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A United States-based patient-reported adult polyglucosan body disease registry: initial results

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Abstract

Background: Adult Polyglucosan Body Disease (APBD) is an ultra-rare, genetic neurodegenerative disorder caused by autosomal recessive mutations in the glycogen branching enzyme gene. Knowledge of the demographic and clinical characteristics of APBD patients and the natural history of the disease is lacking. We report here initial results from a patient-reported registry of APBD patients.

Objectives: (1) Maximize the quality of the APBD Registry survey data; (2) provide an initial report on APBD disease progression and natural history using these data; and (3) specify next steps in the process for testing potential new therapies.

Design: Data are from members of the APBD Research Foundation (New York), surveyed from 2014 by the Columbia APBD Patient/Family (CAP) Registry. Inclusion criteria are: disease onset at age 18+ and progressive clinical triad of peripheral neuropathy, spasticity, and neurogenic bladder.

Methods: Genetic testing results were used when available. Respondents found to not have APBD in clinical records were excluded. All changes and exclusions were recorded in a database edit log. Results are reported in frequency tables, bar graphs, time plots, and heat maps.

Results: The 96 respondents meeting inclusion criteria were predominantly (96.8%) White, highly educated (89.3% at least some college education), and mostly (85.1%) of Ashkenazi Jewish descent. 57.1% had at least one parent born in the United States, with at least one grandparent from Europe (excluding Russia; 75.4%), the United States (42.1%), or Russia (33.3%). 37.2% reported a family history of APBD, and 33.3% had an affected sibling. Median APBD onset age was 51 [Interquartile range (IQR) 11], and median age of diagnosis 57 (IQR 10.5). The 75 reported prior misdiagnoses were mainly peripheral neuropathy (43, 60.6%) and spinal stenosis (11, 15.1%).

Conclusion: Although from a demographically constricted survey, the results provide basic clinical information for future studies to develop treatments for APBD.

Plain language summary

A United States based patient-reported adult polyglucosan body disease registry: initial results

Adult Polyglucosan Body Disease, or APBD, is an ultra-rare neurological disorder caused by mutations of the GBE1 gene. While potential therapies exist, to establish if they work we need a "natural history" study that shows the normal path of the disease. Our goal was to provide the first patient-reported natural history study of APBD.

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We analyzed survey data from 96 patients recruited by the APBD Research Foundation (New York), aged 18 or older, who self-reported having APBD. We maximized data quality by using results from genetic testing when these were available, and by excluding respondents if we could not review clinical records confirming they had APBD.

More than 95% of our 96 patients were white. They were highly educated: 89% had at least some college education. Most (85%) were of Ashkenazi Jewish descent. More than half (57.1%) had a parent born in the United States. Many had at least one grandparent from Europe (excluding Russia) (75.4%), the United States (42.1%), or Russia (33.3%). More than a third (37%) reported a family history of APBD, and a third reported that they had a brother or a sister with a history of the disease. Their average age at APBD onset was 51, and their average age at APBD diagnosis was 57. Previous misdiagnoses were common: 75 were reported. Most were for peripheral neuropathy (60.6%) or spinal stenosis (16.7%).

Although our data come from a survey of patients who are demographically similar, they provide a report on the characteristics of patients with APBD and basic information that is essential for studies to develop treatments for the disease.

Keywords: Adult polyglucosan body disease, clinical manifestations, demographics, registry

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Introduction

Adult Polyglucosan Body Disease (APBD) is an ultra-rare, genetic neurodegenerative disorder characterized by progressive spastic paraparesis, sensory deficits in the distal limbs, neurogenic bladder, gait impairment leading to loss of ambulation, and premature death due to complications of myelopathy and peripheral neuropathy.[1,2] It is caused by autosomal recessive mutations in the glycogen branching enzyme gene (*GBE1*) that diminishes enzyme activity to 8–25% of normal levels, and symptoms typically present after the fifth decade of life. The neuropathological hallmarks of APBD are polyglucosan bodies (PBs), which are accumulations of sparsely branched insoluble glycogen both in the central and peripheral nervous system. In neurons, PBs in axons impair flow of cellular components between the cell body and peripheral terminals and lead to central nervous system demyelination, gliosis, and degeneration of peripheral nerves.[3–9] In part due to its rarity, the disease is often initially misdiagnosed as multiple sclerosis, benign prostatic hypertrophy, or amyotrophic lateral sclerosis.[1,2]

