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Original Article

Further Characterization of *SMC1A* Loss of Function Epilepsy Distinct From Cornelia de Lange Syndrome

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Abstract

Cornelia de Lange syndrome is a rare developmental malformation syndrome characterized by small stature, limb anomalies, distinctive facial features, developmental delays, and behavioral issues. The diagnosis of Cornelia de Lange syndrome is made clinically or on the basis of an identified variant in one of the genes associated with Cornelia de Lange syndrome. *SMC1A* variants are the cause of 5% of the cases of Cornelia de Lange syndrome. *SMC1A* is located on the X-chromosome and is thought to escape X-inactivation in some females. Patients with *SMC1A* variants are being increasingly identified through panel testing or exome sequencing without prior clinical suspicion of Cornelia de Lange syndrome. In general, intractable epilepsy is not considered a prominent feature of Cornelia de Lange syndrome, yet this is found in these patients with *SMC1A* variants. Here we report on a series of patients with *SMC1A* variants and intractable epilepsy. In contrast to patients with typical *SMC1A*-associated Cornelia de Lange syndrome, all of the identified patients were female, and when available, X-inactivation studies were highly skewed with truncating variants. We describe the medical involvement and physical appearance of the participants, compared to the diagnostic criteria used for classical Cornelia de Lange syndrome. We also report on the clinical characteristics of the epilepsy, including age of onset, types of seizures, electroencephalographic (EEG) findings, and response to various antiepileptic medications. These findings allow us to draw conclusions about how this population of patients with *SMC1A* variants fit into the spectrum of Cornelia de Lange syndrome and the broader spectrum of cohesinopathies and allow generalizations that may impact clinical care and, in particular, epilepsy management.

Keywords

epilepsy, genetics, variant, antiepileptic drugs, developmental disability

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Introduction

Cornelia de Lange syndrome (CdLS) is a rare developmental malformation syndrome characterized by small stature, limb anomalies, distinctive facial features, developmental delays and behavioral issues as well as potential involvement of most body systems. Congenital heart disease is found in 25%, renal anomalies in 10%, cleft palate in 20%, cryptorchidism in 80% of males, bicornuate uterus in 19% of females, and brain anomalies are rare.[1] Seizures occur in about 20% of individuals. The diagnosis of Cornelia de Lange syndrome is typically made clinically or by identifying a pathogenic or likely pathogenic variant in one of the genes associated with Cornelia de Lange syndrome (*NIPBL*, *RAD21*, *SMC3*, *HDAC8*, *SMC1A*, *ANKRD11*, and *BRD4*), present in nearly 80% of affected patients.[1] The genes are components of the cohesin complex or cohesin regulators, involved in the packaging of chromosomes for the process of segregation, and also involved in the control of gene expression.[2,3]

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Table 1. *SMC1A* Variants Found in Study Participants and Results of X-Inactivation Studies.

Patient no.	Variant	De novo?	Predicted effect	X-inactivation studies
1	c.421G>A, p.E141K	Y	Missense	100:0 (highly skewed)
2	c.1900C>T, p.Q634X	Y, mosaic	Nonsense/truncating	86:14 (moderately skewed)
3	c.140T>G, p.F47C	Y	Missense	74:26 (random)
4	c.3046_3048delGTGinsG, p. V1016AfsX28		Frameshift, nonsense/truncating	Random
5	c.2394dupA, p.R799fs	Y	Frameshift, truncating	
6	c.20_23del, p.17Rfs*42		Deletion causes frameshift and PSC	81:19 (moderately skewed)
7	c.2873delA, p.Q958Rfs*6	Y	Frameshift, nonsense/truncating	66:34 (random)
8	c.1609delG, p.V537Ffs*42	Y	Nonsense/truncating	100:0 (highly skewed)
9	c.615+1G>C	Y	Affects donor splice site, causes PSC	83:17 (moderately skewed)
10	c.2769dupC, p.S924Qfs*2	Unknown	Nonsense/truncating	
11	c.287G>C, p.R96P	Y	Missense	59:41 (random)
12	c.615G>A, p.=		Synonymous change	Uninformative
13	c.3549_3552dupGGCC, p.I1185Gfs*23	Y	Frameshift, truncating	Uninformative

