The Consistent 50% Excess Male Infant Mortality from Sudden Infant Death Syndrome (SIDS) and Other Respiratory Diseases is Evidence of an X-Linkage.

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Abstract

The male excess of infant mortality is well known but without causal explanation. We have inadvertently discovered while investigating sudden infant death syndrome (SIDS) that many causes of infant respiratory death have virtually the same male fraction as SIDS of about 0.61 male, subject to slight sampling variation. The only possible explanation for this consistency is that a recessive X-linkage is involved. We review the literature on infant mortality and propose that there exists a presently unidentified responsible X-linked gene that has a dominant allele with frequency p ≈ 1/3 and a corresponding recessive allele with frequency q ≈ 2/3, such that p+q=1. Either the dominant allele codes for an enzyme allowing anaerobic oxidation in respiratory control neurons or the recessive allele codes for a protein blocking anaerobic oxidation process in them. The gene and its alleles would only penetrate if, and only if, a susceptible infant attains an acute anoxic encephalopathy leading to critical respiratory control neuron death in the brainstem where the blood oxygen tension is the minimum in the entire body. Should the genetically susceptible infant dodge the potentially fatal anoxic condition, the gene may still penetrate later in childhood or adult life. Given an approximate 5% male birth excess, ~2/3 of the XY males will be at risk of having the recessive allele and q² = 4/9 of XX females will be at similar risk. Therefore for ~1050 males born per 1000 females, ~700 males and ~444 females will be at risk with male fraction x = 700/(700+444) = 0.612. We show for 11 respiratory causes of death with over one half million cases, that the male fraction is ~0.604. It has not escaped our notice that a possible mode of prevention of SIDS may be possible.

Keywords: SIDS; X-Linkage; Male excess; Genetic predisposition; Acute anoxic encephalopathy

Abbreviations

ASSB: Accidental Suffocation and Strangulation in Bed; ARI: Acute Respiratory Infection; AGV: Anomalies of the Great Veins; BPD: Bronchopulmonary Dysplasia; CARS: Congenital Anomalies of the Respiratory System; CDC: U.S. Centers for Disease Control and Prevention; COPD: Chronic Obstructive Pulmonary Disease; HLHS: Hypoplastic Left-Heart Syndrome; HMD: Hyaline Membrane Disease; ICD: International Classification of Diseases; RDS: Respiratory Distress Syndrome; SIDS: Sudden Infant Death Syndrome; SIFFO: Suffocation by Inhalation of Food or Foreign Object; SRD: Sudden Respiratory Death; UNK: Unknown and Other Ill-defined or Unspecified Causes; WHO:World Health Organization.

Introduction

The excess in male infant mortality is well known but its cause has been unexplained [1,2]. Waldron [2] has thoroughly reviewed possible causes of the male excess child mortality including X-linked recessive diseases but concluded that "the contribution of those [X-linked recessive] diseases to sex differences in mortality is limited because they are rare." This may be because Naeye et al. [3], who concluded that the common male excess in neonatal infant mortality "must" be caused by an unknown X-linkage, was not considered by Waldron [2]. They concluded that the well-known male disadvantage for X-linked recessive conditions, that arose because the XX female had two chances to get a protective dominant allele while the XY male had only one chance, must be responsible. However, Naeye et al. [3] only claimed that this would apply to neonatal infants and made no efforts to quantify the frequency of a putative X-linked recessive allele. Had they done so they could have discovered that the male fraction of their neonates was about 0.60. (Naeye et al. autopsied 1,137 male and 783 female liveborn neonates who died within 72 hours of birth. If we subtract out the 128 males and 123 females who died with evidence of antenatal aspiration of amniotic fluid (squamous cells in terminal air spaces) there were 1009 male and 660 females remaining. Their male fraction is x=1009/(1009+660)≈0.6046). This possibility of an X-linkage to explain the common excess in male infant mortality received no further mention in the literature for the next 21 years when in 1992, one of us (DTM, PhD Chemical Engineering) discovered that sudden infant death syndrome (SIDS) had a consistent male fraction of ~0.61 in almost all the data sets on the lognormal age distribution of SIDS that he was modeling. One of us (EMD, PhD Genetics) then recognized that this constant male excess was characteristic of an X-linked recessive genetic trait in Hardy-Weinberg Equilibrium and that the recessive allele frequency could be thereby calculated and lead to the identification of the gene. It should be noted that at that time a genetic cause of SIDS was ruled out by Guntheroth and others [4,5], primarily based on Kukolich et al. [6] who wrote "If genetic conditions played a major role in SIDS one would expect to see recurrence rates as high as 25% to 50%. Earlier studies have failed to show a high recurrence rate." The high 25% to 50% range would be expected if a putative gene was autosomal. Thus an X-linkage was never contemplated by any previous researchers other than Naeye et al. [3] perhaps because the constant ~0.6 male fraction and its implication went unrecognized. For example, Froggatt et al. [5] noted the modest degree of male preponderance in SIDS but emphasized
that it was not important because the same male excess held for all infant mortality [4]. As we will show this is true for almost all infant deaths by respiratory causes but false for deaths by most cardiac causes. Consequently Guntheroth did not include the male excess of SIDS as one the 10 most significant facts in the epidemiology of SIDS (Table III.1 in [4]) and concluded that there was "No evidence of a genetic link." We will show in the following sections with reference to some of our own publications [7-21] that the male excess in SIDS points to its cause and may be the most important fact because it may lead to a prophylaxis against SIDS and possibly prevent other causes of infant and adult respiratory deaths.

