

Severe Intellectual Disability Associated with Recessive Defects in *CNTNAP2* and *NRXN1*

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Key Words

CNTNAP2 · Epilepsy · Intellectual disability · Mental retardation · *NRXN1*

Abstract

While heterozygous variants in *CNTNAP2* and *NRXN1* are reported as susceptibility factors for neuropsychiatric disorders, homozygous or compound heterozygous defects in either gene were reported as causative for severe neurodevelopmental disorders. This review provides an overview of the clinical aspects in patients with recessive defects in *CNTNAP2* and *NRXN1*.

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History of the Syndrome

During recent years, heterozygous copy-number and missense variants in *CNTNAP2* and *NRXN1* have repeatedly been reported as susceptibility factors for a wide spectrum of neuropsychiatric disorders such as developmental language delay and autism spectrum disorders, epilepsy and schizophrenia [Verkerk et al., 2003; Feng et al., 2006; Autism Genome Project Consortium, 2007; Beloso et al., 2007; Alarcón et al., 2008; Arking et al., 2008;

Bakkaloglu et al., 2008; Friedman et al., 2008; Kim et al., 2008; Kirov et al., 2008; Marshall et al., 2008; Vrijenhoek et al., 2008; Zahir et al., 2008; Bucan et al., 2009; Rujescu et al., 2009; Awadalla et al., 2010; Bradley et al., 2010; Ching et al., 2010; Magri et al., 2010; Mefford et al., 2010; Wiśniowiecka-Kowalnik et al., 2010].

A homozygous stop mutation in *CNTNAP2* in 10 Old Order Amish children was reported to cause a distinct disorder, cortical dysplasia-focal epilepsy syndrome (MIM 610042), characterized by cortical dysplasia and early onset, intractable focal epilepsy leading to language regression, and behavioral and mental deterioration [Strauss et al., 2006; Jackman et al., 2009]. Recently, homozygous or compound heterozygous defects in *CNTNAP2* or *NRXN1* were reported to cause a severe intellectual disability disorder resembling Pitt-Hopkins syndrome (MIM 610954) [Zweier et al., 2009]. These 4 patients had an initially negative TCF4-testing and showed severe intellectual disability and additional variable symptoms such as epilepsy, breathing anomalies and stereotypies.

In total, 13 patients with homozygous or compound heterozygous defects in *CNTNAP2* and 1 patient with a compound heterozygous defect in *NRXN1* are reported to date.

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Table 1. Clinical findings in patients with recessive *CNTNAP2* or *NRXN1* defects

	<i>CNTNAP2</i> (n = 13)	<i>NRXN1</i> (n = 1)
Age at clinical assessment	2–20 years	18 years
Normal body height	11/13	1/1
Head circumference	1 <P3, others P18–P99, mean >P75	P50–P75
Severe intellectual disability	13/13	1/1
Age of walking	normal–30 months	2 years
Speech	none or single words	none
Developmental regression	11/13	1/1
Seizures with age of onset	13/13, 4–30 months	0/1
MRI anomalies	CD 3/10, CH 1/10, PL 1/10	0/1
Behavioral anomalies	9/13	1/1
Decreased deep tendon reflexes	9/10	1/1
Breathing anomalies	3/3	1/1

P = Centile; CD = cortical dysplasia; CH = cerebellar hypoplasia; PL = periventricular leukomalacia. Data for *CNTNAP2*: Jackman et al., 2009; Strauss et al., 2006; Zweier et al., 2009. Data for *NRXN1*: Zweier et al., 2009.



Fig. 1. Facial appearance of patients with compound heterozygous defects in *CNTNAP2* (A) or *NRXN1* (B). Note a wide mouth in the patient with *NRXN1* defects but otherwise unsuspecting facial gestalts in both patients. Reprinted from Zweier et al. [2009], with permission from Elsevier.

Clinical Features (table 1)

Facial Gestalt

In contrast to patients with Pitt-Hopkins syndrome, the facial phenotype in patients with recessive *CNTNAP2* and *NRXN1* defects is rather unsuspecting. Two patients with a homozygous deletion within *CNTNAP2* [Zweier et al., 2009] had previously been published as possible Pitt-Hopkins syndrome patients due to a wide mouth and thick lips [Orrico et al., 2001], but as indicated by Peippo et al. [2006] and supported by the present knowledge and perspective, they do not have the distinct Pitt-Hopkins syndrome facial phenotype. The remaining patients do not show specific facial dysmorphisms [Zweier et al., 2009] (fig. 1), neither are any reported for the Amish patients [Strauss et al., 2006; Jackman et al., 2009].