SMC1A (*S*tructural *M*aintenance of *C*hromosomes *1A*) pathogenic variants are the cause of approximately 5% of the cases of Cornelia de Lange syndrome.[4] Its transcript spans 9.7 kB and comprises 25 exons, and the protein is composed of 1233 amino acids. It resides on chromosome Xp11.22 and is reported to escape X-inactivation in some, but not all, females.[5] Individuals with *SMC1A* variants initially identified as having Cornelia de Lange syndrome on the basis of their distinctive facial features and other criteria are generally found to have missense or small in-frame deletions of this gene[4,6,7] and are typically milder than those seen in patients with *NIPBL* variants.

Patients with *SMC1A* variants are increasingly being identified on the basis of next-generation sequencing technologies, without necessarily a clinical suspicion of Cornelia de Lange syndrome prior to this test result. In general, intractable epilepsy is not a prominent feature of Cornelia de Lange syndrome,[8] yet this is a feature of many of these patients diagnosed with mostly truncating loss-of-function *SMC1A* variants.[9–12]

Case reports of girls with pharmacoresistant epilepsy and *SMC1A* variants were initially reported in the literature.[9–11] Subsequently, Huisman and colleagues[13] reported on 51 individuals with *SMC1A* variants, 5 of whom were all female and had what was described as a Rett-like phenotype with intractable epilepsy. Symonds and colleagues[12] presented a case series of 10 girls with truncating *SMC1A* variants and emphasized the tendency toward clustering of seizures, similar to *PCH19*-related epilepsy, and an association with developmental regression. In these reports, a wide range of seizures have been described, including infantile spasms, epilepsy of infancy with migrating focal seizures, focal, atypical absence, tonic, myoclonic, and generalized tonic clonic seizures.[9–12,14] Seizures typically present between infancy and 2 years of age. Electroencephalographs (EEGs) typically have focal or multifocal abnormalities, as well as subclinical runs of generalized spike and wave activity.[12]

Our goals were to better characterize the phenotype of patients with pathogenic *SMC1A* variants and epilepsy, better elucidate how patients with these variants fit into the spectrum of Cornelia de Lange syndrome, and better characterize their epilepsy.

Patients and Methods

Eligible patients were recruited based on communication with their treating clinicians, through outreach from the Cornelia de Lange Foundation, and through an *SMC1A* Facebook group. Patients were eligible if they had a documented *SMC1A* variant and epilepsy. Patients were clinically evaluated through the multidisciplinary aging clinic for Cornelia de Lange syndrome, held twice a year at Greater Baltimore Medical Center, where patients undergo medical records review, extensive medical history, and detailed physical examination. They are evaluated by providers in a number of disciplines and receive education about Cornelia de Lange syndrome. The families' concerns are discussed and recommendations are synthesized. As part of this study, patients with *SMC1A* variants underwent the same structured genetic and neurologic examinations and a standardized interview regarding their epilepsy (Supplemental Materials). In addition, X-inactivation studies were sent on blood samples.

Results

Patient Demographics

In this cohort of patients, there was a clinical suspicion of Cornelia de Lange syndrome prior to genetic testing for only 1 patient (1/13). All of the patients (13/13) were female. Nearly half (6/13) of the patients were between 2 and 5 years of age; 4 of 13 were 6-10 years; 2 of 13 were 11-15 years; and 1 of 13 was between 16-20 years. All patients were from the United States.

Variant Classifications

Table 1 lists the *SMC1A* variants found in the patients, along with whether it is de novo, if known. In all 9 cases where a determination was made, the change was de novo, and in 1 case, mosaic. Nine of 13 were predicted to be frameshift, nonsense, or truncating variants and 3 of 13 were predicted to be missense variants. One of 10 was a synonymous change

Figure 1. Study participants with *SMC1A* pathogenic variants, ordered based on scoring for classical Cornelia de Lange syndrome criteria (high to low).

predicted to affect splicing. Interestingly, all 3 missense variants fell in the N-terminal NTPase domain of the protein involved in binding ATP found at amino acids 4-148.[15]

X-Inactivation Studies

X-Inactivation studies were completed for 11 of 13 participants. Two of 11 studies were uninformative, and 5 of 9 informative studies (56%) were highly or moderately skewed. For the patients with truncating variants and completed X-inactivation studies, 4 of 5 (80%) were highly or moderately skewed. For patient with missense variants and completed X-inactivation studies, 2 of 3 were random.

