***An APBD Prevalence Estimate for Orphan Drug Designation***

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***Introduction***

Genetically, the Adult Polyglucosan Body Disease (APBD) stems from *GBE1 and other gene* mutations. These gene mutations reduce glycogen branching enzyme activity considerably below normal levels----causing the build-up of starch-like bodies in the neurons of brain cells and the blockage of normal brain messaging. This impeded brain messaging results in neurologically-related health problems and even premature death. For more details on APBD: <https://apbdrf.org/about-us/background>

APBD is concentrated in Jews of Ashkenazi ancestry (referred to as AJ hereafter). Currently, 100 people are on an APBD registry, but many more are suspected of being under-diagnosed or misdiagnosed for multiple sclerosis[[2]](#footnote-2), ALS and other diseases.

Ruth Kornreich of Mount Sinai Health System estimated an AJ carrier frequency of 1:48, based on a screening of 2,775 AJ people.[[3]](#footnote-3) The average duration of APBD is about 25 years---from the average age of 45 for first symptoms to an average survival age of 70.  However, there are no official estimates for the APBD incidence and prevalence.

APBD clinical trials may involve a drug or medical food. As part of the regulatory process, it is worth considering an orphan drug designation from the Office of Orphan Products Development (OOPD) in the FDA. The orphan disease designation offers a powerful incentive for drug development: Grants Pharma exclusive rights to use a drug for a period of seven years (otherwise five years).

To be eligible for the orphan drug designation, the prevalence population must not exceed 200,000 people in the United States. OOPD requires a peer-reviewed published study showing such a low APBD prevalence population. Unfortunately, at this writing, there is no published study along these lines. Instead, OOPD will accept prevalence estimates from three experts, along with their reasoning or methods.[[4]](#footnote-4)

***Research Plan and Results***

In this research plan, I first explore whether sister AJ diseases to APBD approximate Hardy-Weinberg (referred to as HW hereafter) equilibrium.[[5]](#footnote-5) And if they do, I then exploit the HW principle to estimate the missing incidence for APBD. In turn, the APBD prevalence proportion would be estimated from the APBD incidence proportion and the estimated average duration of this disease.[[6]](#footnote-6) Finally, I would use current Census population statistics to convert these APBD proportions into their corresponding afflicted populations----most importantly, whether diagnosed or not.

Based on this research, I estimate that somewhat more than 200 AJ people are APBD-afflicted annually (incidence), whether diagnosed or not. And somewhat more than 5,000 AJ are APBD-afflicted cumulatively today (prevalence), whether diagnosed or not. This evidence supports an orphan drug designation for Pharma to develop, clinically test, and use a medical food or drug in the treatment/cure of APBD.

***Sister AJ Recessive Diseases Approximate HW Equilibrium***

I found that estimates for both AJ carrier frequency and incidence proportions in the United States were limited to Canavan, Gaucher, and Tay-Sachs diseases. Their incidences and carrier frequencies came from a variety of sources. Unfortunately, the other AJ rare diseases lack estimates for both incidences and carrier frequencies.[[7]](#footnote-7)

Table 1 shows the incidence proportion and carrier frequency for the three AJ recessive genetic diseases in the first two columns. The last column shows the expected carrier frequency as predicted by the HW framework.[[8]](#footnote-8)

***TABLE 1: Sister AJ Recessive Diseases***

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**AJ Disease Incidence Proportion (IC) Actual Carrier Frequency (CF) HW-Expected CF**

Canavan 1/6,400-1/13,500 1/40-1/58 1/40.5-1/58.6

Gaucher 1/450 1/15 1/11.1

Tay Sachs 1/3,600 1/27 1/30

The HW-expected carrier frequencies for these three diseases are quite close to their actual carrier frequencies. From a biological perspective, this finding may seem strange. Strange because some assumptions of the HW equilibrium are not strictly met in the real world today. For example, it is undeniable that these rare diseases violate the HW assumption of large populations or of the AJ population in isolation from the non-AJ population today----especially with intermarriage at more than a 50 percent rate in recent years. In the aggregate, however, such violations of the HW assumptions have not as yet affected the current gene pool very much.

***APBD Likely Approximates HW Equilibrium too***

Lots of clustering among AJ and its genetic diseases. In **September 2014,** Shai Carmi and others showed that today's Jews are descended from only 350 individuals some 600–800 years ago.[[9]](#footnote-9) A classic HW case of an isolated population. Also, Ruth Kornreich showed such clustering in 2016: “8 out of 10 AJ individuals tested for 58 disorders will screen positive.”[[10]](#footnote-10) Finally, continuing with the clustering of AJ and its genetic diseases, I have shown that Canavan, Goucher, and Tay-Sachs diseases approximate HW equilibrium today. As a sister genetic disease, APBD is likely to approximate HW equilibrium today as well.