Intellectual Disability

Intellectual disability is reported to be severe in all patients. Developmental testing of 3 patients with cortical dysplasia-focal epilepsy syndrome at the ages of 32, 40 and 73 months revealed global mental ages of 21, 17 and 13 months, respectively [Strauss et al., 2006]. Particularly severe speech impairment is severe with either no or very limited speech development or regression of speech abilities. Both receptive and expressive language was reported to be maintained at the 1-year level in a 7-year-old patient [Jackman et al., 2009]. In comparison, motor delay is rather mild with a normal or mildly delayed walking age. Developmental regression was not noted in 2 patients

[Orrico et al., 2001], but was reported in the other patients with *CNTNAP2* defects, starting at the same age as onset of epilepsy between 4 and 30 months [Strauss et al., 2006; Zweier et al., 2009]. Later on, the degree of mental impairment seems to be stable. The early onset mandatory epilepsy with concurrent developmental regression in patients with *CNTNAP2* defects might be a discriminating aspect regarding other disorders with regression phenotypes such as Rett syndrome. Furthermore, the discrepancy between severe speech impairment and rather mild motor delay seems to be quite specific for recessive *CNTNAP2* defects. Similarly, in the patient with the *NRXN1* defect, only mild motor delay with a walking age of 2 years but no speech development was reported [Zweier et al., 2009].

Seizures

The single patient with biallelic *NRXN1* defects does not have epilepsy [Zweier et al., 2009]. Due to the limited number of patients, no conclusion about frequency of seizures in *NRXN1* related intellectual disability can be made.

All patients with recessive defects in *CNTNAP2* do show epilepsy with an early onset between 4 and 30 months of age [Strauss et al., 2006; Jackman et al., 2009; Zweier et al., 2009]. Concurrent with the onset of epilepsy, language regression and deterioration of social behavior occur in most of the patients [Strauss et al., 2006]. Regarding available data reported by Strauss et al. [2006], the average peak seizure frequency (number of events per week) is 50 with complex partial, simple partial, secondarily generalized, and status epilepticus types of seizures.

Growth Parameters

As far as data is available, birth measurements are normal. Apart from 2 siblings with short stature [Orrico et al., 2001; Zweier et al., 2009], later body measurements are reported to be normal as well. Interestingly, many patients show a tendency to rather large head circumferences in relation to body height [Strauss et al., 2006]. This might be a suitable discriminating factor in differential diagnosis to other severe intellectual disability disorders where microcephaly is common.

Behavioral Observations

Behavioral anomalies with autistic traits or pervasive developmental delay, stereotypic movements and attention deficit-hyperactivity disorder are common [Strauss et al., 2006; Jackman et al., 2009; Zweier et al., 2009].

Magnetic Resonance Imaging

MRI examination of the brain showed focal malformations in 3 patients. Two of them had unilateral dysplasia of the anterior temporal lobe, and 1 had a malformation of the left striatum [Strauss et al., 2006]. In 2 other patients, periventricular leukomalacia [Jackman et al., 2009] and cerebellar hypoplasia were observed, respectively [Orrico et al., 2001; Zweier et al., 2009].

Other Findings

Breathing anomalies [Zweier et al., 2009] and decreased deep tendon reflexes [Strauss et al., 2006; Jackman et al., 2009] were reported in some patients; hepatomegaly was observed in 1 girl [Jackman et al., 2009].

Natural History

CNTNAP2

Early infant development appears to be normal or with only mild motor delay and is followed by onset of seizures, language regression or no speech development, with social and behavioral disturbances, and moderate to severe intellectual disability by late childhood [Orrico et al., 2001; Strauss et al., 2006; Jackman et al., 2009; Zweier et al., 2009].

NRXN1

The development of the patient was reported to be normal for the first year before severe intellectual disability with a walking age of 2 years and no speech development was noted [Zweier et al., 2009].

Recommendations for Management

Not much information about treatment is available. In 1 patient, zonisamide was used for treatment of seizures [Jackman et al., 2009]. Electrocorticography-guided epilepsy surgery for disabling complex partial seizures in 3 patients resulted in a temporarily seizure-free period of 6–15 months but with recurrence after this time [Strauss et al., 2006].