Phenotypic Analysis

Facial criteria. Patients underwent a standardized genetic examination and were scored for facial characteristics associated with Cornelia de Lange syndrome.[16] Cardinal facial features associated with classical Cornelia de Lange syndrome include synophrys; short nose, concave nasal ridge, and/or upturned nasal tip; and long and/or smooth philtrum. Only 1 patient was determined to have facial features more typical for Cornelia de Lange syndrome (patient 1), the same patient suspected clinically to have Cornelia de Lange syndrome prior to genetic testing. An additional 7 girls also had synophrys (patients 4-7 and 9-11), of whom 2 (6 and 11) were deemed to meet facial criteria but to be minimally typical or atypical. Of the 3 patients with features suggestive of Cornelia de Lange syndrome, 2 girls had missense variants. Unlike classical Cornelia de Lange syndrome, all of the patients tended to have normal philtrums and small mouths with well-formed upper lips, but a few have downturned corners. Photographs of the girls are presented in Figure 1, ranked from high to low with regard to scoring of Cornelia de Lange syndrome–related facial criteria.

The girls with the *SMC1A* variants causing severe epilepsy had an overall recognizable facial gestalt, consisting of an oval or long face, synophrys or distinctive eyebrow arch, long eyelashes, prominent supraorbital ridge, shallow orbits, occasional ptosis, normal well-formed philtrum, and small mouth with the upper lip having a distinctive cupid's bow, small and posteriorly rotated ears, and open-mouth habitus. They also had long tapered fingers and long hands.

Table 2. Epilepsy Characterization of Participants.[a]

Patient no.	Seizure onset	Focal	Generalized	Unknown/unclassified	Status epilepticus	Clusters	Intractable
1	10 wk	FIAT	A, GTC		+	+	+
2	3 mo	FIAM	GT, GTC		+	+	+
3	3 mo		GA, GTC	U	+	+	+
4	Newborn		GTC	U	+	+	+
5	4 mo	FIAT, FBTC	GTC		+	+	+
6	15 mo		GA, GT		+	+	+
7	3 mo	FAA, FIAC	GTC		-	+	+
8	5 mo	FNMA	GTC		+	+	+
9	1 mo		GTC	UBA, UES	+	+	+
10	2 y	FIAT, FBTC	GTC		+	+	+
11	18 mo	FIAT, FIAE	GTC	UA	+	+	+
12	13 mo	FIAC, FIAT, FBTC	GM, GT	U	+	+	+
13	16 mo			UA, UM	-	+	+

Abbreviations: A, absence; FAA, focal aware automatisms; FBTC, focal to bilateral tonic clonic; FIAC, focal impaired awareness clonic; FIAE, focal impaired awareness emotional; FM, focal impaired awareness myoclonic; FIAT, focal impaired awareness tonic; FNMA, focal nonmotor autonomic; GA, generalized atonic; GM, generalized myoclonic; GT, generalized tonic; GTC, generalized tonic clonic; U, unclassified; UA, unknown onset atonic; UBA, unknown onset behavioral arrest; UES, unknown onset epileptic spasm; UM, unknown onset motor.

[a]Seizure types are reported based on parental report of seizure semiology, and listed according to 2017 International League Against Epilepsy (ILAE) classifications.[17] Focal seizures are named for the earliest prominent sign or symptom other than awareness. Unclassified seizures comprise both seizures with patterns that do not fit into other categories, or seizures with insufficient information to allow categorization.

Developmental and behavioral criteria. The main developmental criteria for a diagnosis of Cornelia de Lange syndrome are either global developmental delays and/or intellectual disability. The vast majority of the girls (12/13, 92%) were nonverbal or at most had a few words or signs. The outlier (patient 13), who has verbal expressive language, has a frameshift variant in exon 24 (of 25), so the mRNA product may escape nonsense mediated decay. Five of the 13 girls (39%) met behavioral criteria, typically with mild aggression or mild self-injurious behavior. This is in marked contrast to the pronounced behavioral issues typical of classical Cornelia de Lange syndrome.

