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Deciphering the natural history of SCA7 in children

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Conflict of interests

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Abstract

Background: Childhood-onset autosomal dominant cerebellar ataxia type 7 (SCA7) is a severe disease which leads to premature loss of ambulation and death. Early diagnosis of SCA7 is of major importance for genetic counselling and still relies on specific genetic testing driven by clinical expertise. However, the precise phenotype and natural history of paediatric SCA7 has not yet been fully described. Our aim was i) to describe the natural history of SCA7 in a large multicentric series of children of all ages, ii) to find correlates to parameters defining this natural history.

Methods: We collected and analysed clinical data from 28 children with proven SCA7. All had clinical manifestations of SCA7 and either a definite number of CAG repeats in *ATXN7* or a long expansion >100 CAG.

Results: We identified four clinical presentations patterns related to the age at onset. Children of all groups of ages had cerebellar atrophy and retinal dystrophy. Our data combined with those of the literature suggest that definite ranges of CAG repeats determine paediatric SCA7 subtypes. The number of CAG repeats inversely correlated to all parameters of the natural history. The age at gait ataxia onset correlated accurately to the age at loss of walking ability and to the age at death.

Conclusion: SCA7 in children has four presentation patterns that are roughly correlated to the number of CAG repeats. Our depiction of the natural history of SCA7 in children may help monitoring the effect of future therapeutic trials.

Introduction

Autosomal dominant spinocerebellar ataxia type 7 (SCA7) was first identified as a dominant progressive cerebellar degeneration associated with progressive blindness (later found to be a cone-rod macular dystrophy) and coined as autosomal dominant cerebellar ataxia type II [1]. It is due to pathological CAG repeat expansions in the *ATXN7 g*ene [2,3]. Its product is involved in the transcriptional coactivator Spt-Ada-Gcn5 acetyltransferase complex, implicated in the development of the visual system in flies and zebrafish [4,5]. While normal alleles contain 4-35 CAG repeats in exon 1, individuals with SCA7 have 36 repeats or more. Alleles containing 28-35 CAG are not disease-causing but may expand (mutable normal alleles) [6]. The anticipation phenomenon in SCA7, i.e. the decreasing age at onset with successive generations, is due to the instability of this CAG repeats tending to expand during meiosis [7,8] and to the inverse correlation between the number of CAG repeats and the age at disease onset [9–11]. Larger expansions are more frequently transmitted by fathers rather than mothers [10,12]. Cerebellar ataxia usually precedes visual loss in patients with SCA7 beginning after 30 years, while the maculopathy usually comes first in patients with earlier onset [10,12]. Thus, the number of CAG repeats influences both the age at disease onset and clinical presentation patterns. This was also verified for children.

Children (<16 years old) in large SCA7 families presented with earlier motor and visual impairments, as well as earlier death as a consequence of a more severe progression of the disease correlated with larger CAG repeat expansions. Two paediatric clinical presentations have been identified: i) "juvenile SCA7" affecting children >3-4 years old, comprising progressive retinal and cerebellar degeneration [9,13,14], ii) "infantile SCA7" due to larger stretches of CAG, affecting children younger than 2 years old with retinal/neurological degeneration and cardiac involvement (patent ductus arteriosus, cardiac hypertrophy) [14–17]. Precise descriptions of these phenotypes have been provided in 14 patients carrying definite CAG expansions, including nine children with infantile SCA7[15–21] and five with the juvenile type aged 3-10 years [9,13,22,23]. Reports of children younger than 2 years old confirmed the infantile phenotype, to which kidney involvement due to glomerular and/or tubular dysfunction was added [17,21]. SCA7 in school-aged children, however, was associated with either neurological onset [9], ophthalmological onset [13,23], or concurrent neurological/ophthalmological involvements [22].

Knowledge of the clinical history of SCA7 is made necessary by i) the possible emergence of future therapies [24] ii) the inability of most whole exome sequencing pipelines to detect CAG expansions, implying that the disease must be clinically suspected to be detected. This study reports the largest clinical series of children with SCA7 to our knowledge. We aim to: i) emphasize the different natural histories of SCA7 in children to reassess its previous phenotypical classification, ii) establish potential correlates between parameters of the natural history (age at disease onset, age at gait ataxia onset, age at loss of ambulation and age at death) likely to predict the disease course, iii) identify the role of family histories in the making of the diagnosis of SCA7 in children and the transmission of pathological *ATXN7* alleles.

