CLINICAL REPORT

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Biallelic Mutations in Huntington Disease: A New Case with Just One Affected Parent, Review of the Literature and Terminology

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Patients with biallelic mutations for Huntington disease (HD) are rare. We present a 46-year-old female with two expanded Huntingtin (*HTT*) alleles with just one known affected parent. This is the first reported patient with molecular studies performed to exclude *HTT* uniparental disomy (UPD). The proband had biparental inheritance of *HTT* alleles (42/44 CAG repeats). Given the negative UPD results, the proband's unaffected mother either had a reduced penetrance allele that expanded into the full mutation range during transmission to our patient or an unknown full *HTT* mutation and died before symptom onset, unlikely given no family history of HD and asymptomatic at age 59. We made the novel observation in our literature review that most patients with biallelic HD did not have two full *HTT* mutations. Most had one *HTT* allele that was in the intermediate or reduced penetrance ranges or 40 CAG repeats, the lowest limit of the full mutation range. Although the number of patients is small, when an allele in these size ranges was present, generally the age of HD onset was in the 50s. If the second *HTT* allele had >45 repeats, then onset was typically 20s–30s. While similar ages of onset have been reported for patients with one or two *HTT* mutations, patients with biallelic mutations may have later onset if an expanded *HTT* allele has ≤40 CAG repeats. Finally, we propose that "biallelic mutations" or "compound heterozygosity" are more accurate descriptive terms than "homozygosity" when there are two non-identical expanded *HTT* alleles. © 2015 Wiley Periodicals, Inc.

Key words: Huntington disease (HD); biallelic mutations; biallelic Huntington disease; compound heterozygote; compound heterozygosity; homozygotes; homozygosity; reduced penetrance alleles; intermediate alleles; uniparental disomy (UPD)

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INTRODUCTION

Huntington disease (HD) is an autosomal dominantly inherited neurological condition with progressive cognitive, motor, and psychiatric symptoms. The mean age of onset is 35–44 years [Warby et al., 1998]. Huntington disease is caused by a CAG trinucleotide repeat expansion in the *HTT* gene on chromosome 4 with repeat numbers defined as: full mutation (40 or more), reduced penetrance (36–39), intermediate (27–35) and normal (26 or less) [ACMG/ASHG Huntington Disease Genetic Testing Working Group 1998; Potter et al., 2004]. Intermediate and

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reduced penetrance alleles are unstable and can expand into the full mutation range when transmitted, primarily in paternal transmissions [Goldberg et al., 1993, 1995; Maat-Kievit et al., 2001a; Semaka et al., 2006, 2010, 2013a; Brocklebank et al., 2009; Sequeiros et al., 2010; Aziz et al., 2011; Semaka and Hayden, 2014].

The prevalence of HD is estimated to be 12–15/100,000 in individuals of European descent [Warby et al., 1998; Evans et al., 2013; Fisher and Hayden, 2014]. Patients with biallelic CAG expansion alleles have previously been described as "homozygous", but we suggest that the terms "biallelic" or "compound heterozygous" would be more accurate. Biallelic HD has occurred in diverse ethnic groups (Table I) and the prevalence in two large family studies of affected individuals ranged from 0.1%, N = 1007 [Kremer et al., 1994] to 0.4%, N = 263 [Alonso et al., 2002]. Studies of patients with biallelic HD have generally reported similar features, age of onset, and disease course as heterozygous individuals [Young et al., 1986; Wexler et al., 1987; Myers et al., 1989; Kremer et al., 1994; Durr et al., 1999; Laccone et al., 1999; Alonso et al., 2002; Costa et al., 2003]. One study [Squitieri et al., 2003a] suggested that the clinical course is more severe and progression more rapid in patients with biallelic HD.

In the absence of a second known affected parent and after excluding technical artifacts or limitations (e.g., primer issues, somatic mosaicism, very long repeats requiring Southern blotting for identification), possible explanations for biallelic HD include: (1) non-paternity (non-maternity is implausible except in IVF cases with egg donation or a father and present partner raising a child from an undisclosed previous relationship) (2) an intermediate or reduced penetrance *HTT* allele in the unaffected parent (3) a full mutation allele in an asymptomatic parent who died prematurely or has not lived long enough to develop symptoms (unlikely if no family history of HD) or (4) *HTT* uniparental isodisomy.