In APBD, the ratio of glycogen synthase to GBE activity is increased. This indicates targets for potential therapies,[10,11] such as decreasing glycogen synthase activity or increasing GBE activity *via* antisense oligonucleotide treatments to correct splicing of intronic mutations[12] or viral mediated gene replacement therapy.[13] There are also therapeutic efforts to decrease polyglucosan accumulation with small molecules.[10,14] However, these drug development efforts, and any eventual clinical trials, will require detailed knowledge about the natural history of the disease. While one prior publication reports its natural history retrospectively in a small cohort of subjects ($N=50$),[15] there is a dearth of information on the natural history of the disease. This is primarily due to its ultra-rarity; there are over 200 genetically confirmed APBD cases worldwide, though it is estimated to affect up to 4000 individuals globally, the majority of whom are of Ashkenazi Jewish descent.[16,17] To overcome the challenges presented by a small prevalence, we used a patient-reported registry to perform the largest natural history study of APBD to date.

Aims and research objectives

This project analyzes and reports on data from the first patient-reported registry for APBD which was launched in 2014. The Columbia University APBD (CAP) registry is a collaboration between Columbia University Irving Medical Center APBD investigators and the APBD Research

Foundation leaders and its Scientific Advisory Board. The Foundation team shared information about the CAP registry with its community *via* the Foundation website and newsletters. Additionally, they contacted patients and family members to inform them about the importance of participating in the registry and support the recruitment efforts. The specific objectives for the analysis were: (1) to maximize the quality of the APBD Registry survey data; (2) to provide an initial report on APBD disease progression and natural history using these data; and (3) to specify next steps in the process for testing potential new therapies.

Methods

The data collected in the APBD survey include demographics, age-at-diagnosis, age-at-onset, birth country of parents and grandparents, parents' consanguinity, and family history of APBD. The criteria for inclusion in the current analysis are the disease onset of at least 18 years of age and progressive manifestation of symptoms, signs, or both of the triad of peripheral neuropathy, spasticity, and neurogenic bladder.

To achieve our first goal of maximizing data quality, free-text responses on parents' and grandparents' countries of birth were standardized to generate accurate frequency counts. Duplicate dataset entries with conflicting information were then reconciled. Although the earliest age-at-onset for APBD has not been clearly defined, some previous research has used 30 years as the criterion. To investigate this question, in addition to the inclusion criterion of onset at 18 years and older, the clinicians reviewed all cases with a reported onset age of 30 or younger. Needed clarifications on variables of interest were sought from patients for whom contact information was available. Variables were updated for those who responded, and missing values recorded for those who did not. Genetic testing results were used when available. Respondents found to not have APBD in clinical records available to the clinical team were excluded. A detailed database edit log recording all changes and exclusions was created.

The results are reported in frequency tables, bar graphs, time plots, and heat maps.

Table 1. APBD respondent demographics (Overall $N = 96$).

Demographic information	*N* (%)
Sex ($N = 94$)	
Male	51 (54.3)
Race ($N = 92$)	
American Indian/Alaska Native	0 (0.0)
Asian	0 (0.0)
Black/African American	1 (1.1)
Native Hawaiian/Pacific Islander	1 (1.1)
White	91 (96.8)
Other/More than one	1 (1.1)
Ethnicity ($N = 88$)	
Non-Hispanic	87 (98.9)
Ashkenazi Jewish descent ($N = 87$)	
Yes	74 (85.1)
Highest completed education ($N = 66$)	
Some education, but no high school diploma	2 (3.1)
High school graduate	5 (7.7)
Business, trade, vocational school or some college	10 (15.4)
College or university graduate	25 (38.5)
Professional training beyond a 4-year college or university	23 (35.4)

APBD, adult polyglucosan body disease.

Results

126 individuals responded to the initial APBD Research Foundation survey. After data review and cleaning, 96 of these met the criteria for APBD and are included in the current analysis. Table 1 reports their demographic characteristics. Median age of APBD onset is 51 (IQR 11), and median age of diagnosis is 57 (IQR 10.5; Table 2).

Our 96 respondents reported receiving a total of 75 prior misdiagnoses from a pre-specified list of peripheral neuropathy, spinal stenosis, amyotrophic lateral sclerosis (ALS), multiple sclerosis

Table 2. Age at APBD Onset and Diagnosis.

Ages at onset and at diagnosis	Median	IQR	Min	Max
Age at onset (*N* = 92)	51	11.0	22	67
Age at diagnosis (*N* = 91)	57	10.5	23	73

APBD, adult polyglucosan body disease; IQR, Interquartile range.

Table 3. Previous Misdiagnoses Reported by APBD Patients (Overall *N* = 96 patients).

