine synthesis regulation defect

The *PITX3* gene activates the tyrosine hydroxylase promoters

PITX3 deficiency causes a loss of tyrosine hydroxylase expression, and this leads to a reduction of dopamine levels.

HVA ↓ **5-HIAA ↓** **Biopterin ↓**

Metabolic work-up

Secondary defects

- Lead to abnormal CSF neurotransmiter metabolites
- Not involved on synthesis, catabolism or transport pathways of neurotransmitters.

Genetic testing

No pathological variants were found on BH_4 metabolism related genes

A probably pathogenic variant of autosomal dominant inheritance was found on *SCN2A* gene.

SCN2A

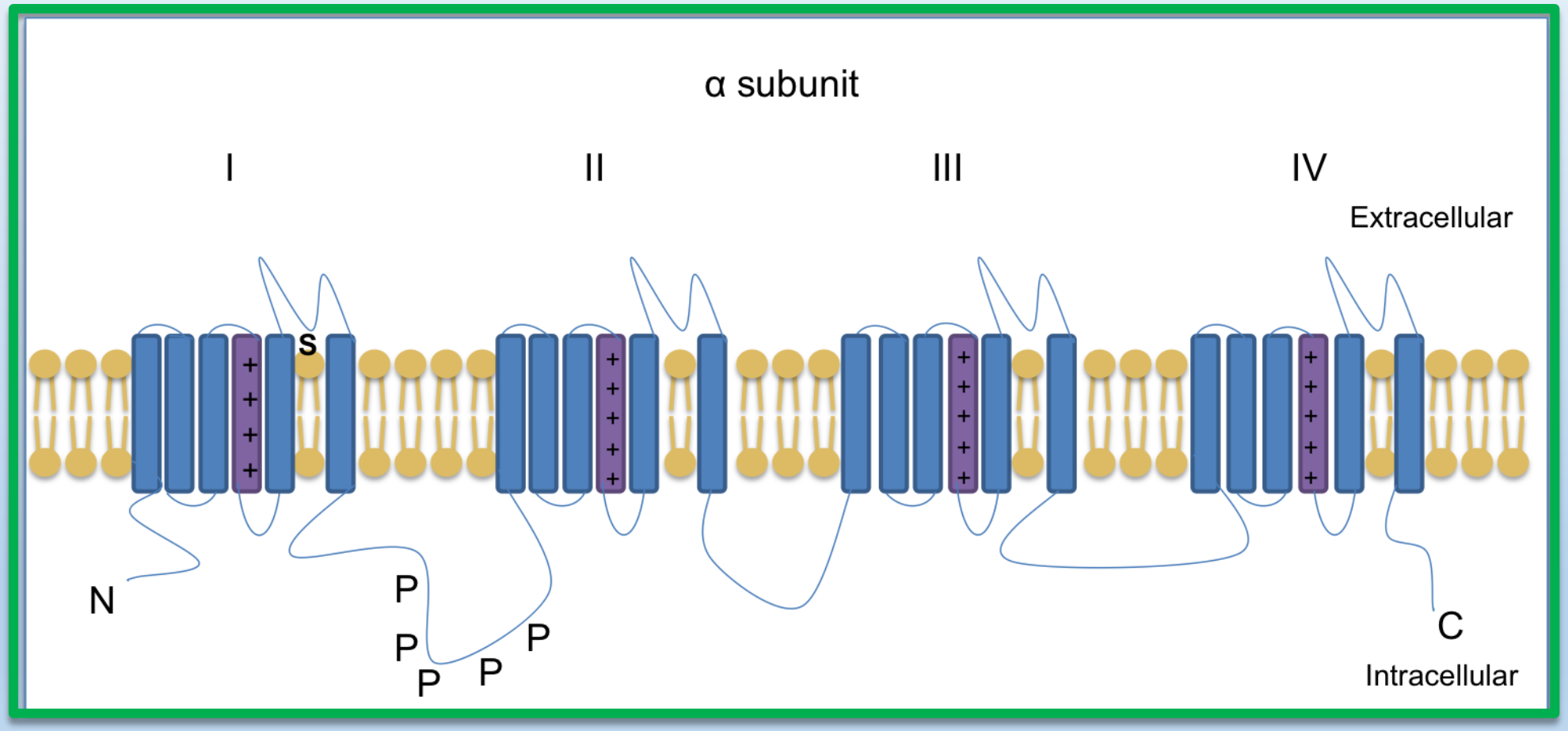
Predictable effect in protein: p.Arg1235*

