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LETTER TO THE EDITOR

Early-onset phenotype of bi-allelic *GRN* mutations

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We read with great interest the original article 'Homozygous *GRN* mutations: new phenotypes and new insights into pathological and molecular mechanisms' by Huin *et al.* (2020).

Mono-allelic *GRN* (progranulin gene) mutations have been a well described cause of dementia (Baker *et al.*, 2006; Galimberti *et al.*, 2010), pathophysiologically presumed to be linked to low progranulin levels in serum (Ghidoni *et al.*, 2012). Only more recently have rare cases of bi-allelic *GRN* mutations emerged (Smith *et al.*, 2012; Almeida *et al.*, 2016; Faber *et al.*, 2017; Kamate *et al.*, 2019; Isik *et al.*, 2020) and have been linked to ceroid neurolipofuscinoses (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 frontotemporal 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 frontotemporal dementias.

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

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Case reports

Family A (NM_002087.3, c.1477C>T, p.Arg493Ter, bi-allelic)

Family A 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 valproic acid). 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, and EEG reveals multifocal epileptiform discharges (maximum frontotemporal 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 2 min. Seizure frequency since then varies between once every 2 months and once per year. His school performance has always been normal and has not changed following the development of seizures. To date the neurological exam is unremarkable.

Family B (NM_002087.3, c.813_816delCACT, p.Thr272Serfs*10, bi-allelic)

Family B is an Italian family from presumably distant consanguineous healthy parents (71 and 72 years old). The first son (40 years old) developed normally until the age of 15, when he presented with impaired vision, which deteriorated to complete blindness by the age of 20. At that time 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 one to four times per month) and occasionally progression to secondary generalization (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 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 and is bedridden and therefore not directly examinable.

Family C [del(17)(21.31); chr17: 42,425,910-42,456,209, deletion of the entire coding sequence, bi-allelic]

Family C is a Kurdish-Iraqi family from consanguineous healthy parents (at age 33 and 34). The eldest 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, and 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.

Cerebral MRI 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 (NM_002087.3, c.768_769dupCC; p.Gln257Profs*27 bi-allelic)

Family D 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 onset of symptoms 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 declined from the age of 19. At the age of 20 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, elicited during photostimulation. The cerebral MRI 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 (NM_002087.3, c.1477C > T, p.Arg493Ter, bi-allelic)

In Family E, the patient is a Caucasian 17.5-year-old male from non-consanguineous parents, both asymptomatic (aged 36 and 38 years) heterozygous carriers of the same mutation. He has one younger sister aged 12 years, who was healthy at the 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 began 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 four 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 March 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 the pharyngeal phase of swallow and severe obstructive sleep apnoea syndrome requiring uvulopalatopharyngoplasty. Neurological examination at 17.5 years 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. Cerebral MRI 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

Previous to the paper published by Huin *et al.* (2020), only four families (five cases) of bi-allelic *GRN* mutations had been described, as summarized by Huin *et al.* (2020). We have contacted all authors and now provide clinical follow-up data of those four families (Table 1). An additional case was published in April 2020 (Isik *et al.*, 2020). Given there is no follow-up data yet, it is not included 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 anti epileptic 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).

As 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 of the four families still have healthy parents (aged between 40 and 64 years), in one family both parents developed severe FTLD, the mother (who also had additional features of corticobasal syndrome) has died as an immediate consequence of her disease. In her family the mother suffered from dementia, two siblings suffer from dementia plus parkinsonian symptoms, and two from corticobasal syndrome.

Conclusion

Huin *et al.* proposed 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 (Box 1):

(i) Key symptoms are progressive vision impairment, ataxia (± dysarthria), pharmacologically refractory epilepsy, and mild-to-severe cognitive decline following normal initial development.

(ii) 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).

(iii) Among reported cases, age of onset was variable and ranged from 5 to 25 years.