Query (*N* of patients responding)	*N* reporting misdiagnosis (%)
Neuropathy (*N* = 71)	43 (60.6)
Spinal stenosis (*N* = 66)	11 (16.7)
Amyotrophic lateral sclerosis (*N* = 64)	3 (4.7)
Multiple sclerosis (*N* = 64)	7 (10.9)
Prostate cancer (*N* = 66)	3 (4.5)
Benign prostatic hyperplasia (*N* = 65)	8 (12.3)
Total	75

APBD, adult polyglucosan body disease.

(MS), prostate cancer, and benign prostatic hyperplasia (BPH). Peripheral neuropathy was the most frequent, reported by 43 patients (60.6%). Spinal stenosis was the second most frequent, reported by 11 patients (16.7%).

Other selected misdiagnoses were ALS (3), MS (7), prostate cancer (3), and BPH (8) (Table 3). Of the patients who reported any misdiagnoses, 30 reported one, 15 reported two, and 5 reported three. All 20 patients who reported more than one misdiagnosis reported peripheral neuropathy.

The majority of patients had at least one parent born in the United States (57.1%) [Figure 1(a)], while an overwhelming majority of patients (75.4%) had at least one grandparent born in Europe (excluding Russia). The next most common birth countries for at least one grandparent were the United States (42.1%) and Russia [33.3%; Figure 1(b)].

Among 78 respondents, 29 patients (37.2%) reported having 'any' family history of APBD. Twenty-six patients reported a sibling with a history of the disease and five reported more than one relative with a history (Table 4). Twelve patients reported parental consanguinity.

Discussion and conclusions

APBD has not previously been studied prospectively.[15,18] The current retrospective analysis provides an initial foundation for further characterization of the disease. The results can be used to allow more informed planning and design steps for future studies and potential clinical trials for new therapies.

Potential biases of the study include: (i) recall bias for self-reporting ages-at-onset and diagnosis. The survey was patient-reported and, due to the neurodegenerative nature of the disease, recall of age-at-onset or age-at-diagnosis without clinical records could lead to inaccurate results. (ii) Location bias: the APBD Research Foundation is based in the US, which could lead to geographic bias of results. (iii) Socio-economic status bias: it is well known that socioeconomic factors have a sizable effect in healthcare outcomes and research.[19–24] As shown in Table 1, this study population is highly educated, with over 70% of patients having a college degree or higher, making it worth considering that the study population may not be an accurate representation of the actual patient population. As genetic testing may not be available for all APBD patients, the patient population with this disease could be larger, spanning wider socioeconomic classes.

As is usual with ultra-rare diseases, the small sample size presents significant challenges in terms of statistical power; however, the APBD survey dataset provides the largest body of information on APBD patients to date. Overall, the results presented here provide the basic information which may lay the groundwork for future prospective natural history studies and clinical trials for potential treatments for APBD.

Moving forward, we plan to use these results to design a prospective natural history study to better understand the progression of the disease.