Uniparental disomy (UPD) occurs in a number of genetic conditions [Engel, 2006; Kotzot, 2008; Yamazawa et al., 2010]. Maternal UPD for chromosome 4 has been reported [Kuchinka et al., 2001; Spena et al., 2004; Middleton et al., 2006; Cottrell et al., 2012; Ding et al., 2012] and there is one published paternal segmental UPD(4) clinical report [Elli et al., 2012]. No reports of UPD for HD were identified in our literature review.

We present a 46-year-old female with biallelic *HTT* mutations with one affected parent (father), in whom we performed UPD testing to rule out the possibility that she inherited two paternal *HTT* alleles. We also reviewed the literature and summarize the genetic test results and ages of onset reported to date in individuals with biallelic HD.

MATERIALS AND METHODS

This study was approved by the University of Michigan Medical School Institutional Review Board, which operates under 45 CFR 46. Both the subject of this report and her husband provided informed consent.

Clinical Report

The 46-year-old female patient was evaluated by a neurologist (RLA) because of a 1–2 year history of progressive incoordination and declining memory. She had a history of recurrent depression requiring medical treatment. The patient reported increasing difficulty with performing her manual labor job. Family members noted involuntary limb movements. Saccadic eye movements were slowed with involuntary head turning and involuntary blinking during saccade initiation. There was a mild intermittent rotatory head tremor. Rapid finger movements were moderately slowed, tone and casual gait were normal, with mildly impaired tandem gait. Choreoathetosis was noted in fingers and toes.

Limited family history information (Fig. 1) and medical records were available. The patient's father was cared for by RLA and had HD, confirmed by autopsy, with onset in his early 50s and deceased at age 68. The patient had a brother and a sister. Her brother, also followed by RLA, developed HD in his late 20s and died at age 43; no genetic testing or autopsy was performed. By family report, her asymptomatic 37-year-old sister had positive presymptomatic genetic test results for HD. The children of the patient's siblings, two daughters and a son, were reported to be asymptomatic. The patient's mother died at age 59 of a cerebral aneurysm and was not reported to have a family history of HD or any other neurologic conditions. There was no parental consanguinity. The patient was diagnosed with manifest HD at age 46.

CAG Repeat Size Analysis and Uniparental Disomy Studies

A blood sample was obtained from the patient and DNA was isolated. The *HTT* gene was amplified in three separate reactions using the polymerase chain reaction (PCR) followed by capillary electrophoresis of the fluorescent PCR products to determine the CAG triplet repeat lengths. The three reactions amplify the $CAG_n + CCG_n$ region, the CCG_n region alone and the CAG_n region alone. These tests may not detect expansions of greater than 80 trinucleotide repeats. A Coriell cell line (NA13510) with 15 and 44 CAG repeats was used as a positive control (sequencing confirmed CAG repeat numbers).

Molecular polymorphism studies were performed to rule out the possibility that the patient had inherited two copies of the paternal *HTT* allele as a result of UPD. The patient's mother was deceased so no maternal DNA was available. DNA was isolated from the patient's blood sample and her deceased affected father's brain tissue. Markers used (Supplemental Online Table SI) included microsatellites flanking the *HTT* gene [primer information and mapping data is available for all microsatellites through the National Center for Biotechnology Information (NCBI)]. Markers were genotyped by PCR using fluorescently labeled primers, with PCR products quantified on an ABI 310 Prism Genetic Analyzer (ABI, Foster City, CA).

RESULTS

The result from the first reaction amplifying the $CAG_n + CCG_n$ region was 43 and 45 repeats. The result from the second reaction amplifying the CCG_n region alone was seven repeats. Amplifying

TABLE I. Studies that Reported Individuals with Biallelic Huntington Disease[1]

