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Estimating the Prevalence of the Adult Polyglucosan Body Disease at the Gene Level for Ashkenazi Jews in the United States

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ABSTRACT

Objectives: To estimate the prevalence of Adult Polyglucosan Body Disease for Ashkenazi Jews (AJ) in the United States and the degree of misdiagnoses; to meet FDA requirements for an Orphan Drug Designation.

Background: Adult Polyglucosan Body Disease is a rare genetic disorder that mostly affects AJ, causing neurologically-related health problems and premature death. The population of this disease is limited to a small number of diagnosed cases and carrier frequency screenings. According to retrospective studies, many afflicted with Adult Polyglucosan Body Disease are heavily misdiagnosed-making the compilation of cases from its medical records misleading.

Materials and Methods: Sister rare diseases to Adult Polyglucosan Body Disease have incidence proportions at the case level as well as carrier frequencies. Theses sister diseases approximate the Hardy-Weinberg (HW) equilibrium. With a common AJ ancestry, we argue that Adult Polyglucosan Body Disease also approximates the HW equilibrium-where by its incidence proportion at the gene level is associated with its carrier frequency. Epidemiologically, the prevalence proportion of Adult Polyglucosan Body Disease at the gene level for AJ is a function of its gene incidence proportion and the duration of the disease.

Results: The prevalence of Adult Polyglucosan Body Disease at the gene level ranged from 3,400 to 6,300 AJ in the United States. Under current conditions, we expect that a newly afflicted AJ with the disease would be misdiagnosed for eight years.

Discussion: The estimated prevalence for Adult polyglucosan Body Disease meets the FDA definition of a rare disease in the United States. In rare diseases, the FDA would grant an Orphan Drug designation to encourage Pharma to develop a drug for a treatment or cure.

The misdiagnoses of the Adult Polyglucosan Body Disease may be reduced by educating physicians and the AJ community about its typical clinical and imaging features.

This study has broad significance for any rare genetic disease worldwide. Whenever their case counts are suspect, the Hardy-Weinberg equilibrium and epidemiological measures may be useful to estimate prevalence at the gene level for these diseases.

Keywords: Adult polyglucosan body disease; Orphan drug designation; Carrier frequency; Hardy-w

INTRODUCTION

According to Dr. Or Khaklon (one of the authors), the Adult Polyglucosan Body Disease (APBD) is a rare genetic disorder that is caused by a deficiency of the Glycogen Branching Enzyme (GBE). Due to this GBE deficiency, Polyglucosan Bodies (PBs) accumulate in muscle, nerve and various other tissues of the body; the PBs are insoluble inclusions that feature poorly branched glycogen, structurally closer to starch than to spherical and soluble glycogen. Although it is not known for sure, it is thought that the accumulation and aggregation of the PBs in axons may clog them-leading to poor capacity for the central nervous system (brain and spinal cord) to send and receive messages throughout the body. PB accumulation and aggregation may also cause the dysfunction of the peripheral nervous systems-which involves motor and sensory nerves, as well as the autonomic nervous system controlling involuntary body functions (eg., blood flow, breathing, and heartbeat).

Typically, APBD symptoms develop around the fifth decade of life. Many times, the initial sign of the disease is the loss of urinary control (neurogenic bladder). Other times, the early sign of APBD is a feeling of numbness or weakness in the hands and feet (paresthesia). Eventually, most individuals require assistance to walk, starting with acane or walker and culminating in a wheelchair. Finally, APBD-afflicted individuals may develop mild cognitive impairment, which in some cases might progress to loss of memory and intellectual abilities (dementia) [1,2].

According to Dr. H Orhan Akman (one of the authors), the most common misdiagnoses of APBD are multiple sclerosis, hereditary spastic paraplegia, Charcot-Marie-Tooth disease, adrenomyeloneuropathy, and prostate hypertrophy in men with early urinary symptoms. Some patients might be misdiagnosed with multiple system atrophy or ALS. In older patients, misdiagnosis of APBD may include white matter leukoencephalopathies that are associated with severe hypertension or NOTCH3 mutation. A retrospective study of 30 patients showed that such APBD misdiagnoses remain for an average of 6.8 years +/-4.8 years [1]. It is, therefore, neither surprising that the National Library of Medicine (NLM) recorded only 200 cases of APBD worldwide [3], nor surprising that the Adult Polyglucosan Body Disease Research Foundation (APBDRF) accounted for 100 cases in its patient registry as of January 2020.