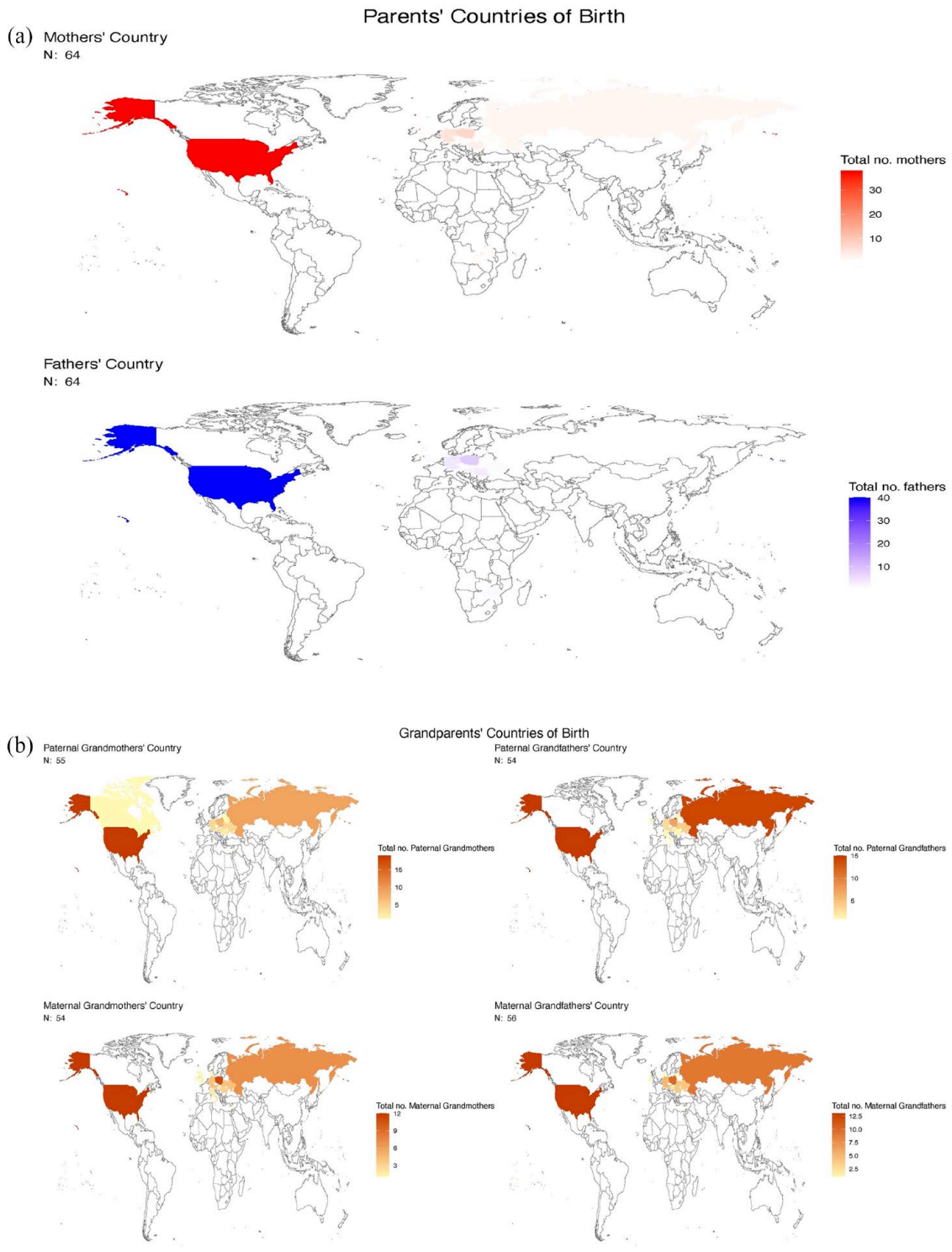

Figure 1. Legend: Countries of birth of parents (a) and grandparents (b) are displayed. Colorcoded heat maps indicate relative numbers of parents (a: mothers = red, fathers = blue) and grandparents (b: orange-yellow) in each geographic region.

Table 4. Reported responses of family history of APBD (Overall $N = 96$).

Response	Any	Father	Mother	Other	Siblings
Yes	29	2	3	3	26
No	43	19	16	13	2
Don't know	6	0	2	4	1
Responders	78	21	21	20	29
Non-responders (Missing)	18	75	75	76	67

APBD, adult polyglucosan body disease.

Potential outcomes to measure the disease progression will focus on the APBD symptom triad and other understudied and potentially under-reported symptoms such as cognitive changes, sexual dysfunction, loss of vision, impaired thermoregulation, and fatigue. Identifying and describing these key outcome measures will allow us to evaluate potential future therapies.

Declarations

Ethics approval and consent to participate

The study was conducted under a Columbia University approved IRB protocol (AAAM7351). All subjects signed an electronic consent form.

Consent for publication

Subjects signed an electronic consent form, which included permission to publish de-identified data.

Author contributions

Jacy Sparks: Data curation; Formal analysis; Writing – original draft; Writing – review & editing.

Francesco Michelassi: Data curation; Writing – original draft; Writing – review & editing.

John L. P. Thompson: Data curation; Formal analysis; Writing – original draft; Writing – review & editing.

Richard Buchsbaum: Data curation; Software; Writing – review & editing.

Natacha Pires: Conceptualization; Data curation; Writing – review & editing.

Janet T. DeRosa: Data curation; Writing – review & editing.

Kristin Engelstad: Conceptualization; Investigation; Project administration; Writing – review & editing.

Salvatore DiMauro: Conceptualization; Funding acquisition; Methodology; Project administration; Resources; Supervision; Writing – review & editing.

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Michio Hirano: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Writing – original draft; Writing – review & editing.

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Competing interests

There are no competing interests.

Availability of data and materials

Data that support the findings of this study are available from the corresponding author upon request.