Study/year (location)	Number of patients with biallelic HD[1]	Parents' status	Parents related?	CAG repeat numbers (allele 1/allele 2)	Status/age (years) of onset or age at time of study if asymptomatic (A)	Gender (number)
Young et al. [1986] (Maracaibo, Venezuela)	18 (possible)	Both affected	Not provided but all from isolated community	Neurologic examination only	3-adult-onset 2-juvenile-onset 8-soft signs 5-, –	F (11) M (7)
Wexler et al. [1987] (Maracaibo, Venezuela)	4 (in same sibship)[2]	Both affected	First cousins once removed.[3]	Linkage	1-Definitive HD 1-Soft signs 1-Neurologically normal 1-, –	– – – –
Myers et al. [1989] (New England, USA)	4 (possible, in three sibships)	Both affected	First cousins (two matings), second cousins (one mating).	Linkage	34 46 58 74(A)	– – – –
Huntington's Disease Collaborative Research Group [1993] (Maracaibo, Venezuela and USA)	5 in same Venezuelan sibship[4]; 1-American family	Both affected –	Related by marker studies Likely related[5]	First CAG analysis report; specific repeat numbers not provided	"age of onset appears to parallel repeat length"[6]	– –
Kremer et al. [1994] (Worldwide study)[7]	2	1- Mother affected, father unaffected (died in 40s) 2- Father affected, mother unaffected and negative family history[8]	– –	37/43 39/42	50 25(A)	F F
Sanchez et al. [1996] (Spain)	1	Mother affected; father clinically normal	Not known to be related but both from same village of 700 inhabitants	40/53	54	F
Durr et al. [1999] (France)	1	Both affected	First cousins	42/46	33	M
Laccone et al. [1999] (Multicenter study in Austria, Germany, Switzerland)	23	–	–	39/62 39/43 21 with allele >39 had 2nd allele 31–39 repeats	22 55 –	– – –

TABLE I. (*Continued*)

Study/year (location)	Number of patients with biallelic HD[1]	Parents' status	Parents related?	CAG repeat numbers (allele 1/allele 2)	Status/age (years) of onset or age at time of study if asymptomatic (A)	Gender (number)
Maat-Kievit et al. [2001a] (The Netherlands)	3 (in same sibship)	Father affected, mother suspected affected	–	36/46	A (had children)	F
				36/46	A (reproductive age)	F
				36/45	A (had children)	M
Alonso et al. [2002] (Mexico)	1	Both suspected affected	Not known to be related but both from same town with <1,000 inhabitants	39/41	52	–
Costa et al. [2003] (Portugal)	6	1- mother affected	–	39/51	31	M
		2- mother affected	–	36/47	24(A)	F
		3- mother affected	–	32/43	51	F
		4- father affected	–	32/42	50	F
		5- father affected	–	29/52	32	M
		6- mother affected	–	28/49	28	F
Squitieri et al. [2003a] (Multicenter study in Australia, Canada, France, Italy, Scotland)	8	1-mother affected	–	42/44	57	M
		2-both affected	–	40/46	57	F
		3-mother affected	–	40/44	49	M
		4-, –	–	40/41	58	F
		5-mother affected	–	39/43	40	F
		6-both suspected affected	–	37/40	60	M
		7-mother suspected	–	36/44	51	F
		8-, –	–	36/37	45	M
Wexler et al. [2004]/The U.S.-Venezuela Collaborative Research Project (Maracaibo, Venezuela)	18[9]	Not provided but in earlier studies both parents were reported affected	Not provided but all from isolated community. In earlier studies, consanguinity reported in some cases.	15-both alleles $\geq$ 40	12/15 had mean age of onset 28.75 ± 6.17[10]	–
					3/15, –	–
				3-1 allele $\geq$ 40 and 2nd allele 35–39	3/3 had mean age of onset 35.33 ± 7.23[10]	–
Lee et al. [2012] (HD-MAPS, COHORT, PREDICT-HD, REGISTRY, Massachusetts, USA)	10	–	–	42/42	–	–
				8 – 1 allele 35–39[11]	4 had onset 50s+[11]	–
Shi et al. [2012] (China – Han ethnic group)	1	Mother affected (42/20). Father unaffected at age 66 (37/17)	Not known to be related	37/42	38(A)	–

TABLE I. (Continued)

Study/year (location)	Number of patients with biallelic HD[1]	Parents' status	Parents related?	CAG repeat numbers (allele 1/allele 2)	Status/age (years) of onset or age at time of study if asymptomatic (A)	Gender (number)
Uhlmann et al. (Michigan, USA)	1	Father affected (21/42). Mother unaffected (died at 59) and had negative family history	Not known to be related	42/44[12]	~44	F