(iv) Visual symptoms are described in 11 of 12 cases. Most common is a progressive vision loss. Second, focal seizure onset with visual signs (or photo-sensitivity) are described (all in line with focal EEG abnormalities of the posterior regions). Cerebral MRI in these cases does 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.

(v) Cognitive impairment is observed frequently (8 of 12 cases) and seems to naturally progress if present. A correlation with generalized tonic-clonic seizures is observable, but small sample number does not allow statistical analysis.

(vi) 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 remains difficult to treat.

(vii) Large ethnic variety.

(viii) Family history of FTLD needs to be carefully assessed. Explicit screening of relatives may be advised since behavioural changes as one of the early symptoms of FTLD may be overlooked by family members.

Table 1 Clinical follow-up data of all previously published bi-allelic GRN mutations

Published by	Faber *et al.* (2017)	Smith *et al.* (2012)	Smith *et al.* (2012)	Almeida *et al.* (2016)	Kamate *et al.* (2019)
Mutation	c.768_769dupCC p.Gln257Profs*27	c.813_816delCACT p.Thr272Serfs*10	c.900_901dupGT p.Ser301Cysfs*60	c.912G>A p.Trp304Ter	
Sex	Female	Female	Male	Female	Female
Age at last FU exam (date)	27 y (July 2018)	33 y (May 2019)	36 y (May 2019)	40 y (March 2020)	15 y (January 2020)
Parents	Healthy (mother 47 y, father 48 y)	Healthy (father 64 y, mother 60 y)	*Id.*	Heterozygous mother (died at 60 y) FTLD + features of CBS, heterozygous father (61 y) FTLDvb, severe state	Heterozygous, healthy (father 45 y, mother 40 y)
Other relatives	None reported ill	FTLD in maternal grandfather, paternal grandmother and great uncle	*Id.*	Maternal grandmother dementia (70 y), two maternal siblings dementia plus parkinsonian signs (50 y), two maternal siblings CBS (50 y)	Sister died at 16 y, seizures (8 y) and dementia, MRI cerebellar atrophy, no genetic testing
Neurological examination					
Motor signs	Ataxia worsened, wheelchair-bound, spasticity lower extremities, increased reflexes	Ataxia worsened, needs consistent help for walking	Ataxia worsened, needs consistent help for walking	Early ataxia (28 y), unable to walk at age 37 and at 40 y bedridden; mild pyramidal signs, dystonia	Wide gait, independent in all ADL, slight gait ataxia (new)
Vision impairment	Declined, still functional	Rapid vision loss (22 y), almost blind (35 y), retinal dystrophy	Deterioration of vision (25 y), almost blind, retinal dystrophy	Rapid progressive visual deficit with onset at 25 y; severe amaurosis at 28 y, retinal dystrophy	Vision still normal, fundoscopy normal
Memory dysfunction	Frontotemporal symptoms, severe decline, entirely dependent for ADL	No memory decline	Executive functions borderline	Mild memory dysfunction (started at 36 y)	Borderline IQ, poor short time memory, poor analytic functions, attends school (15 y), grades are falling
Psychiatric comorbidities	Mood lability and delusions (onset at 23 years), deteriorated to severe apathy, poor verbal contact	Visual hallucinations (enhanced by AED)	Mild depression	Very repetitive behaviour, anxiety, emotional lability since age 37	None
Epilepsy features					
Seizures controlled?	No	Yes	Yes	Yes	Partially
Type(s) of seizure	Focal (photosensitive) and generalized seizures persisted.	Non-motor onset (visual) impaired awareness bilateral tonic clonic seizures, visual symptoms 'new'	Non-motor onset (eye deviation) impaired awareness bilateral tonic clonic seizures	Jerks elicited by sudden sounds since the beginning, but not classified as epileptic	Tonic-clonic seizures (one short generalized seizure per year), photosensitivity
EEG pattern (at FU)	Slow wave background activity + epileptiform discharges in posterior regions during photostimulation	Background activity 7 Hz + brief sequences of slow waves + few spikes occipital regions	Background activity 7 Hz + brief sequences of slow waves + few spikes occipital regions	Normal at beginning; FU EEGs refused	Generalized epileptiform discharges, background activity normal (March 2019)
AEDs trialled (current AED)	LTG, LEV, CLB	Barbiturates, LEV, ZNS, VPA, PER	PB, VPA, LEV, ZNS, PER	n.a.	CBZ, CLB, LEV
Cerebral MRI	Global and severe cerebellar atrophy	n.a.	n.a.	Severe global atrophy with marked cerebellar atrophy	Cerebellar atrophy
Serum progranulin level	n.a.	<0.6 ng/ml (serum)	<0.6 ng/ml (serum)	<6 ng/ml (serum)	n.a.