Patients and Methods

This study is based on data prospectively and retrospectively collected in medical records of children with SCA7, including those of the SPATAX registry (located at the ICM, Institut du Cerveau et de la Moelle Epinière, ethical IRB authorisation RBM-029) and through collaboration calls (DéfiScience, AnDDI-Rares and Brainteam French rare disease networks, Société Française de Neuropédiatrie and Société Européenne de Neuropédiatrie) over one year and a half. We included 28 patients from 25 families with first signs of SCA7 occurring between birth and 15 years old and with >36 CAG repeats. Participating referral paediatricians, geneticists and neurologists were asked to fill in a questionnaire to collect clinical, radiological and molecular data.

Molecular studies were performed in several laboratories after obtaining informed consents from patients' representatives. In six cases, the quality of the DNA samples and the methods used for the detection of CAG repeats allowed to determine the presence of a "large expansion" (LEx), i.e. above 100 repeats, but not the precise number of triplets.

We used the Wilcoxon-Mann Whitney test to compare two series of data, the Pearson's correlation test for linear correlations and Spearman's correlation test for non-linear correlations. We included patients of the literature with sufficiently detailed data for some of these calculations.

Results

Fifteen out of 28 patients with SCA7 were deceased at the time of the study, 11 were alive, two were missing. Sixteen (57.1%) were females, 12 (42.9%) were males.

Disease onset and duration. Detailed data are reported in Tables S1 (P1 and P2), S2 (P3 and P4), S3 (P5-P13) and S4 (P14-P28). Fig. 1 provides a graphical representation of these data. Mean age at onset was 6 ± 4.4 years (median age 6, range [0-15]). First signs of SCA7 were dependent on the age at onset : i) the two youngest affected children had hypotonia and global developmental delay from the first month of life, ii) motor regression with loss of sitting and standing abilities was the first sign in two older infants who had not achieved walking, iii) SCA7 started with gait ataxia in nine children aged 1.5 to 4.5 years who had achieved walking, and iv) visual symptoms initiated the disease in 15 children aged 6 years or older (in three of them gait ataxia appeared concurrently).

Mean age at death was 6.6 ± 5.1 years (median 4, range [1.8-19], n=15) after a mean disease duration of 3.2 ± 2.2 years (median 2.3, range [0.8-9], n=15). Mean age at onset of the deceased patient was 3.3 ± 3 years (median 1.8, range [0-10], n=15).

The age at death was correlated to the age at disease onset (Pearson $r=0.98$, $p<0.001$). Interestingly, the correlation was stronger with the age at gait ataxia onset ($r=0.99$, $p<0.001$), as shown in Fig. 2A. The linear relationship between the onset of ataxia and the age at death was defined as follows: age at death = age at ataxia onset x 1.58 + 0.78 ± 0.3 years.

Neurological involvement in the disease course. The two patients with neonatal hypotonia did not achieve developmental milestones, had severe feeding difficulties requiring gastrostomy and absent eye contact until they died. Neurodegeneration progressed rapidly in the two infants with motor regression before 1 year old. In the 12 patients with initially isolated visual symptoms, the neurological involvement appeared at a mean age of 13.2 ± 4.9 years (median 12, range [7-22

years]), i.e. 3.4 ± 2.2 years on average (median 3, range [1-8.5]) after ophthalmological symptoms. Considering all 24 patients who had achieved walking, gait ataxia worsened over time following different rates. Sixteen of them lost walking ability at a mean age of 10.9 ± 9.1 years (median 9.8, range [2-30]) and 2.8 ± 2.6 years on average after ataxia onset (median 1.5, range [0.3-8]). The age at loss of ambulation was unknown for four patients. The age at loss of ambulation was strongly correlated to the age at ataxia onset ($r=0.99$, $p<0.001$), as shown in Fig. 2B. The graphical depiction of this relationship gave a linear regression defined as follows: age at loss of ambulation = age at ataxia onset x 1.36 ± 0.73 years. The age at loss of ambulation was less strongly correlated to the age at disease onset ($r=0.97$ and $R^2=0.93$).