***Estimate of APBD Incidence Proportion for AJ***

Table 2 shows that the APBD carrier frequency of 1/48 is within Canavan’s range of 1/40-1/58.5 for AJ. With both diseases approximating HW equilibrium, the APBD incidence proportion would fall in Canavan’s range of 1/6,400-1/13,500. Using the HW relationship between carrier frequency and incidence proportion (shown in footnote 8), I (iteratively) estimate that the APBD incidence proportion is 1/9,100.

***TABLE 2: Canavan and APBD Diseases for AJ***

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**AJ Disease Incidence Proportion Actual Carrier Frequency (CF)**

Canavan 1/6,400-1/13,500 1/40-1/58

APBD 1/9100 est. 1/48

***Estimate of the APBD Prevalence Proportion for AJ***

As indicated earlier, the epidemiological relationship between prevalence, incidence and the duration of the disease is as follows for a rare disease:

Prevalence proportion=incidence proportion x the average duration of the disease (in years). Substituting values in this equation, the prevalence proportion is equal to

(1/9,100) x 25= 25/9,100=1/364 for AJ.

***Estimate the Incidence and Prevalence Populations for AJ***

I now work with U.S. population statistics to translate the APBD incidence and prevalence proportions into corresponding APBD-afflicted populations, whether diagnosed or not. Table 3 summarizes the U.S. total and AJ populations by age brackets.

Specifically, in Table 3, the total AJ population between the ages of 45 and 70 (the duration of the APBD) is 1,915,200. This total is the sum of two parts. The first part is simply the total of the AJ population from age brackets 45 to 69 or 1,878,000. The second part interpolates the AJ population for the 70th year in the five-year age bracket of 70-74: 1/5 of 186,000 AJ or 37,200 AJ.

***Table 3. U.S. Population Statistics by Age Brackets***

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***Age Bracket Total Population (mil)\* AJ Population (000s)\*\****

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45-49 22.7 454

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

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**\* “Age and Sex Composition: 2010”, 2010 Census Briefs.**

**\*\* Based on a number of sources, the U.S. Jewish population represents about 2.2 percent of the U.S. population; 90 percent of which is estimated as AJ or 2 percent of the total. But this procedure assumes that the age distribution of the AJ population in the United States approximates that of the total U.S. population, although the AJ population is slightly older.**

I now calculate the estimated APBD incidence and prevalence populations for AJ. The estimated APBD incidence population for AJ is 210 per year, whether diagnosed or not; the incidence proportion of 1/9,100 x 1,915,200 AJ population. The estimated APBD prevalence population for AJ is 5,262 cumulatively, whether diagnosed or not; the prevalence proportion of 1/364 x 1,915,200 AJ population.

However, the OOPD requires that the prevalence population be updated with the latest estimated Census data. The 2010 U.S. decennial census enumerated 308.7 million people, but the 2016 U.S. interim census estimated 325 million people---a 5.28 percent increase. Applying the 5.28 percent increase to the 2010 AJ data, the most current estimate of the APBD prevalence population is 5,540 for AJ, whether diagnosed or not; the updated APBD incidence population is 221 per year for AJ, whether diagnosed or not.

**Misdiagnoses and APBD Prevalence Population**

The APBD misdiagnoses for MS may help explain a major part of the estimated 5,539 APBD prevalence population for AJ. Appendix A shows that as many as 4,000 APBD-afflicted AJ people may be misdiagnosed for MS cumulatively today; also explains a possible partnership with the National MS Society to reduce APBD misdiagnoses for MS.

More generally, in “Frequent misdiagnoses of adult polyglucosan body disease” Journal of Neurology, July 2015, Mark Hellmann and others retrospectively examined the records of 30 APBD patients and found that ***everyone*** was initially misdiagnosed with some other disease. In addition to MS, Hellmann found that other initial APBD misdiagnoses included ALS, peripheral neuropathies, and cerebral vessel disease.

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**APPENDIX A: APBD MISDIAGNOSIS for MULTIPLE SCLEROSIS**

**What is the general scientific evidence about misdiagnosis?**

In 2015, the National Academy of Medicine reported that most people will receive an incorrect or late diagnosis at least once in their lives, sometimes with serious consequences. More specifically, the Mayo Clinic published a study in April 2017 that showed that 21 percent of its patients over a two-year period had their diagnosis completely changed; Van Such, Monica and others, J., Journal of Evaluation in Clinical Practice. Finally, Mark L. Graber----founder of the Society to Improve Diagnosis in Medicine---- said “There are 10,000 diseases and only 200 to 300 symptoms.”; quoted in Bernstein, L. “*20 percent of patients with serious conditions are first misdiagnosed,” Health* and Science, Washington Post, April 4, 2017.

**Why do physicians misdiagnose APBD for MS?**

In “Frequent misdiagnoses of adult polyglucosan body disease” Journal of Neurology, July 2015, Hellmann and others concluded that the misdiagnosing of APBD for MS (and other diseases) stems from “physicians’ unfamiliarity with the typical clinical and imaging features of APBD….”