The studies are presented by publication date to provide a historic perspective. Given that several studies were on individuals from Maracaibo, Venezuela, some of the same patients may appear in multiple studies. In some studies, neurological status was not provided either to preserve patient confidentiality, the objectivity of researchers, or because participants were too young for symptom onset. CAG repeat ranges: Normal (≤26), Intermediate (27–35), Reduced Penetrance (36–39), Huntington Disease (>39)
F- Female, M - male; A- asymptomatic; –, not provided.
[1]In the literature, these studies use the terms "homozygotes," "homozygous" and "homozygosity" for Huntington disease.
[2]Likely these individuals were included in Young et al. [1986] study.
[3]Figure text states parents of homozygotes are second cousins once removed but pedigree shows they are 1st cousins once removed (Figure 1, p. 195).
[4]Same homozygotes reported by Wexler et al. [1987].
[5]Figure legend states individual homozygous for the same HD chromosome (Figure 8, p. 978).
[6]p. 978.
[7]Six continents, 43 national and ethnic groups including individuals of Canadian, European, Asian, black South African, Arab and Native American descent.
[8]She was a 57-year-old control subject, with no family history of HD in >3 generations, and unexpectedly was found to have 39 CAG repeats.
[9]Presume some individuals were included in above Venezuela studies.
[10]Members of Venezuelan kindreds manifest statistically significant earlier ages of HD onset in comparison to Americans and Canadians (p. 3502). Of note, age of onset was later when one *HTT* allele in the compound heterozygotes had 35–39 CAG repeats.
[11]Figure 1C, p. 691.
[12]Asymptomatic son was presymptomatic positive for HD (18/44 CAG repeats). Deceased brother (43) had HD onset late 20s. Asymptomatic sister had positive presymptomatic genetic test results for HD by report (results unavailable).

the CAG region alone yielded 42 and 44 repeats. No normal alleles were seen. A second blood sample was obtained from the patient, which confirmed these results. As two different allele sizes were observed, a regional deletion or allele drop-out was unlikely. A combination of allele drop-out and somatic mosaicism of the single paternal allele remained a possibility. The CAG studies performed on the father's brain tissue yielded 21 and 42 repeats. The patient's asymptomatic son had presymptomatic genetic testing and had 18 and 44 CAG repeats; this sample was run concurrently with the mother's sample. Therefore, analysis of samples from the patient's father and son further confirmed the presence of two allele sizes of 42 and 44 repeats.

When testing for UPD in the patient, a non-paternal (presumably maternal) allele was noted for five chromosome 4 markers used including D4S127, which is located less than 40 kb telomeric to the first exon of the HD gene, and D4S412. The D4S412 marker was informative on the centromeric side and is located approximately 100 kb from the centromeric side of the HD gene. Thus, segmental UPD was essentially ruled out.

DISCUSSION

This is the first reported patient with biallelic *HTT* mutations where UPD was excluded. The patient had two *HTT* alleles in the full mutation range and one of the higher combinations of CAG repeat numbers (42/44) reported to date (Table I). Only one parent had diagnosed HD and the patient's parents were not related and did not come from a small community.

Given that only the patient's father was known to be affected with HD and the rarity of biallelic mutations for this condition, it was important to confirm this finding and determine etiology. Uniparental disomy was regarded as an unlikely cause because it has not been documented for HD and all but one patient [Elli et al., 2012] with reported UPD(4) to date have been maternal in origin [Kuchinka et al., 2001; Spena et al., 2004; Middleton et al., 2006; Cottrell et al., 2012; Ding et al., 2012]. We excluded full and segmental paternal UPD. Non-maternity is quite rare and there was no reason to consider it in this family. We believe that the patient's mother either had (1) a reduced penetrance allele that expanded into the full mutation range during transmission to the patient (a rare event) or (2) an unknown full *HTT* mutation and died before symptom onset (unlikely given no family history of HD and lack of symptoms at age 59).

