Genotype-phenotype correlations in SCN8A-related epilepsy: a cohort study of Chinese children in southern China

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We read with great interest the article recently published in Brain by Johannesen and colleagues,1 which revealed the clear genotype-phenotype correlations between the age at seizure onset, type of epilepsy and gain-of-function (GOF) or loss-of-function (LOF) effects of SCN8A variants. The authors collected the largest cohort of individuals with SCN8A-related epilepsy from a multi-country study and found that generalized epilepsy with absence seizures is the main epilepsy phenotype of LOF variant carriers and the extent of the electrophysiological dysfunction of the GOF variants is a main determinant of the severity of the clinical phenotype in focal epilepsies. Their pharmacological data indicated that sodium channel blockers (SCBs) present a treatment option in the SCN8A-related focal epilepsy with onset in the first year of life.1

We believe that this study constitutes to the understanding of SCN8A-related epilepsy. However, we would also like to discuss the similarities and discrepancies with respect to our results based on a cohort study of Chinese children and propose an interpretative linking on the findings of the study.

Specifically, we recruited 21 children (13 males and eight females) with SCN8A de novo missense variants from three hospitals in Southern China between January 2017 and February 2021 (Table 1); two of the patients were identical twins. All children experienced their first seizure during infancy with the average onset age of 3.9 ± 2.97 months and the maximum onset age of 9 months. Among the 21 cases, five experienced onset during the neonatal period. All 21 cases were de novo heterozygous mutations estimated as either pathogenic or likely pathogenic based on the American College of Medical Genetics and Genomics guidelines,2 and 14 sites have not been reported previously: c.2654T > C, p.I885T; c.5303A > G, p.N1768S; c.4378A > G, p.I1460V; c.4384G > A, p.V1462I; c.656T > C, p.L219F; c.1243G > A, p.E415K; c.4814T > C, p.I1605T; c.3815T > A, p.A982S; and c.2945C > T, p.A982V. Seven variants were previously confirmed as pathogenic: c.1099A > G, p.M367V;3 c.667A > G, p.R223G;4 c.3953A > G, p.N1318S;6 c.5614C > T, p.R1872W;7 c.638T > C, p.I213P;8 c.2300C > T, and p.T767I.4 The domains in the voltage-gated sodium channel amino acid sequence were grouped according to approximate functional domains based on the method reported by Holland et al.9: the pore region was defined as segments S5, S5-S6, and S6, while the voltage sensor region was classified as S4 and its associated linkers of S3-S4 and S4-S5. Other transmembrane segments and their linking regions (TMOs) were grouped, and the intracellular loops linking domains I-III were also grouped together (Loops). The inactivation gate, N-terminus, and C-terminus were also grouped separately. The clinical data from all patients were also collected, focusing on the age of onset, the forms of seizures, the frequency of seizures, neurological development at onset, the effect of SCBs during follow-up, and neurologic and EEG evaluations during follow-up.

As a result, in our cohort, only five out of 21 cases had a good response to SCBs, with the frequencies of seizures significantly reduced up to 75% after treatment. All five patients had combined anti-seizure medications (ASMs) with valproate...
(VPA) plus lamotrigine (LTG) for two cases, levetiracetam and LTG for one case, and VPA plus oxcarbazepine for the remaining two cases. Second, four of 21 cases had only a partial response to SCBs. Third, 7 of 21 patients had only some response to SCBs, i.e. the administration of SCBs could not reduce the frequencies of seizures, but the SCBs could not be stopped during treatment, because if reduced, status epilepticus would occur. Finally, the other five remaining patients had a negative response to SCBs, as non-SCBs had limited seizures controlled by VPA, with normal cognitive development; two children belonged to the IE group, with a better response to SCBs than the other phenotype groups; two children belonged to the GE group, one with seizures controlled by VPA + LTG and the other one with seizures controlled by levetiracetam. Interestingly, the study by Johannesen et al. revealed that the patients with BFIE or IE showed a mild GOF, whereas the patients with GE had severe developmental delay/intellectual disability. The findings of our study showed that the clinical phenotypes significantly correlated with the effect of SCBs (Fisher = 13.198, P = 0.016, r = 0.646). For example, one girl belonged to the BFIE group, having self-limiting seizures controlled by VPA, with normal cognitive development; two children belonged to the IE group, with a better response to SCBs than the other phenotype groups; two children belonged to the GE group, one with seizures controlled by VPA + LTG and the other one with seizures controlled by levetiracetam. Interestingly, the study by Johannesen et al. revealed that the patients with BFIE or IE showed a mild GOF, whereas the patients with GE had the LOF mutation of SCN8A. Similarly, our data supported the above findings.

