

Letter to the Editor

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To the editor,

With great interest we have read the original article “Homozygous GRN mutations: new phenotypes and new insights into pathological and molecular mechanisms” by Huin et al. (Huin et al. 2020)

Mono-allelic *GRN* (progranulin gene) mutations have been a well described cause of dementia (Galimberti et al. 2010; Baker et al. 2006), patho-physiologically presumed to be linked to low progranulin levels in serum (Ghidoni et al. 2012). Only more recently rare cases of bi-allelic *GRN* mutations have emerged (Smith et al. 2012; Almeida et al. 2016; Faber et al. 2017; Kamate et al. 2019) and have been linked to ceroid neuropilofuscinoses (CLN), a rare and heterogenous group of lysosomal storage disease. Subtype CLN11, caused by bi-allelic *GRN* mutations, is only grossly described phenotypically as juvenile onset epilepsy, vision loss and ataxia. For the first time Huin et al have managed to shed some light on the intriguing pathophysiological link between progranulin and lysosomal storage in neurons (Huin et al. 2020).

Furthermore, they describe three cases presenting clinical manifestations, that bear more resemblance to the previously well described mono-allelic form of fronto-temporal lobe dementia (FTLD) and propose an age-based distinction of these two different phenotypical manifestations of bi-allelic *GRN* mutations. In addition, they propose visual hallucinations as a “red flag” in neuronal ceroid lipofuscinoses and fronto-temporal dementias.

We would like to share clinical information from another four unrelated families with bi-allelic *GRN* mutations, as well as to provide follow-up data from all previously published cases.

Case reports

Family A (c.1477C>T, p.Arg493Ter, bi-allelic)

This is a Pakistani family with consanguineous parents (heterozygous carriers, healthy at 47 years of age). Two sons are homozygous and show a similar phenotype, the sister is a heterozygous carrier and currently asymptomatic.

The oldest 20-year-old son showed an unremarkable development (except for low school performance) until he presented with a bilateral tonic-clonic seizure arising during sleep at 10 years of age. Seizures became more frequent and eventually drug resistant (bilateral tonic-clonic seizures also during wakefulness, focal motor seizures with cloni, current medication VPA). In parallel a rapid decline of memory function as well as a loss of acquired memories was noted. He is currently only able to recall the names of his closest relatives. Furthermore, at the age of 12 years he started to experience progressive vision impairment, ataxia and a tremor.

His vision is currently heavily impaired, and his ataxia has worsened to complete wheelchair-dependence.

Cerebral MRI shows severe cerebellar atrophy, EEG reveals multifocal epileptiform discharges (maximum fronto-temporal region).

His 10-year-old brother developed normally until 7 years of age, when he presented with a focal impaired awareness seizure with lip smacking, head version and ictal vomiting lasting for two minutes. Seizure frequency since then varies between once every two months and once per year. His school performance has always been normal and has not changed after the development of seizures. Until now the neurological exam is unremarkable.

*Family B (c.813_816del, p.Thr272Serfs*10, bi-allelic)*

This is an Italian family from presumably distant consanguineous healthy parents (71 and 72 years). The first son (40 years) developed normally until the age of 15, when he presented with impaired vision, which deteriorated to complete blindness by the age of 20. At 20 years of age he presented a focal aware non motor (visual) onset bilateral tonic clonic seizure, followed by persistent focal awareness seizures with flashes in one part of the visual field (occurring 1-4 times per month) and occasionally progression to secondary generalisation (once per year). Seizures could only be partially reduced and are medically refractory (currently on valproic acid, carbamazepine). At the age of 25 years he developed ataxia, progressing slowly. At 40 years he needs support but is not wheelchair-bound. In addition, a steady cognitive decline of executive and memory functions has been noticed.

Cerebral MRI (cMRI) shows marked cerebellar with mild supratentorial atrophy, the EEG reveals slow background activity and rare epileptiform discharges over both posterior regions. Progranulin levels were undetectable.

The patient's sister is reported to have a similar clinical manifestation including vision impairment, seizures and ataxia, but did not agree to be examined.

Family C (del(17)(21.31); chr17: 42,425,910-42,456,209, bi-allelic)

This is a Kurdish-Iraqi family from consanguineous healthy parents (at age 33 and 34). The oldest daughter developed normally until presenting with a focal to bilateral tonic-clonic seizure

at 5 years of age. Seizure frequency increased leading to frequent seizure-related falls, despite multiple drugs only partial seizure control could be achieved (bilateral tonic clonic seizures momentarily controlled with levetiracetam, zonisamide and clobazam). She additionally developed ataxia and marked muscle weakness, along with visual impairment and nystagmus. At 15 years of age she is able to attend school, but performance has always been below average.

cMRI shows a marked supratentorial and mild cerebellar atrophy. EEG reveals slow background activity with multifocal epileptiform discharges, most prominent in the left posterior quadrant, but also present in the frontal regions. Whether visual auras precede focal seizures (given posterior focality of EEG) could not be determined due to a language barrier.

Family D (c.767_768insCC, bi-allelic)

This is a Brazilian family from consanguineous parents. The father died from an acute myocardial infarction and had not been tested for any genetic diseases, the mother is a confirmed heterozygous carrier and healthy at the age of 55 years.