One patient had systematic neurological examinations because he was known to carry an *ATXN7* CAG repeat expansion. Others were assessed when neurological symptoms appeared. First neurological examinations of these patients disclosed signs of cerebellar involvement in all of them: gait ataxia (27/27), intention tremor (14/27), dysarthria (7/27), nystagmus (3/27) and/or slow saccades (4/27). Other oculomotor anomalies (strabismus n=3, vertical or horizontal ophthalmoplegia n=8) were present in 11/27 patients and palpebral ptosis in 3/27. Half of the patients (14/27) had signs of corticospinal tract involvement (brisk reflexes, Babinski sign and/or spasticity) and two had dystonic postures. Three had impaired proprioception. Nonepileptic myoclonic jerks appeared during the disease course in two individuals. They were associated with chorea in one of them. One infant had epilepsy. Most patients (n=26, 92.8%) had dysphagia at the time of the study. Swallowing difficulties required gastrostomy tube feeding in 14 of them (50%) at a mean age of 6.1 ± 4.5 years old (median 4.8, range [1.5-15], n= 12).

All children had normal head circumference. Brain MRI revealed cerebellar atrophy in 23/28 cases associated with brainstem atrophy in eight cases, irrespectively of the mode of disease presentation (Fig. S1).

Extra-cerebral involvement including retinal dystrophy. Visual decline was the first visual symptom in 12 patients; it was associated with dyschromatopsia in two of them and with photophobia in another. The first visual symptom was not specified in three patients. The precise age at complete visual loss was not determined. Fundoscopy examinations revealed a pigmentary retinal dystrophy (cone-rod dystrophy) in most patients (24/26), regardless of the first signs of the disease. One of them with a late onset also had optic atrophy confirmed by an OCT. Three patients had normal initial fundoscopy, including two in which the dystrophy appeared during the disease

course. The ERG was performed and found altered in 14 patients with a known abnormal fundoscopy; it was normal in one patient with normal fundoscopy before disease onset.
Three patients younger than 18 months at disease onset had a diagnosis of nephrotic syndrome at 20-24 months. One of them also had hypertrophic cardiomyopathy. None had structural cardiac anomalies. Poor weight gain was noted in three infants prior to swallowing difficulties.

Genotype/phenotype correlation. Affected children carried 52 to 235 CAG repeats in *ATXN7* (mean 89 ± 45; median 71, n=22) or a LEx (>100 CAG, n=6). Children with age at disease onset <5 years had >85 CAG repeats (up to 235, n=13) and those with age at disease onset >5 years old carried 52-76 CAG. The number of CAG repeats was negatively correlated to the age at disease onset (Spearman r=-0.97, p<0.001), the age at death (r=-0.92, p<0.001), the age at ataxia onset (r=-0.95, p<0.001) and the age at loss of ambulation (r=-0.97, p<0.001). These results are provided in Fig. 3 and Fig. 4.

Diagnoses and transmission. In 12/28 (42.8%) children, the diagnosis of SCA7 was made during the follow-up because one family member at least was known to be affected. In other cases, a neurological disease was known in the family but the diagnosis of SCA7 was not made (n=9) or no other family member with a neurological disorder was known (n=7, including one adopted patient). Six diagnoses were performed in deceased children after that of the affected parent. Six SCA7-transmitting parents were asymptomatic when the disease started in their children. In 5/16 cases, the diagnosis in affected children revealed the diagnosis in affected ascendants. The mean age at disease onset in affected parents was 27.9 ± 9.3 years (median 27, range [15-46] n=24).
SCA7 was transmitted by fathers in 17/27 cases (63%), by mothers in 10/27 (37%). The mean anticipation amplitudes (age at disease onset parent - age at disease onset child) were significantly larger for paternal transmissions than for maternal transmissions, (27.7 ± 8.2 *versus* 15 ± 5.4 years, Wilcoxon test p < 0.001). All four paediatric SCA7 with earliest age at disease onset (up to 1.5 years) were paternally transmitted (Fig. 5). SCA7 with age at disease onset >1.5 years was paternally and maternally transmitted in 60% and 40% of cases, respectively.
The number of CAG was known in 15 parent-child pairs, with similar increase of CAG repeats during paternal (49.1 ± 55, n=9) *versus* maternal (41.5 ± 42, n=6) transmission (Wilcoxon test p=0.5). In two patients, the CAG repeat expansion occurred *de novo* on paternal normal mutable alleles comprising 32 and 33 CAG.

Discussion

We report the first large series of children with SCA7. Analysed data suggest to distinguish four different types of clinical history. The current knowledge on childhood-onset SCA7 is based on family series with paediatric cases and on a small number of detailed clinical reports [25]. Series defined the general rules following which the number CAG repeats is inversely correlated to the age at disease onset, disease duration and the age at death [2,26]. Reports of single individuals or single families highlighted clinical differences between affected infants and older children resulting in their distribution into "infantile" and "juvenile" types.