Also causing diagnostic difficulty, APBD mimics MS in two main ways.  First, early signs of APBD are similar to those of MS---including fatigue, numbness, neurogenic bladder, spasticity, and gait difficulties.  Second, as with MS, APBD health problems typically start in early adulthood and progressively worsen----often resulting in premature death.

***Are there personal stories about APBD misdiagnoses for MS?***

Many members of the Adult Polyglucosan Body Disease Research Foundation (APBDRF) experienced their local neurologist misdiagnosing APBD for MS. Their corrected diagnosis for APBD occurred in different ways. In the case of Susan S., her local physical therapist questioned the MS diagnosis, and a radiologist with a world-renowned clinic diagnosed her APBD. In Lori W’s case, it was a geneticist who finally re-diagnosed MS to APBD, while Deborah G’s APBD was discovered by another neurologist at a prestigious medical center in New York City.

More generally, the APBDRF chat group (25 members) indicated that it took an average of 9.2 years to receive an APBD diagnosis from the first sign of the disease. Many of these APBD-afflicted people were misdiagnosed for MS and were prescribed MS medicines with potentially dangerous side effects.

**How many APBD-afflicted AJ in the United States are currently misdiagnosed for MS?**

It appears that there may be a few thousand APBD-afflicted AJ in the United States who are now misdiagnosed for MS.  Of the nearly one million diagnosed with MS in the United States (recent preliminary National MS Society report), the AJ proportionate share (two percent of the total) amounts to 20,000 of them. General reports indicate that serious diseases are misdiagnosed about 20 percent of the time by physicians, suggesting that the APBD misdiagnoses for MS may amount to 4,000 people.

***What hope Is there to reduce the APBD misdiagnoses for MS?***

The author has been working with senior leadership at the National MS Society to form a partnership to reduce APBD misdiagnoses for MS. Removing APBD-afflicted people from the MS roles is in everyone’s best interest. These individuals can join an APBD registry and participate in upcoming clinical trials. And these same individuals could no longer participate in and taint MS clinical trials.

1. ***What can the National MS Society do?***

If the National MS Society’s web site would include APBD as one of its “other conditions to rule out” before diagnosing MS, then physicians would become more aware of APBD in diagnosing their patients.

Also, if the National MS Society would alert the readers of its magazine, Momentum, about the potential for misdiagnosing APBD-afflicted people for MS, then these people could check out APBD on the web site of the APBD Research Foundation (APBDRF).

1. ***What can the APBDRF do?***

The APBDRF has been underwriting the use of an at-home saliva collection kit to test for APBD----and would extend the offer to members of the National MS Society. This would help MS-diagnosed patients find out if they, in fact, have APBD----at no cost or inconvenience to them.

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1. **Reviewed by** **Dr. Belinda Cornes, population geneticist, Sima4genomics, Inc.; by Olivia Montano, Senior Director, Pathways for Rare and Orphan Studies (PROS); and by members of the APBD Research Foundation. Errors of omission or commission remain with the author.** [↑](#footnote-ref-1)
2. **Many in the APBD community report earlier misdiagnosis for MS; see Appendix A for the details.**  [↑](#footnote-ref-2)
3. **Ruth Kornreich, “*Glycogen Storage Disease Type 1V/Adult Polyglucosan Body Disease Carrier Screening”*, December 2016 APBDRF Scientific Advisory Board Meeting.** [↑](#footnote-ref-3)
4. **OOPD**, **SOPP 420, Version #1, effective November 9, 2010.** [↑](#footnote-ref-4)
5. **Hamamy, H., “*Applications in Population Genetics*,” Department of Genetic Medicine and Development, Geneva, 2012.** [↑](#footnote-ref-5)
6. **For rare diseases**, p**revalence proportion=incidence proportion x average duration of the disease**. **In “*Prevalence and Incidence of Rare diseases*,” Orphanet Report Series, January 2018, this relationship is sanctioned. Also, this relationship is grounded in epidemiology.** [↑](#footnote-ref-6)
7. **On actual AJ carrier frequencies, I used Ruth Kornreich’s 2016 estimates for Tay-Sachs and Gaucher diseases because they were the most recent. But the Canavan web site had a different AJ carrier frequency (1/40) than Kornreich’s (1/55); in this case I used the 1/40-1/58 range indicated in Right Diagnosis.** **On actual AJ incidences, I used the web site figure for Gaucher (1/450); but used Nord’s 2017 entry for Tay Sachs (1/3,600) and Right Diagnosis range for Canavan (1/6,400-1/13,500) because the disease web sites did not have these figures.** [↑](#footnote-ref-7)
8. **With the HW framework, the expected carrier frequency is estimated from the incidence proportion as follows: CF=2 x [(Square root of IC) x (1- Square root of IC)]. This is the “2pq” heterozygote term in HW (see footnote 5).**  [↑](#footnote-ref-8)
9. **Carmi, S. and others, “*Sequencing an Ashkenazi reference panel supports population-targeted personal genomics and illuminates Jewish and European origins,*” Nature Communications, 2014.** [↑](#footnote-ref-9)
10. **Same as footnote 3.** [↑](#footnote-ref-10)