However, some differences based on the outcomes of our cohort were as follows. The first discrepancy was regarding the outcomes of a subgroup of DEE patients. Johannesen and colleagues revealed that missense variants in most patients with DEE showed a strong GOF and only 3/34 patients with LOF exhibited DEE. Most patients with DEE revealed frequent resistance to ASMs. In our Chinese

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Table 1 Clinical features of twenty-one cases with SCN8A-related epilepsy

| No | Sex | Age (m) | Seizure | MRI | DEV | Diagnosis | Age (mo) | ASMs/Therapy | Current dev. (DQ/IQ) | Variants | Location | Drug response | Effect of SCBs |
|----|-----|--------|--------|-----|-----|----------|---------|-------------|------------------|----------|----------|---------------|-------------|
| 1  | Male| 9      | CGFS   | Normal | Normal | DEE     | 26      | VPA,LTG     | 48 c.2654T > C, p.I885T | Pore     | DE       | +++          |             |
| 2  | Female| 8    | CGFS   | Normal | Normal | BIFE   | 29      | VPA        | 91 c.5303A > G, p.N1768S | C-terminus | C-terminus| –            |             |
| 3  | Male | 2     | GS     | Normal | Normally | IE     | 36      | VPA,OXC   | 65 c.4378A > G, p.I1460V | Pore     | DE       | +++          |             |
| 4  | Male | 2     | GS     | Normal | Normally | DEE     | 48      | VPA,OXC,LCM,NZP | 33 c.4384G > A, p.V1462I | Inactivation gate | DR | ++          |             |
| 5  | Male | 3     | GS     | Normal | R       | DEE     | 18      | VPA,OXC   | 45 c.1099A > G, p.M367V | Pore     | DE       | +++          |             |
| 6  | Female| 7    | GS     | Normal | Normal | DEE     | 13      | VPA,NZP,TPM,VGB/ACTH | 42 c.656T > C, p.L219F | VSR     | DR | –            |             |
| 7  | Female| 3    | CGFS   | Normal | R       | DEE     | 48      | VPA,TPM,LCM | 31 c.1243G > A, p.E415K | Loops   | DR | ++          |             |
| 8  | Male | 3     | GS     | Normal | Normal | DEE     | 12      | OXC       | 61 c.4814T > C, p.I1605T | VSR     | DR | ++          |             |
| 9  | Male | 6     | GS     | Atrophy | R       | DEE     | 36      | VPA,LEV,LCM | <20 c.667A > G, p.R223G | VSR     | DR | –            |             |
| 10 | Male | 3     | GS     | Atrophy | R       | DEE     | 36      | VPA,TPM,LCM | <20 c.2549G > A, p.R850E | VSR     | DR | +            |             |
| 11 | Male | 0     | CGFS   | Normal | ID     | DEE     | 11      | OXC,TPM/ACTH | <20 c.3815T > A, p.V1272E | TMOs   | DR | +            |             |
| 12 | Female| 6    | GS     | Normal | Normal | GE     | 60      | LEV,LTG  | 48 c.4798A > G, p.M1600V | TMOs   | DE | +++          |             |
| 13 | Female| 2    | GS     | Normal | Normal | IE     | 60      | VPA,LTG  | 34 c.3953A > G, p.N1318S | VSR     | DE | +++          |             |
| 14 | Female| 8    | GS     | Normal | Normal | DEE     | 32      | OXC,LTG,OXC,VPA,TPM | 45 c.2942G > C, p.S981T | Loops   | DR | +            |             |
| 15 | Male | 3     | GS     | Normal | DEE     | DEE     | 20      | LEV,OXC,LCM,VPA,NZP | <20 c.5614C > T, p.R1872W | C-terminus | DR | +            |             |
| 16 | Male | 6     | GS     | Normal | Normal | DEE     | 21      | VPA,LEV,LCM,VPA,NZP/KD | 30 c.638T > C, p.L213F | VSR     | DR | –            |             |
| 17 | Male | 0     | FS     | Normal | ID     | DEE     | 10      | VPA,LTG,LEV | <20 c.2300C > T, p.T767I | TMOs   | DR | +            |             |
| 18 | Male | 0     | CGFS   | Normal | ID     | DEE     | 26      | CBZ,CZP  | <20 c.2944G > T, p.T767I | Loops   | DR | +            |             |
| 19 | Male | 0     | CGFS   | Normal | ID     | DEE     | 26      | CBZ,CZP  | <20 c.5614C > T, p.R1872W | TMOs   | DR | +            |             |
| 20 | Male | 0     | CGFS   | Normal | ID     | DEE     | 4       | PB,OXC,TPM,NZP | <20 c.2627G > A, p.G876D | Pore     | DR | +            |             |
| 21 | Female| 7    | GS     | Normal | Normal | GE     | 96      | LEV      | 40 c.4948G > T, p.A1650S | VSR     | DE | –            |             |