The phenotypes of childhood-onset SCA7. Analysis of the clinical histories of SCA7 in infants younger than 1 year old showed that the disease may start either during the first month of life in children with hypotonia/developmental delay or may appear after a short period of normal development. Both groups were previously melted in the "infantile type" because they share extra-cerebral/retinal involvements. The two children of our series belonging to the first group had congenital hypotonia, poor eye contact and did not achieve initial developmental milestones, like one previously reported patient [16]. In other patients of the literature [15,17,19], hypotonia/developmental delay was mentioned at first examination (3-5 months old). Although it is unclear whether their hypotonia was congenital or not, their disease histories are close to that of our two patients (Table S1). Achievement of psychomotor skills was poor or null and their vital functions deteriorated within months. Poor weight gain was frequent, not only related to feeding difficulties, possibly to extra-cerebral involvements. Death occurred at age 0.4-2.3 years. The two infants of our series belonging to the second group had initially developed normally and motor regression occurred before they achieved walking as the first manifestation of SCA7. This clearly progressive course starting at 0.7-12 months old has been previously reported in three infants [18,20,21] (Table S2). Neurodegeneration progressed and death occurred at age 1.8-3 years old. Although having different developmental trajectories, infants of both groups shared common features: i) brain MRI showed cerebellar atrophy in most cases, sometimes associated with supratentorial [15,18] and/or brainstem atrophy, ii) retinal dystrophy was present in most of them, iii) extra-cerebral/retinal involvement may have occurred in the form of patent ductus arteriosus (in earliest cases) [15–17,27] or hypertrophic cardiomyopathy (both groups) [17,21] or various

renal dysfunctions (glomerular and/or tubular) [17,21], with nephrotic syndrome being the most frequent.

The term "juvenile SCA7" is usually used for school-aged children with normal development in "which the phenotype is indistinguishable from the adult cases except for earlier onset and faster progression" [15]. Our series agrees with this statement, except that the first signs of SCA7 are different according to the age at disease onset. In children aged 1.5-4.5 years old at disease onset, gait ataxia was the first manifestation of SCA7, whereas in children with onset >5 years old, visual disturbance initiated the disease. This is also verified in the literature reporting children with onset between 3-10 years old and a definite number of CAG repeats [9,13,22,23] (Table S3 and S4). Most children (7/9) of the first juvenile group also had retinal involvement at first fundoscopy or during the disease course. As previously suggested, "minor decrease of visual acuity may remain for years unnoticed [in this group of young children unable to express visual impairment]. This may be the reason why the ataxia appears as the first clinical symptom" [14]. However, functional visual impairment may become obvious with time [9]. Like in adults, besides ataxia, the progressive neurological course included intention tremor, dysarthria, pyramidal signs and less frequently ophthalmoplegia, in both groups. Death occurred as a consequence of neurodegeneration at 3-7 years old in the early juvenile group and after 9 years old in the late juvenile group. None of these children had extra-cerebral/retinal involvement.

To conclude, SCA7 in children of our series as well as in those of the literature comprises four clinical presentation patterns (Table 1). These four types define clinical frames into which clinical histories are homogeneous. They follow each other along the continuous chronological axis of the age at onset with which main features of the disease (i.e. ages at ataxia onset, at loss of ambulation and at death) are correlated.

Determinants of the natural history of SCA7 in children. It is well known that the number of *ATXN7* CAG repeats is negatively correlated to the age at disease onset and to the severity of SCA7 [7,9,10,27], which also applies to paediatric SCA7 (Fig. 3 and Fig. 4). In our series, phenotype/genotype correlation was hampered by the small number of patients, by the fact that the actual number of CAG repeats was not routinely provided by diagnostic laboratories (LEx) and by the relative accuracy of usual genetic testing. This may explain why expansions >85 CAG were found in all children of our series with onset <5 years old, including those with congenital, late infantile and early juvenile types, implying that it could not differentiate between them. However,

a partial correlation between the number of CAG repeats and clinical subtypes appears when combining our series and the literature, since all previously reported infants carried >180 CAG [15–21,27] and children with late juvenile SCA7 had <86 CAG [13,22,23]. Finally, combined data provide a provisional correlation between ranges of CAG repeats and ranges of ages of onset (Table 1).

The number of CAG repeats was inversely correlated to all studied parameters of the natural history. The number of CAG repeats was more significantly (inversely) correlated to the age at loss of ambulation and to the age at disease onset. Nevertheless, the error of prediction provided by the power regression curve remains notable for some individuals when considering their young ages (up to 3 years). The use of the number of CAG to predict the age at death is similarly limited.