Nucleotide change: c.3703C>T

Location: 2q24.3

Sodium voltage-gated channel alpha subunit 2 deficiency.

Channelopathies



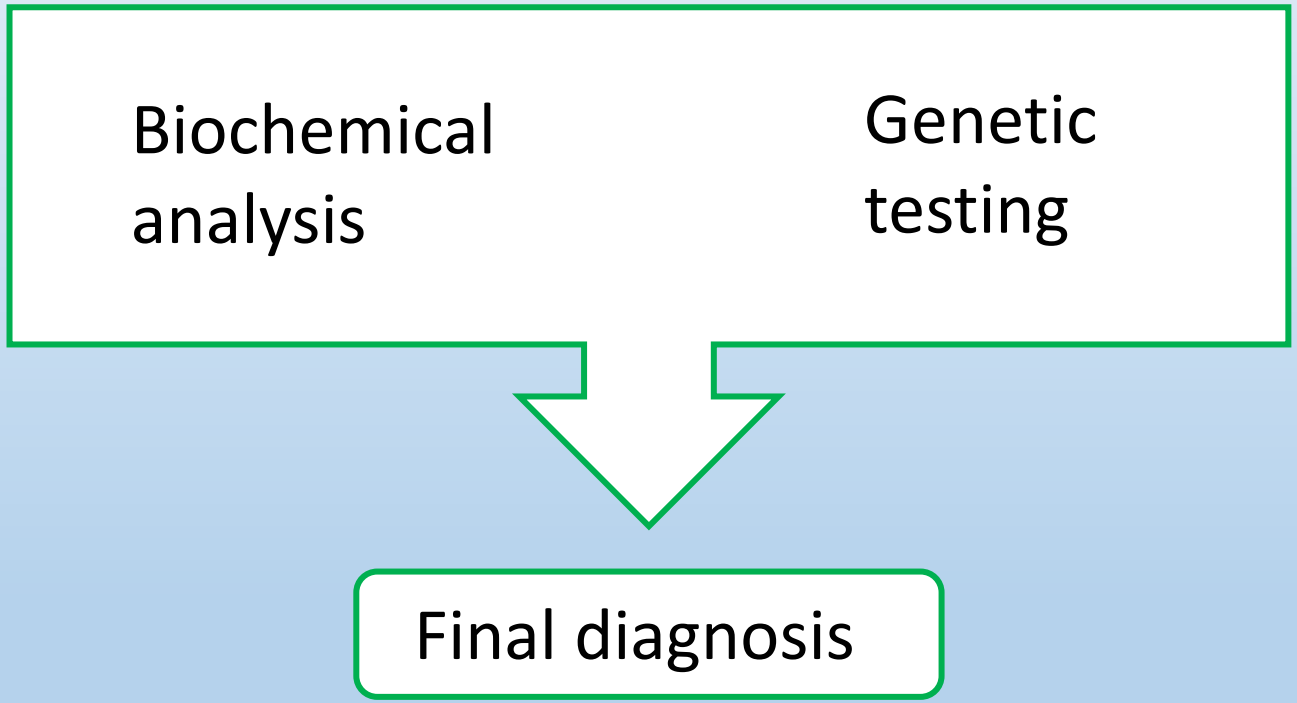
Channelopathies

SCN2A gene

$Na_V1.2$

i. Infantile epileptic encephalopathy
ii. Benign infantile seizures
iii. Autism spectrum disorder/intellectual disability

Conclusions



Thank you for your attention