Growth criteria. In classical Cornelia de Lange syndrome, weight and height are below the fifth percentile for age. Nine of the 13 girls (69%) met criteria for small stature. One of the musculoskeletal criteria is small hands and/or feet, below the third percentile for age. Eight of the 13 girls (62%) with the *SMC1A* variants causing severe epilepsy had small hands and feet.

Other clinical findings. Issues with urinary tract infections and kidney anomalies were common (8/13, 62%), and 6 of the 13 girls (46%) had some degree of early or precocious puberty. Feeding issues were common, requiring a G-tube in 6 of 13 girls (46%). Neurologic examination in all individuals, with the exception of the presence of central hypotonia in all, was nonfocal.

Overall, with the exception of patient 1, the girls did not meet criteria for a clinical diagnosis of classical Cornelia de Lange syndrome. However, in general, the girls with the *SMC1A* variants and severe epilepsy shared a number of issues in common with classical Cornelia de Lange syndrome.

Epilepsy Characterization

Onset of seizures, electroencephalographic (EEG), and magnetic resonance imaging (MRI) findings.. Early onset of seizures: 8 of 13 (62%) had onset in the first 6 months of life (2/13 in the first 2 months) and 12 of 13 (92%) had onset by 24 months of life. EEGs, when reports were available, were normal or demonstrated focal or multifocal activity, with just 1 case of hypsarrhythmia associated with an initial diagnosis of infantile spasms. Initial seizure management was typical, with first agents either levetiracetam (7/13), phenobarbital (4/13), oxcarbazepine (1/14), or topiramate (1/13). All patients underwent MRI of the brain, with a number with relatively nonspecific findings (1 case each of agenesis of the corpus callosum, ventriculomegaly with a thin corpus callosum, slightly small splenium of the corpus callosum, and a Chiari I malformation).

As seizures progressed, a propensity toward clustering of seizures was noted in all girls (13/13), often precipitated by a febrile illness, often typically a urinary tract infection. Although episodes of prolonged seizure meeting criteria for status epilepticus were reported, refractory clusters of typically brief seizures were the predominant concern. Developmental regression, often in the setting of seizure clusters, was reported commonly (8/13). Although precise seizure-related data gathering was limited by the nature of parental report, Table 2 lists a summary of findings. Seizure types are reported based on parental report of seizure semiology and the 2017 International League Against Epilepsy (ILAE) classifications.[17] The epilepsy associated with these *SMC1A* variants is generally intractable, and no clear pattern of response to particular medications emerged. The average number of conventional antiseizure medications trialed was 7.2 (range 4-12; see Figure 2 for the range and frequency of particular medication trials), and the average number of current conventional antiseizure medications was 2.2 (range 0-4).