The age at ataxia onset showed a strong and linear correlation to the age at death and to the age at loss of ambulation. This suggests that parameters influencing the variability of the age at disease onset / age at loss of ambulation / age at death are either similar or strongly interdependent. Our depiction of the natural history of SCA7 in children suggests that the age at ataxia onset allows to predict the age at loss of ambulation and the age at death with an accuracy of 1.5 and 0.6 years, respectively, for 95% of patients.

We conclude that i) ranges of CAG repeats roughly determine the age at disease onset to which parameters of the natural history of SCA7 in children are linked, ii) the age at ataxia onset is likely the best predictor of the age at loss of ambulation and of the age at death, which could be used for evaluating the efficacy of future therapeutic approaches.

Heredity and diagnosis. Several studies of affected parent/child pairs showed that paternal transmission of childhood-onset SCA7 was more frequent than maternal transmission [2,11,28], but this was "less obvious in the Swedish SCA7 families" [27]. In our series patients combined to 14 detailed paediatric cases, both paternal and maternal transmissions were found, with a higher number of paternally (n=29/41, 70.7%) *versus* maternally (n=12/41, 29.3%) transmitted pathogenic allele. This should be balanced by the rate of paternal *versus* maternal transmission decreasing with the age at disease onset (Fig. 5). Our data confirm that SCA7 with congenital onset (and likely larger expansions) is exclusively paternally transmitted, while late infantile SCA7 is mainly paternally transmitted, with rare occurrences of maternal transmissions in the literature [21,27]. However, the rate of paternal transmission is only moderately increased if one considers pathogenic *ATXN7* alleles responsible for early and late juvenile SCA7. These data

taken together are compatible with those provided by previous family series, including the Swedish one.

It is of utmost importance to make the diagnosis of SCA7 in children because of the high risk of recurrence in the kindred. Making the diagnosis is easy if an affected parent is known but becomes challenging otherwise [6]. This is partly due to the anticipation phenomenon, as in several cases of our series. True *de novo* occurrence of SCA7 is another pitfall. Although being a rare event [6,11,29], it was found in two patients of our series (7%). Moreover, the distinctive multisystemic involvement of infants with SCA7 may mislead clinicians into searching for inborn errors of metabolism, as previously outlined [19]. The clinical presentation of SCA2 in infants is close to that of SCA7, including a possible retinopathy [30,31]. The diagnosis of SCA2 needs specific genetic testing to reveal *ATXN2* CAG expansions. Thus, we would recommend to perform SCA7 (together with SCA2) testing in all cases of unexplained progressive cerebellar atrophy in children older than one year old, and in cases of unexplained neurodegenerative disease in younger infants, especially if associated with pigmentary retinopathy, cardiac and/or renal involvement. Concerns about familial consequences of this diagnosis, particularly for presymptomatic parents, should be kept in mind along the diagnostic process.

Data availability statement

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

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Supporting Information

Additional Supporting Information may be found in the online version of this article.

Figure S1. Brain MRI of: A patient P2 with congenital SCA7 (A1: T1-weighted sagittal section, A2: T2-weighted coronal section), B patient P5 with early juvenile SCA7 (B1 and B2: T1-weighted sagittal and coronal sections, respectively), C patient P15 and D patient P14 with late juvenile SCA7 (C1 and D1: T1-weighted sagittal sections, C2 and D2: T1-weighted coronal sections).

Table S1. Genetic and clinical data in eight patients with congenital SCA7.

Table S2. Genetic and clinical data in five patients with late infantile SCA7.

Table S3. Genetic and clinical findings of 10 patients with early juvenile SCA7.

Table S4. Genetic and clinical findings of 19 patients with late juvenile SCA7.

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Legend to Figures

Figure 1. Disease course in the 28 patients with childhood-onset of SCA7 of our series. Blue bars are for deceased patients, red bars for the living, and grey bars for those whom the age at death was unknown. Left end of the bar indicates the age at disease onset, the right end is for the age at death (blue), the current age (red) or the age at last examination (grey). Arrowheads on the left indicate the age of ataxia onset and those on the right the age at loss of walking ability (* is used if unknown, # for patients who never walked). Capital letters at the right end of each bar indicate the first sign of the disease: A is for gait ataxia, H for hypotonia, M for motor regression and V for visual disturbance. "+ECRI" means that the patients had extra-cerebral/retinal involvement. Numbers at the right of these letters indicate the number of CAG repeats or large CAG expansions (LEx).