ADL = activities of daily life; AED = anti-epileptic drug; CBS = corticobasal syndrome; CBZ = carbamazepine; CLB = clobazam; FTLD = frontotemporal lobe dementia; FTLDvb = frontotemporal dementia behavioural variant; FU = follow-up; LEV = levetiracetam; LTG = lamotrigine; n.a. = not available; PB = phenobarbital; PER = perampanel; VPA = valproic acid; ZNS = zonisamide. The reference sequence for *GRN* is NM_002087.3.

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

- Juvenile-onset epilepsy, often bilateral tonic-clonic seizures with focal (visual) seizure onset, followed by focal seizures, mostly pharmacologically refractory, usually first symptom
- Progressive vision impairment, can be first symptom, red flag for *GRN* testing among CLN variations
- Ataxia (± dysarthria), usually preceded by seizures and vision impairment, often debilitating within a few years
- Progressive cognitive impairment, after years of normal development, usually progressing slowly, sometimes severe manifestation
- Age of onset is variable. Reported cases vary between onset at 5 and 25 years of age
- Large ethnic variety
- Screening for FTLD in family members may be advised

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

H.Z.E. is an employee of GeneDx, Inc.

References

Almeida MR, Macário MC, Ramos L, Baldeiras I, Ribeiro MH, Santana I. Portuguese family with the co-occurrence of frontotemporal lobar degeneration and neuronal ceroid lipofuscinosis phenotypes due to progranulin gene mutation. Neurobiol Aging 2016; 41: 200.e1–5.

Baker M, Mackenzie IR, Pickering-Brown SM, Gass J, Rademakers R, Lindholm C, et al. Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17. Nature 2006; 442: 916–9.

Faber I, Prota JRM, Martinez ARM, Lopes-Cendes I, França MC. A new phenotype associated with homozygous GRN mutations: complicated spastic paraplegia. Eur J Neurol 2017; 24: e3–4.

Galimberti D, Fenoglio C, Cortini F, Serpente M, Venturelli E, Villa C, et al. GRN variability contributes to sporadic frontotemporal lobar degeneration. J Alzheimers Dis 2010; 19: S171–7.

Ghidoni R, Paterlini A, Benussi L. Circulating progranulin as a biomarker for neurodegenerative diseases. Am J Neurodegener Dis 2012; 1: 180–90.

Huin V, Barbier M, Bottani A, Lobrinus J, Alexander Clot F, Lamari F, et al. Homozygous GRN mutations: new phenotypes and new insights into pathological and molecular mechanisms. Brain 2020; 143: 303–19.

Isik E, Yilmaz S, Atik T, Aktan G, Onay H, Gokben S, et al. The utility of whole exome sequencing for identification of the molecular etiology in autosomal recessive developmental and epileptic encephalopathies. Neurol Sci 2020; 41: 3729–39.

Kamate M, Detroja M, Hattiholi V. Neuronal ceroid lipofuscinosis type-11 in an adolescent. Brain Dev 2019; 41: 542–5.

Smith KR, Damiano J, Franceschetti S, Carpenter S, Canafoglia L, Morbin M, et al. Strikingly different clinicopathological phenotypes determined by progranulin-mutation dosage. Am J Hum Genet 2012; 90: 1102–7.