| Location          | Years | Male | Female | Male Fraction |
|-------------------|-------|------|--------|---------------|
| Hong Kong         | 87-92 | 38   | 33     | 0.535         |
| Israel*           | 80-83 | 19   | 15     | 0.559         |
| Austria           | 88-92 | 118  | 82     | 0.590         |
| Budapest          | 90-93 | 29   | 20     | 0.592         |
| New York State    | 74-74 | 113  | 77     | 0.595         |
| USA (6 areas)     | 78-79 | 452  | 305    | 0.597         |
| Paris             | 86-91 | 93   | 61     | 0.602         |
| Cardiff**         | 55-74 | 173  | 113    | 0.605         |
| Denmark           | 89-91 | 232  | 151    | 0.605         |
| England & Wales   | 79-83 | 3127 | 2036   | 0.606         |
| Leningrad         | 83-89 | 100  | 65     | 0.606         |
| Tasmania          | 75-97 | 212  | 136    | 0.609         |
| USA***            | 83-87 | 13100| 8381   | 0.610         |
| Niger             | 85-86 | 25   | 16     | 0.610         |
| Scandinavia       | 92-94 | 217  | 138    | 0.611         |
| New Zealand       | 87-90 | 284  | 181    | 0.611         |
| USA***            | 88-91 | 11,687| 7,372 | 0.613         |
| W. Australia      | 80-88 | 247  | 156    | 0.613         |
| Canada            | 81-91 | 2,609| 1,640  | 0.613         |
| Avon****          | 87-88 | 54   | 34     | 0.614         |
| England & Wales   | 86-92 | 4,873| 3,065  | 0.614         |
| Scotland          | 83-90 | 659  | 413    | 0.615         |
| Victoria Australia| 85-93 | 597  | 373    | 0.615         |
| Washington State  | 75-83 | 705  | 435    | 0.618         |
| Hartlepool**      | 60-69 | 31   | 19     | 0.620         |
| Cologne           | 70-75 | 182  | 110    | 0.623         |
| Norway            | 87-92 | 94   | 55     | 0.630         |
| Oklahoma          | 78-81 | 260  | 152    | 0.631         |
| USA 12 areas      | 59-66 | 122  | 71     | 0.632         |
| Scotland          | 81-82 | 187  | 105    | 0.640         |
| Seattle           | 71-74 | 36   | 20     | 0.643         |
| Grimsby**         | 61-64 | 36   | 20     | 0.643         |
expected and actual values goes to zero [23]. Consequently, it was not 0.50 fraction of heads. We recognized the attraction of different SIDS or moderately sized numbers of SIDS cases that had widely varying birth rate ~1050 XY males will be born live per 1000 XX females born fraction of 340 sudden and unattended adult deaths from autopsied in HWE that has a SIDS protective dominant allele A with frequency p linkage model to explain the 0.61 male fraction of SIDS [9] as follows: of SIDS cases in these SIDS studies varied widely about a mean value random process increases, the percentage difference between the expected and actual values goes to zero [23].” Consequently, it was not appreciated that the male fractions of the small or moderate numbers of SIDS cases in these SIDS studies varied widely about a mean value of 0.61 male, in the same manner that an equal small or moderate number of flips of an honest coin will vary widely about the expected 0.50 fraction of heads. We recognized the attraction of different SIDS studies to a 0.61 male fraction when pooled together to increase N, and first presented the X-linkage model as a poster in the 1994 SIDS International Meeting in Stavanger, Norway. We also reasoned that if a genetically susceptible infant passed through childhood and adolescence without an hypoxic challenge requiring the recessive allele to survive, the gene could penetrate in adulthood as well. In 1995 we presented this X-linkage model as an explanation of why the male fraction of 340 sudden and unattended adult deaths from autopsied respiratory causes during the air pollution event of the December 1952 London Fog was 0.624 [7,21]. In 1997 we formally published our X-linkage model to explain the 0.61 male fraction of SIDS [9] as follows:

### The X-Linkage Model

Let there exist a presently unidentified responsible X-linked gene in HWE that has a SIDS protective dominant allele A with frequency \( p = 1/3 \) and a corresponding SIDS non-protective recessive allele a with frequency \( q = 2/3 \), such that \( p+q=1 \). Given a nominal ~5% male excess birth rate ~1050 XY males will be born live per 1000 XX females born live. Then \( q = 2/3 \) of the males, or ~700 will be aY and at risk of SIDS and \( q^2 = 4/9 \) of the females, or 444 will be aa and also be at the same risk of SIDS. The male fraction of \( x = 700/(700+444) = 0.612 \) predicts the observed male fraction of 0.612 we reported [9]. We reasoned that the common target X-linked gene was one of susceptibility to acute anoxic encephalopathy and it was the rarity of the circumstances leading to that potentially terminal anoxia that was responsible for the comparatively much lower rate of SIDS of order 1 per 1000 live births that was previously thought to reject the possibility of a lethal genetic factor [4-6]. This model also predicts the low increased recurrence rate of SIDS for subsequent siblings as follows: Let an XY male infant die of SIDS. His mother who donated his X chromosome had to be either A/A with probability \( 2q = 4/9 \) or aa with probability \( q^2 = 4/9 \), but she no longer had a chance of being A/A with probability \( p^2 = 1/9 \). The next XY male sibling would be at slightly greater risk of susceptibility to SIDS as the risk of receiving his mother’s a allele increases from 6/9 to 6/8, an increase of 12.5%. However, that increased genetic susceptibility would exist only if the subsequent sibling had all the identical non-genetic SIDS risk factors of the proband, such as: the same weight and gestational age at birth; the same sleeping position and sleep environment; the same parental tobacco smoke exposure during gestation and after birth; the same diet (breast milk vs formula); the same exposure to the same respiratory infection; etc. Perhaps the extra parental vigilance after losing the first child to SIDS and better following of SIDS avoidance recommendations leads to the much lower recurrence rate of a few percent higher risk of SIDS as opposed to the increased genetic risk of 12.5%.

### Results

We reported the male fraction of SIDS data from 36 data sets as shown in Table 1 (see [9] for dataset references). For the total of 67,378 SIDS cases, 41,238 were male for a male fraction of \( x=0.6120 \). Note that there is a wide variation of individual data sets with small sample sizes ranging from \( x=0.535 \) in Hong Kong (38 male, 33 female) to \( x=0.689 \) in Scotland (82 male, 37 female). However, where there were large numbers from the U.S. of 21,481 cases and 19,059 cases, the male fractions converged to 0.610 and 0.613 respectively, as following from The Law of Large Numbers [23]. Thus, studies with small sample numbers must be viewed carefully as many such SIDS studies lead to irreproducible conclusions. For example, a recent study in Aarhus, Denmark [24] reported for 1992-1993 there were 26 SIDS, 18 male, \( x=0.69 \) and for 1994-2008 there were 56 SIDS, 33 male, \( x=0.59 \). However, when combined, the 82 SIDS with 51 male had a male fraction of \( x=0.62 \) very close to the 50 male and 0.61 male fraction expected. In contrast, the 1969-1980 Finnish data [25] in our list [9] with 311 SIDS, 201 male, \( x=0.646 \) led to an erroneous estimate of 100% male excess in SIDS by other authors [13] who ignored the context it holds with the larger studies shown in Table 1.

| Cause of Death | Years | ICD7 [27] | ICD8 [27] | ICD9 [28-30] |
|---------------|-------|-----------|-----------|--------------|
|                |       | Total     | Per Above |               |
|               |       |           |           |               |