Unaffected Parent Could Have a Reduced Penetrance or Intermediate Allele

When a patient with HD and biallelic *HTT* mutations has just one affected parent, the unaffected parent with no family history of HD could have a reduced penetrance or an intermediate *HTT* allele. This *HTT* allele could be stably transmitted, contract (less common) or expand, even into the full mutation range. In the general population, approximately 1–6% of individuals have an intermediate allele and approximtely1–3% have a reduced penetrance allele [Huntington's Disease Collaborative Research Group, 1993; Kremer et al., 1994; Goldberg et al., 1995; Raskin et al., 2000; Maat-Kievit et al., 2001a, b; Tassiker et al., 2006;

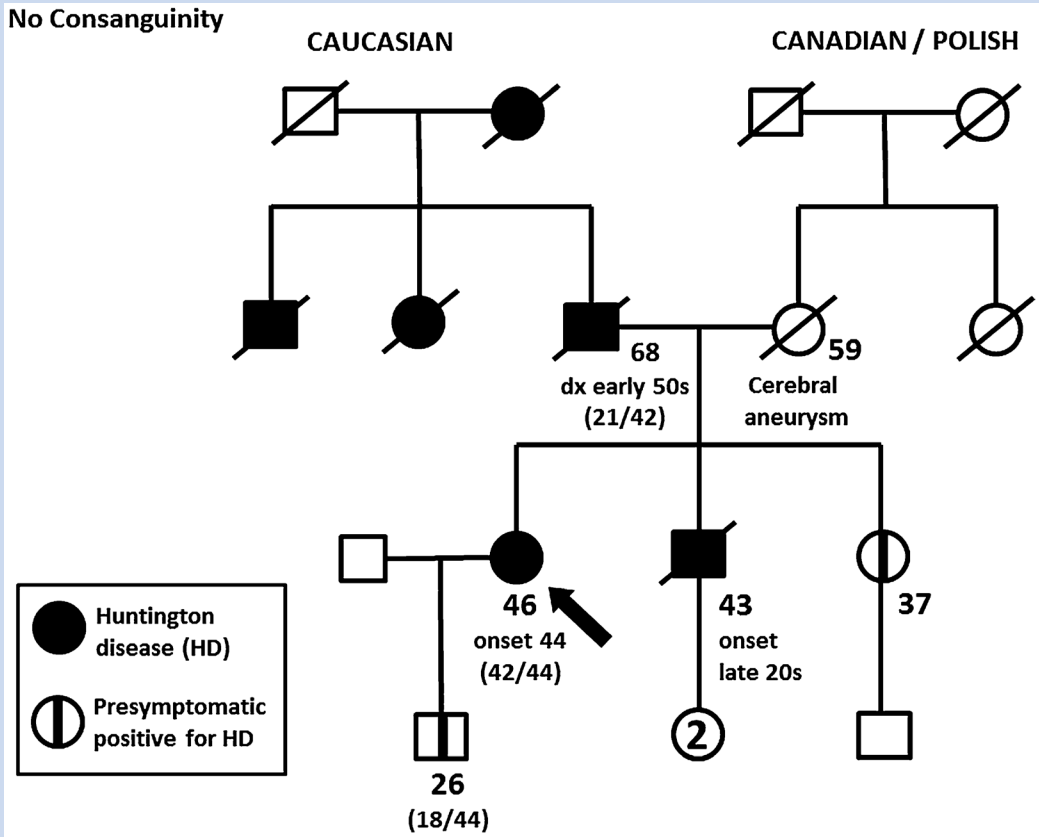

FIG. 1. Pedigree. The known CAG repeat numbers for each *HTT* allele are in parentheses.

Sequeiros et al., 2010; Squitieri and Jankovic, 2012; Semaka et al., 2013b; Semaka and Hayden, 2014].

In our literature review, we noted a number of patients with HD and biallelic mutations with just one affected parent and most of these patients had an intermediate or reduced penetrance allele (Table I). There were three reported patients with both *HTT* alleles in the full mutation range and just one parent (mother) affected: 40/53 repeats [Sanchez et al., 1996], 42/44 and 40/44 repeats [Squitieri et al., 2003a]. Of note, one of Squitieri et al.'s patients had the identical number of CAG repeats as the patient reported here, but a later age of onset (57).

We think it is unlikely that the present patient's mother had an intermediate *HTT* allele because except for one reported patient [Semaka et al., 2015], maternal expansion of an intermediate allele into a full HD mutation has not been reported [Goldberg et al., 1993; Kremer et al., 1995; Maat-Kievit et al., 2001a; Semaka et al., 2006, 2010; Brocklebank et al., 2009; Semaka and Hayden, 2014]. Although rare, maternal expansions of reduced penetrance *HTT* alleles into the full mutation range have been reported [Sanchez et al., 1997; Laccone and Christian, 2000; Brocklebank et al., 2009; Aziz et al., 2011] and this may have occurred with the patient reported here.