* = somewhat response, ++ = partial response, +++ = good response, – = no response

ACTH = adrenocorticotropic hormone; ASMs = anti-seizure medicines; BIFE = benign familial infantile epilepsy; CGFS = combined generalized and focal seizures; CBZ = carbamazepine; CZP = clonazepam; DE = drug effective; DEE = developmental and epileptic encephalopathy; Dev. = development; DQ = developmental quotient; DR = drug refractory; FS = focal seizures; GE = generalized epilepsy; GOF = gain-of-function; ID = intellectual disability; IE = intermediate epilepsy; IQ = intellectual quotient; KD = ketogenic diet; LCM = lacosamide; LEV = levetiracetam; LTG = lamotrigine; mo = months; NZP = nitrodiazepam; OXC = oxcarbazepine; PB = phenobarbital; PER = perampanel; R = retardation; SCBs = sodium channel blockers; TMOs = other transmembrane segment and linking regions; VPA = valproate; VGB = vigabatrin; VSR = voltage sensor region.

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Table 2 Relationship between the effect of SCBs and clinical characteristics in SCN8A-related epilepsy

| Effect of SCBs | Fisher | \( r \) | \( P \) |
|---------------|--------|---------|-------|
| +++           | 10.847 | 0.628   | 0.063 |
| ++            | 18.952 | 0.733   | <0.001|
| +             | 13.163 | 0.632   | 0.010 |
| None          | 7.659  | 0.517   | 0.054 |
|               | 17.168 | 0.671   | 0.046 |

| Age of onset | Newborn | <6 months | >6 months |
|--------------|---------|-----------|-----------|
|              | 0       | 3         | 2         |
|              | 0       | 1         | 0         |
|              | 2       | 1         | 0         |
|              | 0       | 1         | 0         |
|              | 5       | 1         | 0         |
|              | 18.952  | 0.733     | <0.001   |
|              | 13.163  | 0.632     | 0.010    |
|              | 7.659   | 0.517     | 0.054    |
|              | 17.168  | 0.671     | 0.046    |
|              | 10.847  | 0.628     | 0.063    |

| Forms of seizures | Only focal seizures | Only generalized seizures | Generalized seizures+focal seizures |
|-------------------|---------------------|---------------------------|------------------------------------|
|                   | 0                   | 2                         | 3                                  |
|                   | 0                   | 0                         | 4                                  |
|                   | 3                   | 1                         | 4                                  |
|                   | 0                   | 3                         | 3                                  |
|                   | 3                   | 0                         | 1                                  |
|                   | 3                   | 1                         | 4                                  |
|                   | 7.659               | 0.517                     | 0.054                              |
|                   | 17.168              | 0.671                     | 0.046                              |
|                   | 10.847              | 0.628                     | 0.063                              |

| Distribution of missense variants | Voltage sensor region | Inactivation gate + C-terminus + loops | Pore | TMOs |
|-----------------------------------|-----------------------|----------------------------------------|------|------|
|                                   | 1                     | 0                                      | 3    | 0    |
|                                   | 4                     | 3                                      | 0    | 2    |
|                                   | 1                     | 3                                      | 0    | 0    |
|                                   | 1                     | 1                                      | 0    | 2    |
|                                   | 4                     | 3                                      | 0    | 2    |
|                                   | 7.659                 | 0.517                                  | 0.054|      |
|                                   | 17.168                | 0.671                                  | 0.046|      |
|                                   | 10.847                | 0.628                                  | 0.063|      |

| Distribution of missense variants | Clinical phenotype | Total |
|-----------------------------------|--------------------|-------|
|                                   | BIFE               | 5     |
|                                   | IE                 | 4     |
|                                   | DEE                | 7     |
|                                   | GE                 | 5     |
|                                   |                   | 16    |

| BIFE = benign familial infantile epilepsy; DEE = developmental and epileptic encephalopathy; GE = generalized epilepsy, frequently with absence seizures; IE = intermediate epilepsy; SCBs = sodium channel blockers; TMOs = other transmembrane segment and linking regions. |
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