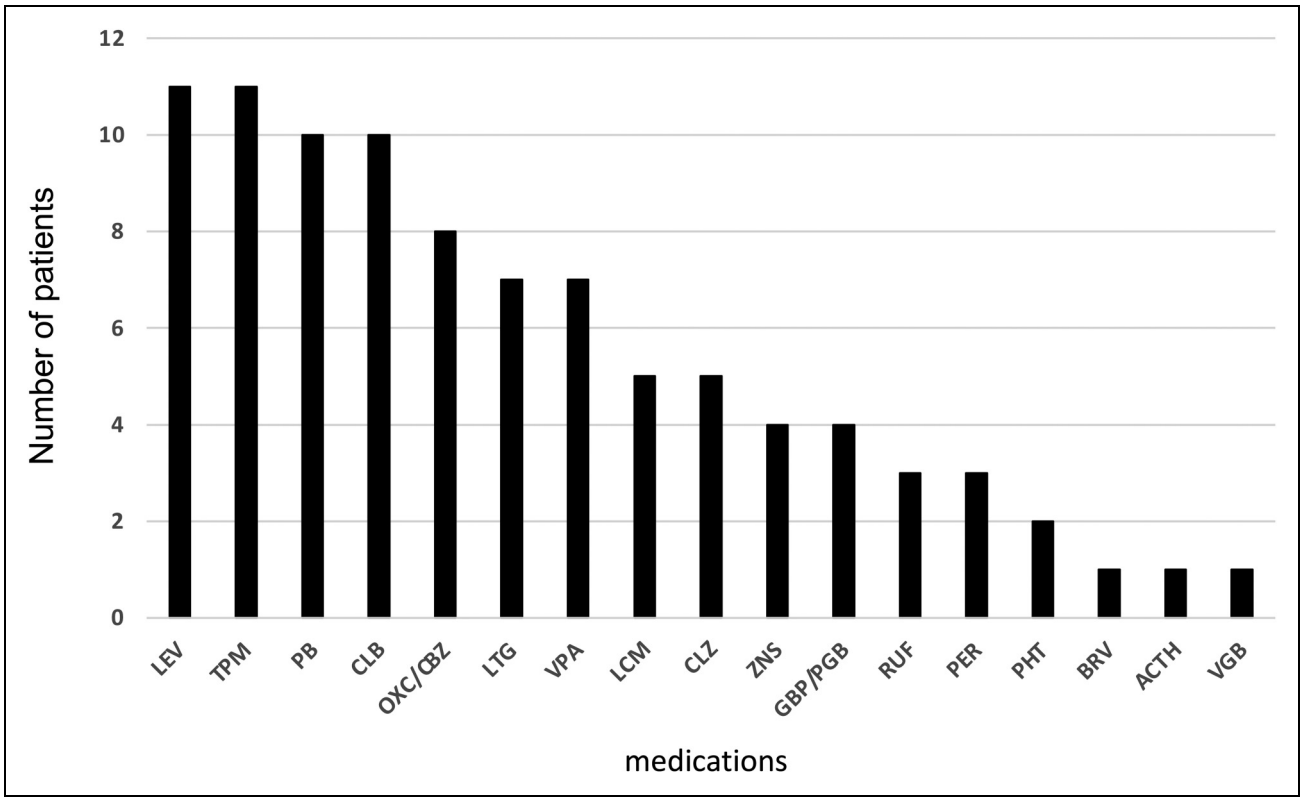

Figure 2. Antiepileptic medications trialed for study participants. ACTH, adrenocorticotropin hormone; BRV, brivaracetam; CBZ, carbamazepine; CLB, clobazam; CLZ, clonazepam; GBP, gabapentin; LCM, lacosamide; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; PB, phenobarbital; PER, perampanel; PGB, pregabalin; PHT, phenytoin; RUF, rufinamide; TPM, topiramate; VGB, vigabatrin; VPA, valproic acid; ZNS, zonisamide.

Ketogenic diet was trialed in 10 of 13, but was only clearly helpful in 2 of 10 (20%). Vagus nerve stimulator had been placed in 5 of 13 girls and was clearly helpful in 3 of 5 (60%). This study was conducted prior to Food and Drug Administration (FDA) approval of Epidiolex; over-the-counter cannabidiol was tried by 8 of 13, and 6 of 13 remained on it. Anecdotally, progesterone was helpful in suppressing catamenial seizures in one of the older girls who had started her menstrual cycle. When including trials of conventional antiseizure medications plus ketogenic diet, vagus nerve stimulator, and cannabidiol, the average number of treatments trialed was 8.9, and the average number of current interventions was 3.2.

Discussion

Here we have presented the largest series to date specifically detailing the phenotypic features of this group of patients with intractable epilepsy associated with primarily truncating *SMC1A* variants, and specifically compare them to the criteria for classical Cornelia de Lange syndrome. It has remained a matter of debate whether *SMC1A* loss of function epilepsy should be considered separate from Cornelia de Lange syndrome, or as a subtype of Cornelia de Lange syndrome.

SMC1A variants leading to severe epilepsy is a distinct subtype of variants in this gene typically causing Cornelia de Lange syndrome. Prior to the recognition of this syndrome, *SMC1A* missense and small in-frame deletions were identified in both males and females with clinical features consistent with classical Cornelia de Lange syndrome but without major malformations or very small stature.[4] In this setting, there is a 2:1 ratio of males to females, with females often having a milder presentation and some females only identified after having male children with a more severe presentation.