Figure 2. Relationship between parameters of the natural history of SCA7 in children. Linear regression curves are shown in both panels. **2A**. Age at death (AD) according to the age at gait ataxia onset (AtO) in 11 patients of our series (blue dots) and three from the literature (red dots). The AD was strongly correlated to the AtO (Pearson r=0.99; p= <0.001, r was similar with or without patients from the literature). **2B**. Age at loss of walking ability (ALOWA) according to the age at gait ataxia onset in 16 patients of our series (blue dots) and two of the literature (red dots). Note that two dots/individuals are superimposed (with AtO=1.5, ALOWA=2.5) and the linear correlation (Pearson r=0.99; p<0.001, r was similar with or without patients from the literature) defined by ALOWA = AtO x 1.36.

Figure 3. Age at disease onset and age at gait ataxia onset according to the number of CAG repeats. A. Ages at disease onset (ADO) in 22 patients with SCA7 of our series (blue) and 14 of the literature (red), according to the number of CAG repeats. The six patients of our series with a LEx, i.e. undetermined numbers of CAG are not represented. As expected, the ADO and the number of CAG repeats were inversely correlated (Spearman r=-0.97; p<0.001). Note the linear distribution of ADO for CAG <86 and >170 and their more scattered distribution in between. **B.**

Ages at gait ataxia onset (AtO) according to the number of CAG repeats in 21 patients of our series (blue dots) and four from the literature (red dots) (Spearman r=-0.95; p <0.001). Note the distribution of AtO into two groups: AtO <6 years old with CAG <80 and AtO <6 years old with CAG >80.

Figure 4. Age at loss of ambulation and age at death according to the number of CAG repeats. A. Ages at loss of walking ability (ALOWA) according to the number of CAG repeats in 14 patients with SCA7 of our series (blue dots) and two from the literature (red dots) (Spearman r=-0.97; p <0.001). Note the distribution into two groups. **B.** Ages at death (AD) of 10 patients of our series (blue dots) and 11 from the literature (red dots) according to the number of CAG repeats. The six patients with a LEx were excluded. As expected, the AD was inversely correlated to the number of CAG repeats (Spearman r=-0.92; p<0.001).

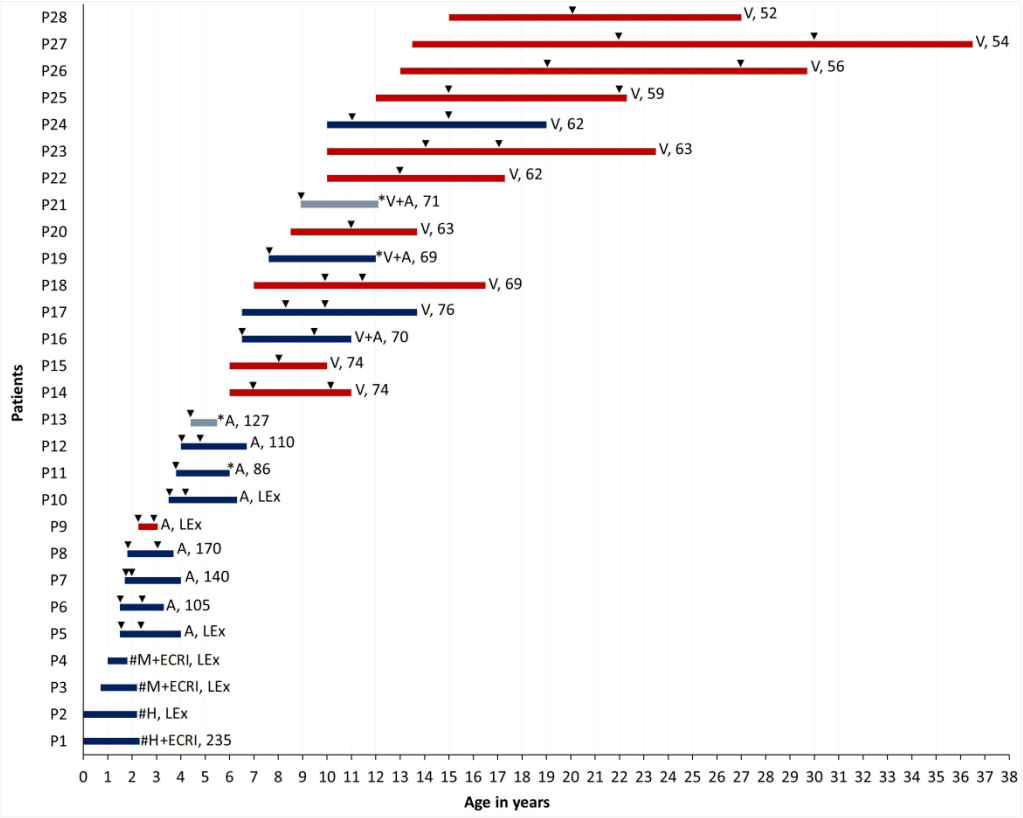
Figure 5. Parental transmission according to the age at disease onset in children with SCA7. Dots are for 14 children of the literature and squares for 27 of our series. The sex of the transmitting parent was unknown for P18. Blue-grey dots and squares are for paternal (pat) transmission, red dots and squares for maternal (mat) transmission.