Consequently, it is not possible to compile accurate APBD cases from insurance, physician, hospital and other records. Instead, we explore the use of the Hardy-Weinberg (HW) equilibrium and epidemiological methods [4-6] to estimate the APBD incidence and prevalence proportions/populations at the gene level-whether diagnosed or not. A similar gene-based or non-case approach was used to estimate the incidence and prevalence of the Recessive Dystrophic Epidermolysis Bullosa disease [7].

This study demonstrates that the main APBD-sister diseases-Bloom, Canavan, Familial Dysautonomia, Fanconia Anemia C, Gaucher, Mucolipidosis IV, Niemann-Pick A, and Tay-Sachs-approximate HW equilibrium. Coming from the same AJ ancestry, we argue that APBD is likely to approximate HW equilibrium as well; whereby, its gene incidence proportion is associated with the carrier frequency of the disease. Moreover, this study "steady state" epidemiological formulation-i.e., the product of the HW-derived incidence and the median duration of the disease-to estimate the APBD gene prevalence for AJ.

FDA offers an Orphan Drug Designation when the prevalence of a disease is less than 200,000 people in the United States [8]. An Orphan Drug Designation extends Pharma's exclusive rights for using a drug from five years to seven years. This provides a powerful incentive for Pharma to develop drugs for the treatment or cure of a disease.

MATERIALS AND METHODS

Carrier frequency screening for APBD

This study is only interested in carrier frequency as a methodological "building block" to estimate APBD prevalence at the gene level.

It does not go into moral and ethical considerations that young adult couples face knowing that any of their offspring have a 1-in-4 risk of getting a genetic disease-whether for APBD with its onset in the fifth decade of life or for the much earlier onset diseases listed in Table 1. In passing, earlier, Orthodox and Hasidic Jews summarily rejected carrier screening because it would stigmatize young adults of "marriageable age" or would suggest abortion if pregnant with a child. But later, under the guidance of leading genetics experts and rabbinical authorities, Dr. Yeshorim established a more acceptable testing approach for these Jews: Anonymously screen premarital young adults for genetic diseases and provide counseling services [9].

Two different screenings for carrier frequency have been reported for APBD. As their methods and results differ, this study uses both of them to estimate the APBD gene incidence and prevalence for AJ in the United States.

In 2016, the Mount Sinai Genetic Testing Laboratory used next-generation carrier screening to analyze APBD gene mutations comprehensively. It tested 2,776 individuals who self-reported to be of AJ heritage. They received a prenatal screening for this possible adult disease. Dr. Ruth Kornreich (one of the authors) presented the results at the 2016 scientific meeting of the APBD Research Foundation. More recently, Sema4 (formerly the Mount Sinai Genetic Testing Laboratory) published their approach on the next-generation carrier screening [10].

Sema 4 detected fifty-eight mutations for APBD in self-reported AJ as follows:

- 38 individuals for molecular change p. Y329S
- 16 individuals for molecular change IV15+5289delins
- individuals for molecular change p. Y329C
- 1 individual for molecular change p. Y535C
- 1 individual for molecular change p. G299X

According to Sema4, the APBD carrier frequency for AJ is approximately 1 in 48 (58/2776).

In a 2012 publication, a higher carrier frequency for APBD was estimated at approximately 1 in 35. It is based on a narrower screening of APBD mutations with a sample of 380 AJ; a sample that was originally part of the prenatal screening for the Tay-Sachs disease, a disease that usually appears in infancy [11].

HW equilibrium

Sister-APBD diseases in HW equilibrium: Frequently, eight APBD-sister diseases are offered in carrier screening for AJ. These sister diseases are listed in Table 1. Its first two columns show their incidence proportions at the case level and actual carrier frequencies, as compiled by the Forward in 2014 [12]. The third column shows their HW-expected carrier frequencies, working with the HW Equation 1 [13] and the incidence proportions at the case level.