Genetics

Information about the Genes and Protein Function

CNTNAP2 is one of the largest genes in the human genome spanning 2.3 Mb on chromosome 7q35–36.1 and

consisting of 24 coding exons (NM_014141). *NRXN1* also belongs to the largest known genes in humans with spanning 1.1 Mb on chromosome 2p16.3. The classical neurexin genes in mammals have 2 promoters, generating longer α - and shorter β - neurexins, and are subject to additional extensive alternative splicing, generating a large number of variants [Missler and Südhof, 1998]. The representative *NRXN1* isoform α 1 (NM_004801) consists of 21 coding exons.

CNTNAP2 encodes for CASPR2, a protein distantly related to the neurexins and regulating neuron-glia contact in vertebrates and glia-glia contact in insects [Bellen et al., 1998]. Vertebrate Caspr2 has been shown to colocalize with Shaker-like K⁺ channels in the juxtaparanodal areas of Ranvier nodes in myelinated axons of both the CNS and PNS [Arroyo et al., 2001; Poliak et al., 2003]. Furthermore, it seems to play a role in human cortical histogenesis as signs of neuronal migration anomalies were observed in brain samples of patients with a homozygous *CNTNAP2* mutation [Strauss et al., 2006].

The presynaptic neurexins like *NRXN1* and their postsynaptic binding partners, the neuroligins, are crucial synapse molecules [Li et al., 2007], with α -neurexins playing a role in normal neurotransmitter release and the function of synaptic calcium channels [Missler et al., 2003].

Recently, findings in *Drosophila* indicated that not only NrxF (NRXN1), but also NrxFIV (*CNTNAP2*) might be involved in synaptic organization and that both proteins might be linked by a common target, presynaptic protein bruchpilot [Zweier et al., 2009].

Mode of Inheritance

The mutations and deletions in the published patients were inherited in an autosomal recessive manner with homozygous or compound heterozygous defects in the patients and heterozygosity for 1 of the defects in each parent [Strauss et al., 2006; Jackman et al., 2009; Zweier et al., 2009]. The carrier parents were reported to be healthy; therefore, penetrance of clinical symptoms associated with heterozygous defects in either gene might be lower than possibly appreciated from previous reports on neuropsychiatric disorders [Verkerk et al., 2003; Feng et al., 2006; Autism Genome Project Consortium, 2007; Belloso et al., 2007; Alarcón et al., 2008; Arking et al., 2008; Bakkaloglu et al., 2008; Friedman et al., 2008; Kim et al., 2008; Kirov et al., 2008; Marshall et al., 2008; Vrijenhoek et al., 2008; Zahir et al., 2008; Bucan et al., 2009; Rujescu et al., 2009; Awadalla et al., 2010; Bradley et al., 2010; Ching et al., 2010; Magri et al., 2010; Mefford et al.,

2010; Wiśniowiecka-Kowalnik et al., 2010]. However, an increased risk for variable neuropsychiatric disorders has to be considered in carrier individuals.

Frequency of Certain Mutations/Copy Number Variations in Certain Patient Cohorts

The number of patients carrying recessive defects in *CNTNAP2* or *NRXN1* is too small to give frequencies of certain mutations/copy number variations. In the Amish population, 1 specific stop mutation c.3709delG in the C-terminal region of *CNTNAP2* is reported [Strauss et al., 2006]. The other published patients either harbor a homozygous deletion of exons 2–9 or a compound heterozygous intragenic deletion of exons 5–8 and a splice site mutation in exon 10 of *CNTNAP2* [Zweier et al., 2009]. For *NRXN1*, to date only a deletion of exons 1–4 in compound heterozygosity with a stop mutation in exon 15 is known.

Genotype-Phenotype Correlation

Some phenotypic differences such as lack of speech development versus regression or the presence/absence of cortical dysplasia and episodes of hyperbreathing between the Amish patients with the C-terminal stop mutation and the other patients with rather N-terminal defects in *CNTNAP2* can be noted [Zweier et al., 2009]. However, it remains currently elusive if these observations might indicate a real genotype-phenotype correlation or if they are due to clinical bias as the phenotype in the Amish patients was classified as an epilepsy syndrome with developmental deterioration, while the other patients were initially classified as having primary intellectual disability with epilepsy.

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