The oldest daughter, aged 25 years, presented with progressive vision loss starting at 15 years and leading to blindness by the age of 19. Initial development up until then was unremarkable. At 19 years she developed focal non motor (visual) onset bilateral tonic clonic seizures as well as non-motor aware seizures with visual symptoms. Seizures were difficult to treat and required triple therapy with valproic acid, phenobarbital and topiramate. Her memory and executive functions decline after 19 years of age. At 20 years she also developed progressive ataxia and dysarthria, leading to severe disability.

Neurological examination showed ataxia and dysarthria, as well as severe cognitive impairment leading to apathy; ophthalmological evaluation revealed retinitis pigmentosa. The EEG showed slow background activity with generalized spikes as well as occipital spikes, elicitable during photostimulation. The cMRI revealed severe cerebellar atrophy.

The patient died from pneumonia aged 25 years. Two younger sisters and one younger brother are heterozygous carriers and are healthy.

Family E (c.1477C>T, bi-allelic)

This is a Caucasian 17.5 years old male from non-consanguineous parents, both asymptomatic (aged 36 and 38 years) heterozygous carrier of the same mutation. He has one younger sister aged 12 years, who was healthy at time of diagnosis. The extended family history is unremarkable.

Initial development was unremarkable and he was a grade-A student until onset of symptoms at the age of 10 with a spontaneous generalized tonic-clonic seizure. Following this he started showing behavioural abnormalities with reduced attention-span and declining school performance, needing transition to a special-needs-class aged 16. Tonic-clonic seizures continued to occur up to 4 times per year, with only one single episode of focal aware motor onset seizure with head cloni and impaired vision, and have become medically refractory (agents used were valproic acid, zonisamide, lacosamide), though adding clobazam in 03/2020 has led to seizure freedom until now.

At 15 years of age he additionally developed progressing visual impairment, dysphagia with moderate to severe impairment in pharyngeal phase of swallow and severe obstructive sleep-apnoea syndrome requiring uvulopalatopharyngoplasty. Neurological examination at 17.5years of age revealed additional dysmetria, and bull's eye maculopathy with temporal disc pallor.

EEG showed interictal generalized spike and wave complexes with photo-paroxysmal response. cMRI showed global atrophy (2019) following an unremarkable scan 6 years earlier. Laboratory investigations including full metabolic screening were normal (progranulin level was not measured)

Follow-up data

Previously to the paper published by Huin et al., only four families (five cases) of bi-allelic *GRN* mutations have been described as summarized by Huin et al. (Huin et al. 2020). We have contacted all authors and now provide clinical follow-up data of those four families in table 1. In summary ataxia and vision impairment worsened significantly in all cases over the years of follow up. Seizures were difficult to treat and have been medically refractory in most cases. Seizure control could be obtained in three cases (with four different antiepileptic agents), one case still suffers from occasional seizures and one is severely refractory. All patients showed mild to moderate cognitive impairment from the beginning, one has deteriorated dramatically (uncontrollable seizures).

Since the patient's parents (heterozygous carriers) at initial report might have been too young to manifest symptoms of dementia, we also inquired about any neurological symptoms within the immediate family. Three out of four families still have healthy parents (aged between 40 and 64 years), in one family both parents developed severe fronto-temporal lobe dementia, the mother (who also had additional features of corticobasal syndrome) has died as an immediate cause of her disease. In her family the mother suffered from dementia, two siblings suffer from dementia plus parkinsonian symptoms, two from corticobasal syndrome.

Conclusion

Huin et al propose an age-based clinical distinction of bi-allelic *GRN* mutations: juvenile-onset (CLN-like) and adult-onset (FTLD-like) phenotype. With the available clinical data (Huin et al. 2020 and the cases presented here) we would like to summarize juvenile-onset bi-allelic *GRN* mutations as follows:

1. Key symptoms are progressive vision impairment, ataxia (+/- dysarthria), pharmacologically refractory epilepsy, and mild to severe cognitive decline after normal initial development.
2. First symptom varies, but is mainly a seizure, followed by vision impairment and ataxia (seizure in 9 of 12 known cases and vision impairment in 3 of 12 cases)
3. Age of onset is variable. Reported cases vary between onset at 5 to 25 years.
4. Visual symptoms are described in 11 out of 12 cases. Most common is a progressive vision loss. Secondly, focal seizure onset with visual signs (or photo-sensitivity) are described (all in line with focal EEG abnormalities of the posterior regions). cMRI in these cases do not show corresponding structural abnormalities. We therefore strongly agree with Huin et al that visual symptoms (these may be visual hallucinations, visual auras or progressive vision loss) in addition to other CLN features should be a red flag for *GRN* testing.
5. Cognitive impairment is observed frequently (8 out of 12 cases) and seems to naturally progress if present. A correlation with generalizes tonic-clonic seizures is observable, but small sample number does not allow statistical analysis.
6. With regards to the natural progression of the disease, ataxia and vision impairment seem to worsen significantly over the years of follow up and are reported to be most debilitating. Early physiotherapy and ergotherapy should be advised. Generalized

seizures seem pharmacologically controllably in most cases, partial seizure remain difficult to treat.

7. Large ethnic variety
8. Family history of FTLD and in its absence explicitly screening for it as behavioral changes as one of the early symptoms of FTLD might be overlooked by family members.

Data availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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Competing interests

The authors report no competing interests.

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Figure Legend

Figure 1: Key points of clinical classification of early-onset bi-allelic GRN mutation (CLN11 phenotype)