### Table 1: Male Fraction of 36 postneonatal SIDS data sets [9] meeting 1969 SIDS definition [22]. *M:F ratio reversed in reference;**100% autopsied; ***Divided to show constancy; ****Subtracted from total England and Wales.
Table 2: ICD Classes of Sudden Respiratory Death and Secondary SIDS (1b) in England and Wales [not all primary SIDS 1(a)]

| Years          | Cause of Death                  | Male     | Female   | Male fraction |
|----------------|--------------------------------|----------|----------|---------------|
| 1965-1968 E&W  | SRD at home                     | 4,081    | 2,782    | 0.5946        |
| 1969-1976 E&W  | SRD at home                     | 7,131    | 4,661    | 0.6047        |
| 1969-1976 E&W  | SRD in hospital                 | 2,375    | 1,564    | 0.6029        |
| 1969-1976 E&W  | All other causes at home*       | 1,299    | 883      | 0.5953        |
| 1969-1976 E&W  | All other causes in hospital*   | 1,344    | 950      | 0.5859        |
| 1979-1983 E&W  | SIDS 1a                         | 3,127    | 2,036    | 0.6056        |
| 1979-1983 E&W  | SIDS 1b                         | 642      | 424      | 0.6022        |
| 1986-1992 E&W  | SIDS 1a                         | 4,927    | 3,099    | 0.6139        |
| 1986-1992 E&W  | SIDS 1b                         | 446      | 244      | 0.6464        |
| 1993-1994 E&W  | SIDS 1a+1b                      | 552      | 360      | 0.6053        |
| 1967-1988 Norway | SIDS 1a                        | 852      | 585      | 0.6013        |
| 1967-1988 Norway | SIDS 1b**                      | 346      | 221      | 0.6102        |

Table 3: shows the male fractions of SIDS, SRD and secondary SIDS 1b in England and Wales 1965-1992 [27-30] and Norway 1967-1988 [31].* Sudden unexpected deaths requiring autopsy, but not SRD or congenital anomaly; **Non-SIDS reclassified as SIDS after review of case files.

| U.S. Cause of Infant Death, 1968-2010 | Male Deaths | Female Deaths | Male Fraction |
|---------------------------------------|-------------|---------------|---------------|
| Accidental suffocation and strangulation in bed (ASSB) | 6,891 | 5,051 | 0.5770 |
| Acute respiratory infections (ARI) | 4,392 | 2,949 | 0.5983 |
| Anomalies of the great veins (AVG) | 1,938 | 1,207 | 0.6172 |
| Bronchopulmonary Dysplasia (BPD) | 7,049 | 4,486 | 0.6110 |
| Congenital anomalies of respiratory system (CARS) | 19,087 | 12,771 | 0.5991 |
| Chronic obstructive pulmonary disease (COPD) | 1,685 | 1,007 | 0.6259 |
| Hypoplastic left-heart syndrome (HLHS) | 12,922 | 8,402 | 0.6060 |
| Respiratory Distress Syndrome (RDS) | 97,323 | 61,025 | 0.6146 |
| Hyaline membrane disease (HMD) | 97,323 | 61,025 | 0.6146 |

Table 3: ICD Classes of Sudden Infant Death Syndrome (SIDS) and Other Respiratory Diseases in England and Wales [not all primary SIDS 1(a)]

| Cause of Death                  | Male     | Female   | Male fraction |
|---------------------------------|----------|----------|---------------|
| Accidental suffocation and strangulation in bed (ASSB) | 5,754 | 3,988 | 0.5770 |
| Acute respiratory infections (ARI) | 4,392 | 2,949 | 0.5983 |
| Anomalies of the great veins (AVG) | 1,938 | 1,207 | 0.6172 |
| Bronchopulmonary Dysplasia (BPD) | 7,049 | 4,486 | 0.6110 |
| Congenital anomalies of respiratory system (CARS) | 19,087 | 12,771 | 0.5991 |
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| Respiratory Distress Syndrome (RDS) | 97,323 | 61,025 | 0.6146 |
| Hyaline membrane disease (HMD) | 97,323 | 61,025 | 0.6146 |
We next reported [8] that many causes of infant respiratory deaths had virtually the same exact male fraction as SIDS implying that they had the same underlying terminal X-linked mechanism as SIDS. This was evident from the reporting of "secondary SIDS" as defined by Emery and Weatherall [26]. That is where the underlying primary non-SIDS cause of death on the death certificate would be given the rubric 1a, 1b for SIDS when a possible secondary cause listed as "sudden death or SIDS was considered but not chosen as 1a." Table 2 shows primary ICD causes of infants' sudden respiratory death certified by coroner (SRD) plus cases where SIDS was mentioned as a secondary (1b) possibility [27-29]. Table 3 shows that the male fraction of these secondary (1b) SIDS is the same as that for primary (1a) SIDS.