Legend to Table

Table 1. Main features of the four phenotypes of childhood-onset SCA7

ADO: age at disease onset, AD: age at death, AtO: age of ataxia onset, n/a: not applicable, ALOWA: age at loss of walking ability, ECRI: extra-cerebral/retinal involvement, PDA: patent ductus arteriosus, HCM: hypertrophic cardiomyopathy, NP: nephrotic syndrome, RD: retinal dystrophy, OA: optic atrophy

Phenotype	CONGENITAL	LATE INFANTILE	EARLY JUVENILE	LATE JUVENILE
ADO (years)	0 - 0.5	0.8 - 1.5	1.5 - 4.5	5.0 - 15
First signs	hypotonia/GDD, failure to thrive	motor regression	gait ataxia	isolated visual loss 80% visual loss + ataxia 20%
AtO: mean/median	n/a	n/a	2.8 / 2.6	11.2 / 9.5
ALOWA: mean/median	n/a	n/a	3.2 / 3	15.7 / 11.5
AD (years)	0.4 - 2.3	1.8 - 3	3 - 7	>11 / survival >35
Fundus oculi	RD	RD	RD	RD +/- OA
ECRI	cardiac (PDA, HCM), renal (NP)	cardiac (HCM), renal (NP)	none	none
CAG repeats	>180	>180	86 - 170	52 - 85
Heredity	paternal 100% maternal 0%	paternal 80% maternal 20%	paternal 60% maternal 40%	paternal 61% maternal 39%



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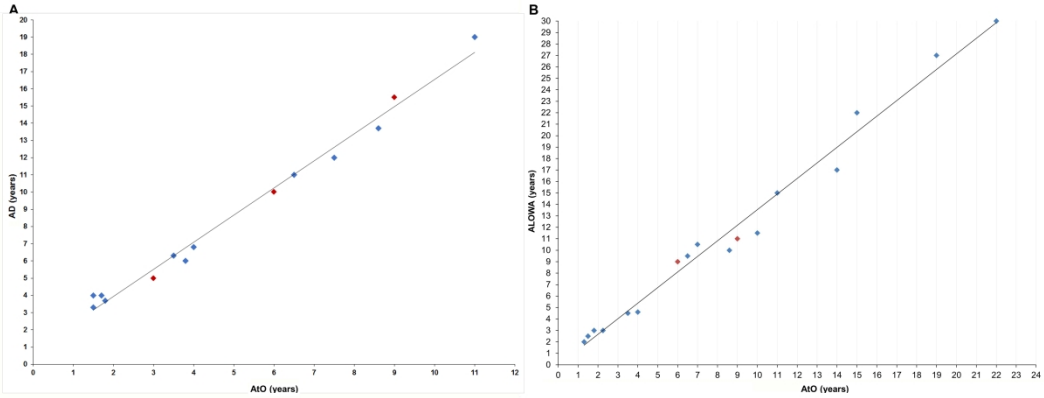

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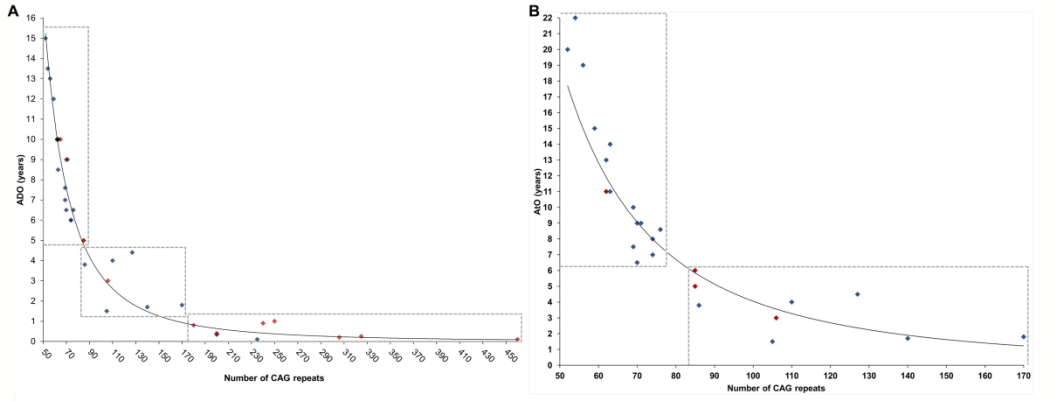