In our cohort of patients with pathogenic *SMC1A* variants and intractable epilepsy, variants were generally, but not invariably, truncating and all patients were female. Presumably, these truncated transcripts are subject to nonsense mediated decay. However, haploinsufficiency cannot be invoked as a mechanism, given that it would lower transcription levels to those seen in normal male patients. It has been proposed that some amount of truncated *SMC1A* transcript may escape nonsense mediated decay, undergo translation, and exert a dominant negative effect.[17] Overall, about half of our patients have skewed X-inactivation, typically the patients with truncating variants, supporting the idea that *SMC1A* is indeed subject to X-inactivation in at least some patients. This may influence the amount of transcript that could potentially escape nonsense

mediated decay and contribute to a dominant negative effect, thereby influencing the severity of the phenotype. However, in our series, there was not an apparent association between either scoring for classical Cornelia de Lange syndrome or severity of epilepsy related to degree of skewing. Further research into allele expression in the setting of these truncating variants will be required to help better understand the underlying mechanism of pathogenicity.

Girls with *SMC1A* variants leading to severe epilepsy have some facial features in common with classical Cornelia de Lange syndrome, but have a distinctive overall gestalt. These girls have a more severe developmental disorder than seen with typical *SMC1A*-related Cornelia de Lange syndrome. Classical Cornelia de Lange syndrome is associated with sometimes severe behavioral issues, including self-injurious behavior. This is not seen in these girls; in fact, they tend to have a pleasant and cheery affect, such that the families have named their Facebook group the "Sunshine Sisters." They do share a number of issues with Cornelia de Lange syndrome, including growth, gastrointestinal and feeding problems, and genitourinary issues. They do not have similar hand findings. The relatively nonspecific MRI findings in our cohort included 3 patients with differences reported in the corpus callosum. This differs from the MRI findings that are most commonly reported in classical Cornelia de Lange syndrome, which include skull base differences, microcephaly, decreased volume, enlarged ventricles, gyral simplification, interthalamic adhesion, and minor vascular differences.[18]

The epilepsy associated with this *SMC1A* cohort is quite different from that which is expected with typical Cornelia de Lange syndrome. Epilepsy occurs in 14% to 25% of patients with Cornelia de Lange syndrome, and seizures are generally easy to control, typically with monotherapy.[8] In *SMC1A*-related epilepsy, seizures typically have onset in the first 1-2 years of life, and there is a marked predilection for clustering of seizures, often provoked by febrile illness, and frequently associated with developmental regression. This is similar to what might be seen in *SCN1A*- and *PCD19*-related epilepsy, but the distinctive facial gestalt, long narrow hands with tapered fingers, and tendency toward growth issues might be potential clues in pointing a clinician to this specific genetic diagnosis. In our cohort, the girls did not have the stereotyped hand wringing that had been reported elsewhere,[13] leading to comparison to a Rett-like phenotype.

The burden of medically intractable epilepsy is apparent in the numbers of trialed medications and other interventions. The ketogenic diet is anecdotally helpful on occasion, and VNS placement was helpful in about half of the patients. No conventional antiseizure medication emerged as being preferentially helpful, but was apparent that certain combinations of agents, including newer agents, could be potentially trialed, such as valproic acid plus lamotrigine and lacosamide plus clobazam.

It will be important to continue to follow this cohort as they age. This cohort skews younger because younger patients are more likely to be offered genetic testing in conjunction with their initial presentation of intractable epilepsy. As older patients return for follow-up to the genetics clinic, additional diagnoses will be made and will increase our understanding of the natural history of this disorder.

Author Contributions

KWB and ADK were responsible for the project conception and designed the study. KWB wrote the manuscript. KWB, AK,SLF, ASE, CH and ADK collected patient data. KWB, AK, SLF and ADK analyzed the data. All authors read, revised and approved thefinal manuscript.

Ethical Approval

This study was approved by the institutional review boards of both Johns Hopkins Medicine and Greater Baltimore Medical Center. Written informed consent for participation in the study and for patient information and images to be published was obtain by the patient's legally authorized representative.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Supplemental Material

Supplemental material for this article is available online.

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