Higher Prevalence of an *HTT* Allele $\leq$ 40 repeats in Biallelic HD and Age of Onset

In our review of the literature (Table I), we made the novel observation that most patients with HD and biallelic mutations (reported as homozygous HD) did not have two full mutations. Most patients had one *HTT* allele in the reduced penetrance or intermediate ranges or at 40 CAG repeats, the lower limit of the full mutation range. Excluding the Venezuela cases (where overall age of onset is thought to be earlier in this extended pedigree), there were 12 patients with onset at age 49 or older and 11 had an allele with 40 or less repeats (the exception is Squitieri et al., [2003a] patient with 42/44 repeats). Five patients had onset at ages 22–33 and all had an allele >45 repeats. For the three patients with both alleles >40, age of onset ranged from 33 to 57.

It was suggested in the literature that patients with biallelic mutations have a similar age of onset as do heterozygotes [Young et al., 1986; Wexler et al., 1987; Myers et al., 1989; Kremer et al., 1994; Durr et al., 1999; Laccone et al., 1999; Alonso et al., 2002; Costa et al., 2003]. Lee et al. [2012] concluded that the presence of a second *HTT* allele did not significantly impact the age of onset of motor symptoms of HD, which they found was primarily deter-

mined by the larger expanded allele. In our compilation of reports (Table I), patients who had biallelic mutations with an expanded *HTT* allele ≤40 CAG repeats generally had symptoms starting in their 50s, which is later than the mean age of HD onset [Warby et al., 1998]. This interpretation is based on a limited number of patients and therefore should be corroborated with a larger number of patients with biallelic mutations. While a later age of HD onset has also been seen in individuals with large normal alleles [Snell et al., 1993; Djousse et al., 2003; Aziz et al., 2009], our interpretation is problematic because it would imply that patients with no normal *HTT* alleles may have a later age of onset than those with just one expanded allele; further investigation is warranted.

Terminology

In our literature review, "homozygotes" was the term universally used to describe individuals with two expanded *HTT* alleles. We propose that "biallelic HD/mutations/expansions" (preferred) or "compound heterozygotes" rather than "homozygotes" are more accurate terms to describe individuals with two expanded *HTT* alleles not identical by descent. The terms "biallelic mutations" and "compound heterozygosity" are used with other autosomal dominant conditions including familial hypercholesterolemia [Yao et al., 2012; Youngblom and Knowles, 2014] facioscapulohumeral muscular dystrophy [Scionti et al., 2012] and hereditary colorectal cancer [Lindor, 2009].

Genetic Counseling

Biallelic HD has significant risk implications for offspring (obligate heterozygotes for an expanded *HTT* allele), the patient's siblings (75% risk to have one or both expanded *HTT* alleles), the patient's parents (obligate heterozygotes) and other relatives. There are challenging counseling and ethical issues to consider when biallelic HD is discovered [Alonso et al., 2002; Costa et al., 2003; Squitieri et al., 2003b]. The ages of children, timing of disclosure, "do no harm" and the preservation of the "right not to know" are significant considerations.

When a patient with biallelic HD is identified with just one affected parent (and parentage is certain) and the other parent has no family history of HD, a likely explanation is that the unaffected parent has an intermediate or reduced penetrance *HTT* allele that has either been stably transmitted or expanded. If the patient with biallelic HD has two full mutations and the mother is unaffected, it is highly likely that she has a reduced penetrance allele. An unaffected father could have a reduced penetrance (more likely) or an intermediate allele that expands upon transmission.

Although the number of reports is limited, we noted in our review that most patients with biallelic HD do not have two full mutations and those with one expanded *HTT* allele of ≤40 CAG repeats generally had onset in their 50s. This could have significant implications for recurrence risks. Analyses of more individuals with biallelic HD and comparison of both of their *HTT* alleles to the known mean ages of onset for the CAG repeats will be important for both assessing if patients with one or two *HTT* mutations have differential ages of onset and providing accurate onset information.

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