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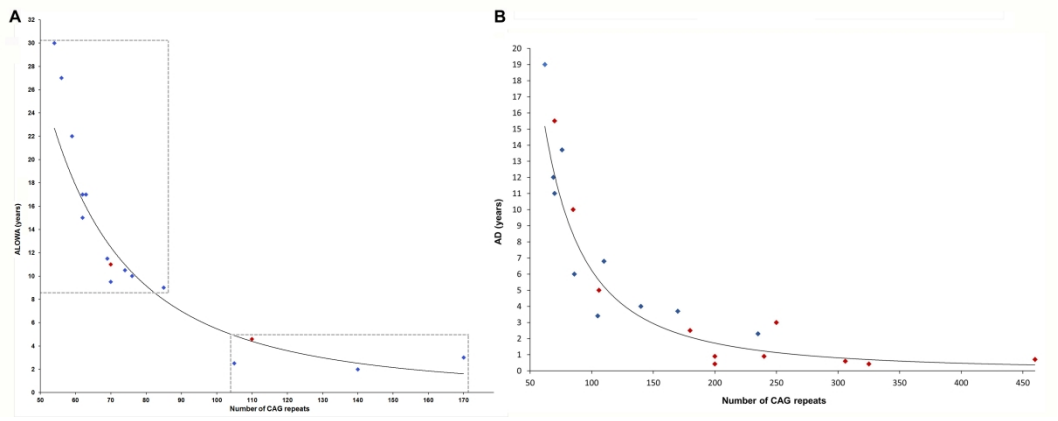

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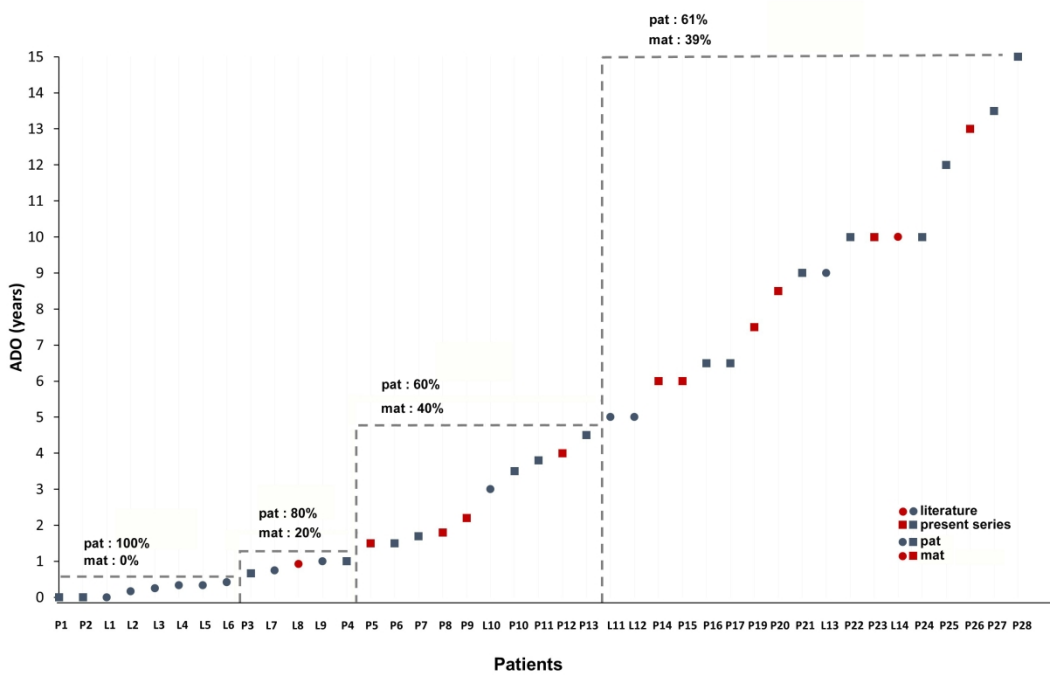

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