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References

1. Bigio EH, Weiner MF, Bonte FJ, *et al*. Familial dementia due to adult polyglucosan body disease. *Clin Neuropathol* 1997; 16: 227–234.
2. Busard HL, Gabreels-Festen AA, Renier WO, *et al*. Adult polyglucosan body disease: the diagnostic value of axilla skin biopsy. *Ann Neurol* 1991; 29: 448–451.
3. Gray F, Gherardi R, Marshall A, *et al*. Adult polyglucosan body disease (APBD). *J Neuropathol Exp Neurol* 1988; 47: 459–474.
4. Lossos A, Barash V, Soffer D, *et al*. Hereditary branching enzyme dysfunction in adult polyglucosan body disease: a possible metabolic cause in two patients. *Ann Neurol* 1991; 30: 655–662.
5. Paradas C, Akman HO, Ionete C, *et al*. Branching enzyme deficiency: expanding the clinical spectrum. *JAMA Neurol* 2014; 71: 41–47.
6. Robitaille Y, Carpenter S, Karpati G, *et al*. A distinct form of adult polyglucosan body disease with massive involvement of central and peripheral neuronal processes and astrocytes: a report of four cases and a review of the occurrence of polyglucosan bodies in other conditions such as Lafora's disease and normal ageing. *Brain* 1980; 103: 315–336.
7. Schroder JM, May R, Shin YS, *et al*. Juvenile hereditary polyglucosan body disease with complete branching enzyme deficiency (type IV glycogenosis). *Acta Neuropathol* 1993; 85: 419–430.
8. Ubogu EE, Hong ST, Akman HO, *et al*. Adult polyglucosan body disease: a case report of a manifesting heterozygote. *Muscle Nerve* 2005; 32: 675–681.
9. Ziemssen F, Sindern E, Schroder JM, *et al*. Novel missense mutations in the glycogen-branching enzyme gene in adult polyglucosan body disease. *Ann Neurol* 2000; 47: 536–540.
10. Kakhlon O, Escriba PV, Akman HO, *et al*. Editorial: using small molecules to treat macromolecule storage disorders. *Front Cell Dev Biol* 2020; 8: 623613.
11. Kakhlon O, Ferreira I, Solmesky LJ, *et al*. Guaiacol as a drug candidate for treating adult polyglucosan body disease. *JCI Insight* 2018; 3: e99694.
12. Akman HO, Kakhlon O, Coku J, *et al*. Deep intronic GBE1 mutation in manifesting heterozygous patients with adult polyglucosan body disease. *JAMA Neurol* 2015; 72: 441–445.
13. Yi HQ, Lim JA, Kishnani PS, *et al*. AAV Gene therapy effectively transduces the central nervous system and prevents polyglucosan body formation in adult polyglucosan body disease mice. *Mol Ther* 2022; 30: 467–468.
14. Kakhlon O, Vaknin H, Mishra K, *et al*. Alleviation of a polyglucosan storage disorder by enhancement of autophagic glycogen catabolism. *EMBO Mol Med* 2021; 13: e14554.
15. Mochel F, Schiffmann R, Steenweg ME, *et al*. Adult polyglucosan body disease: natural history and key magnetic resonance imaging findings. *Ann Neurol* 2012; 72: 433–441.
16. Hellmann MA, Kakhlon O, Landau EH, *et al*. Frequent misdiagnosis of adult polyglucosan body disease. *J Neurol* 2015; 262: 2346–2351.
17. Schwartz L, Lu Q, Liu R, *et al*. Estimating the prevalence of the adult polyglucosan body disease at the gene level for Ashkenazi Jews in the United States. *Am J Rare Dis Diagn Ther* 2020; 3: 4–8.
18. Kohler W, Curiel J and Vanderver A. Adulthood leukodystrophies. *Nat Rev Neurol* 2018; 14: 94–105.
19. Adler NE and Ostrove JM. Socioeconomic status and health: what we know and what we don't. *Ann N Y Acad Sci* 1999; 896: 3–15.
20. Chen SW, Keglovits M, Devine M, *et al*. Sociodemographic differences in respondent preferences for survey formats: sampling bias and potential threats to external validity. *Arch Rehabil Res Clin Transl* 2022; 4: 100175.
21. Muennig P, Fiscella K, Tancredi D, *et al*. The relative health burden of selected social and behavioral risk factors in the United States:

implications for policy. *Am J Public Health* 2010; 100: 1758–1764.

22. Centers for Disease Control and Prevention. Human Development and Disability, Health Equity, https://www.cdc.gov/ncbddd/humandevelopment/health-equity.html (accessed 21 February 2024).

23. National Center for Health Statistics. Health, United States Spotlight: Racial and Ethnic Disparities in Heart Disease, https://www.cdc.gov/nchs/hus/spotlight/HeartDiseaseSpotlight_2019_0404.pdf (accessed 21 February 2024).

24. Whitman A, De Lew N, Chappel A, *et al*. Addressing social determinants of health: examples of successful evidence-based strategies and current federal efforts. Washington, DC: Office of the Assistant Secretary for Planning and Evaluation, 2022.

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