In 2004 we followed up our earlier gender analyses in Tables 1 and 3 [13]. We used CDC data [32] that showed that the same ~50% male excess appeared in almost all the respiratory causes of infant death in the U.S. from 1979 to 1998, and that cardiac causes of infant deaths by leading to cardiac failure had a significantly lower male excess of order ~10%. In 2013 we updated the 2004 paper with additional CDC mortality data that extended the years of U.S. data from 1968 to 2010 as shown in Table 4 [21]. We chose these 11 causes of infant respiratory deaths based on their high numbers of cases and their respiratory terminal events. These cases were: Accidental suffocation and strangulation in bed, including positional asphyxia (ASSB); Acute respiratory infections, excluding influenza (ARI); Anomalies of the great veins (AGV); Bronchopulmonary dysplasia (BPD); Congenital anomalies of the respiratory system (CARS); Chronic obstructive pulmonary disease (asthma, bronchitis and emphysema) (COPD); Hypoplastic left-heart syndrome (HLHS); Respiratory distress syndrome, hyaline membrane disease (RDS, HMD); Sudden infant death syndrome (SIDS); Suffocation by inhalation of food (including gastric content) or foreign object (SIFFO); and Unknown causes (other ill-defined and unspecified causes) (UNK). See [21] for the ICD rubrics corresponding to these respiratory conditions.

Table 5: Infant Respiratory Deaths: Global [9], Australia [33,34], Canada [35], England & Wales [27], Norway [31], European Union [36], and U.S.A. [32], all with ~50% male excess. "Sudden Respiratory Death, while unattended at home, requiring autopsy by coroner. "About 70% of SRDs are due to SIDS." [27]; **"Sudden Respiratory Death, Unexpected while attended in Hospital, requiring autopsy by coroner [27]; ***15 European Countries 1994-1998; 27 European Countries 1999-2010 [36].

Discussion

As we have shown here, all the different causes of infant respiratory death must have the same terminal event because they have the same male fraction. We propose that the common terminal event is the death of respiratory control neurons in the brainstem. There is no other explanation for the common ~0.60 male fraction from all these different causes of death, both the explained and the inexplicable. The explainable respiratory deaths we covered that are apparent at autopsy are ARI, AGV, BPD, CARS, COPD, HLHS, HMD, RDS, SIFFO, UNK. The inexplicable deaths are SIDS and UNK. The deaths by ASSB can be either explained or inexplicable depending on the adequacy of the death scene investigation and the accuracy of the description of the death scene by the person discovering the infant who in virtually all

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**Table 4:** CDC Data on 453,953 male and female infants < 1 year Respiratory Deaths in the U.S. 1968-2010 with male fraction 0.6034 [32].

**Table 5:** Infant Respiratory Deaths: Global [9], Australia [33,34], Canada [35], England & Wales [27], Norway [31], European Union [36], and U.S.A. [32], all with ~50% male excess. "Sudden Respiratory Death, while unattended at home, requiring autopsy by coroner. "About 70% of SRDs are due to SIDS." [27]; **"Sudden Respiratory Death, Unexpected while attended in Hospital, requiring autopsy by coroner [27]; ***15 European Countries 1994-1998; 27 European Countries 1999-2010 [36].

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cases picks up the infant and attempts resuscitation. We neglect here the rare cases of infanticide by gentle suffocation that leave no evidence and result in an incorrect cause of death. Figure 1 from Emery [37], adjusted and used with permissions, shows the possible ways that cerebral hypoxia can be caused that leads to SIDS by degeneration and cell damage within the respiratory centers of the brainstem. Note that the SIDS risk factors of prone sleep, parental smoking, smog exposure, apnea and anemia were added by us to Emery's model along with the X-linkage gate leading to the cemetery as shown. We maintain that an X-linkage leads to death of these respiratory control cells. Only those subjects with the dominant protective X-linked allele can survive the transient hypoxic conditions as shown.

Figure 1: A ~1972 model for SIDS aetiology proposed by the late John L. Emery [37] with shaded items added by the authors, with permission of Dr. Emery and Academic Press, to show six risk factors more recently discovered (apnea, anemia, parental smoking, smog, prone sleep position and an X-linkage).

Conclusions

All infant deaths from the cited natural respiratory causes appear to have a common X-linked recessive terminal event. We have shown previously [21] that if the susceptible infant avoids the conditions leading to cerebral anoxia and subsequent encephalopathy that the same X-linked recessive allele can penetrate post infancy, in childhood or adulthood If the X-linked dominant allele codes for an enzyme that allows the neurons in the brainstem to survive hypoxia through a shift or adulthood If the X-linked dominant allele codes for an enzyme that allows the neurons in the brainstem to survive hypoxia through a shift or adulthood. Only those subjects with the dominant protective X-linked allele can survive the transient hypoxic conditions as shown.

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