Equation 1: $CF = 2[(\sqrt{Ic})\ (1-\sqrt{Ic})]$,

where: CF = carrier frequency

IC = incidence proportion

The fourth column of Table 1 shows the absolute error rates between the HW- predicted and actual carrier frequencies for each APBD-sister disease. Their error rates are very low, except for the Canavan and Gaucher diseases. With a median absolute error rate of three percent (average of 10 percent), this study concludes that the APBD-sister diseases approximate HW equilibrium.

APBD likely in HW equilibrium: There are several reasons why APBD is likely to approximate HW equilibrium as well. First, today's Jews are descended from only 350 individuals some 600-800 years ago [14]. This is a classic HW case of a closed population. Second, Sema4 found that 80 percent of the individuals screened for a carrier frequency would be positive for one or more of 58 AJ disorders. Finally, as shown, the eight main APBD-sister diseases approximate HW equilibrium.

APBD Gene incidence and prevalence proportions: With APBD approximating HW equilibrium, Table 2 shows its estimated incidence and prevalence proportions at the gene level for the two APBD reproductive carrier frequencies. The estimated gene incidence proportions are derived with HW Equation 1 [13] and the carrier frequencies. The estimated gene prevalence proportions are derived from the previously estimated gene incidence proportions and the duration of the disease-according to epidemiological Equation 2 [4-6], Table 3 covers the median duration of the disease, as recorded by the APBD Research Foundation (APBDRF) in November 2019.

Equation 2: $P/(1-P) = IC \times DD$,

where P = Prevalence

IC = Estimated Incidence Proportion

DD = Median disease duration

Table 3 shows the duration of APBD is 20 years as measured from first symptoms (median age of 51) to death (median age of 71). The often-used diagnosis-to-death duration is misleading here because

Table 1: HW-Expected *vs.* actual carrier frequencies for APBD-sister diseases.

APBD-Sister Disease			Carrier Frequency	
	IC	Actual	HW-Expected	Absolute Error Rate
Bloom	1/40,000	1/100	1/101	0.01
Canavan	1/6,400	1/55	1/41	0.34
Familial Dysautonomia	1/3600	1/30	1/31	0.03
Fanconi Anemia C	1/32,000	1/89	1/90	0.01
Gaucher	1/450	1/15	1/11	0.36
Mucolipidosis IV	1/62,500	1/122	1/125	0.02
Niemann-Pick A	1/32,000	1/90	1/90	0
Tay-Sachs	1/3,000	1/30	1/28	0.07

Table 2: APBD Carrier frequency and estimated proportions.

Carrier Frequency	Est. Incidence Proportion	Est. Prevalence Proportion
1/35	1/4,800	1/240
1/48	1/9,000	1/450

there is an eight-year gap between first symptoms and diagnosis. Note that the APBDRF duration data provided in November 2019 was similar to data published earlier [1,2].

RESULTS

In this section, we derive the size of the APBD-afflicted population for the AJ minority community. They have a right to expect the proper APBD diagnosis and to receive the best care and treatment available.

Specifically, the APBD gene incidence and prevalence proportions for AJ are converted into their respective populations with the median symptom-diagnosis ages of the disease, 51 to 71 years old. Table 4 showed the population for 2010 by the relevant age brackets from 50 to 74 [15]; historically, the AJ population in the United States is estimated at two percent of the U.S. population total.

The population for this symptom-to-death duration of APBD totaled 1,409,000 AJ. Using interpolation where necessary, that total came from Table IV as follows: For ages 51-54, 4/5 of the AJ population in the 50-54 age bracket (357,000 AJ); for ages 55-69, the AJ population in the next 55-69 age brackets (978,000 AJ); and for ages 70 and 71, 2/5 of the AJ population in the 70-74 age bracket (74,000 AJ).

To apply for the Orphan Drug Designation, however, the FDA requires that the U.S. population data be as current as possible. The 2010 U.S. decennial census enumerated 308.7 million people [15], but the Census Clock showed a U.S. population total of 330.3 million people through 2019-a seven percent increase. Applying the seven percent increase to the 1,409,000 AJ total for 2010, raises the AJ total to 1,508,000 AJ through 2019.

Working with the APBD incidence and prevalence proportions in Table 2 and with the 1,508,000 AJ susceptible to the disease, the estimated APBD incidence population ranged from about 170 to 300 AJ per year. And its prevalence population ranged from about 3,400 to 6,300 AJ.

DISCUSSION

The estimated prevalence for APBD meets the FDA definition of a rare disease in the United States. In rare diseases, the FDA would grant an Orphan Drug designation to encourage Pharma to develop an APBD drug for its treatment or cure.

Table 3: The duration of APBD.

Statistic	Symptom Age	Diagnosis Age	Deceased Age
Range	32-65	35-70	61-80
Median	51.0	59.5	71.0
Mean	49.7	58.7	70.5
Number of Cases	30	38	10

Table 4: U.S. Population statistics by relevant age brackets.

Age Bracket	Total Population (mil)	AJ Population (000s)
50-54	22.3	446
55-59	19.7	394
60-64	16.8	336
65-69	12.4	248
70-74	9.3	186

APBD misdiagnosis is a significant problem in the United States. As recorded by a retrospective study, APBD patients were initially misdiagnosed with Multiple Sclerosis (MS) and other diseases [1]. Anecdotally, the majority of the APBD patients involved in the APBD Research Foundation experienced MS misdiagnosis. Moreover, it is an open question how many APBD-afflicted AJ are misdiagnosed throughout their lifetimes with MS or other diseases. Preliminarily, we estimate the APBD misdiagnoses for MS in the United States between 2,600 and 2,800 AJ. This accounts for a major portion of the 3,400-6,300 APBD prevalence for AJ at the gene level. The estimate of 2,600- 2,800 AJ misdiagnoses for MS is derived as follows:

- By combing through hospital, physician, insurance and other records, a study found that about 950,000 people have been diagnosed with MS in the United States. This is a major increase from the earlier estimate of 400,000 plus [16].
- A2019 UCLA-Cedar Sinai retrospective study of patients referred by physicians for reevaluation showed an overall MS misdiagnosis rate of 18 percent for other diseases-yielding an adjusted total of 779,000 for properly diagnosed MS in the United States [17]. Also, a retrospective study of APBD patients found that 17 percent were initially misdiagnosed with MS [1];
- With the assumption that AJ has a proportionate share of the total MS rolls in the United States, we estimate that about 15,500 AJ have been diagnosed with MS in the United States; and
- Applying the overall 18-percent or 17-percent MS misdiagnosis rate to the AJ on the MS rolls, we estimate that between 2,600 and 2,800 of the APBD-afflicted have been misdiagnosed with MS. The misdiagnoses of APBD for MS and other diseases may be reduced by educating physicians and the AJ community about the typical clinical and imaging features of APBD.

This study has broad significance for other rare diseases worldwide. When their case counts are suspect, the Hardy-Weinberg framework can be used to estimate the prevalence of a rare disease at the gene level. According to the Genetic and Rare Diseases Information Center (GARD), in the United States, only a few types of rare genetic diseases are tracked when a person is diagnosed-making it difficult to know how many people are affected [18]. Their disease associations may benefit from the HW equilibrium and epidemiological considerations in this paper to estimate prevalence at the gene level.

AUTHOR CONTRIBUTIONS

L Schwartz designed the approach and wrote the material on incidence and prevalence. Q Lu and R Liu reviewed the methodology and estimates of incidence and prevalence. R Kornreich, L Edelmann, and A Birch contributed to the material on the APBD carrier screening. O Kakhlonand, HO Akman drafted the medical aspects of APBD; A Lossos reviewed and finalized their medical write-ups. All of the authors reviewed drafts of the paper.

CONFLICT OF INTEREST

L Schwartz, Q Lu, and R Liu have nothing to report. A Lossos, O Kakhlon, and HO Akman receive grants from the Adult Polyglucosan Body Disease Research Foundation for their research on the disease. R Kornreich, L Edelmann, and A Birch are employees of Sema4.

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