Sex linked deafness: Wilde revisited

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Abstract
Sex linked recessive deafness is a rare cause of male genetic deafness, estimated to account for 6·2% of male genetic deafness in 1966. A male excess was found in the deaf population of Ireland in 1851. Re-evaluation of this survey of 1851 confirms sex linked deafness as a factor in the disproportionate number of deaf males and suggests that 5% of congenital male deafness was the result of sex linked recessive deafness. This study confirms that a small but constant proportion of male deafness is the result of sex linked recessive deafness. The figure derived is used to calculate an empirical risk for carrier status in female sibs of isolated cases of male deafness.

Table 1 Breakdown of Wilde's figures.

4151	Total deaf/mute
3325	Deaf from birth
159	Idiotic/paralysis
400	Deafness of postnatal onset
126	Unknown
140	Others

Table 2 Sex distribution among the deaf.

	Male	:	Female
Congenital	100	:	74·61
Acquired	100	:	91·46

Perhaps better remembered nowadays as the father of Oscar, William Wilde (1815–1876) was a distinguished ear, nose, and throat surgeon of the mid-nineteenth century.[1] [2] He was responsible, in 1851, for conducting the largest survey of deafness which has been undertaken in Ireland.[3] Among his observations he remarked that "in accordance with one of those immutable laws which appear to govern mankind in all countries, more males are born than females: but, as in the first years of life, more boys die than girls, the sexes soon become equalised and subsequently there is, in every population, an excess of women over men. Yet the proportion of male deaf mutes exceeds the female considerably but it differs somewhat in the two great classes of congenital and acquired deafness". Wilde was at a loss to explain his observation fully (tables 1 and 2). However, deafness confined to males only in a family and obeying a pattern of sex linked inheritance has been reported this century. A wide geographical and racial spread of this condition is confirmed by reports from the USA,[4] [5] Australia,[6] Belgium,[7] Norway,[8] Italy,[9] South Africa,[10] and Great Britain.[11]

Sex linked deafness is, however, a rare condition and its exact prevalence is uncertain. Fraser[12] calculated

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that sex linked deafness accounted for 6·2% of male genetic deafness. A reanalysis of the unequal sex distribution of deafness to which Wilde drew attention is undertaken here, to calculate the contribution of sex linked deafness to this male excess. The results correlate well with subsequent estimates of the prevalence of sex linked genes as a cause of deafness.

Methods
To calculate the contribution of sex linked deafness to this survey three groups must be considered.

(1) Sibships with multiple affected deaf boys, who have inherited their deafness from a normally hearing, heterozygous mother.

(2) Sibships with one deaf boy only, who has inherited his deafness from a normally hearing, heterozygous mother.

(3) Boys who have sex linked deafness owing to new mutations.

A total of 459 sibships was detailed with two or more deaf children (table 3). In 122 such sibships males only were affected, while in only 65 families was the deafness confined to females. This excess of deaf males is especially noticeable among those 287 sibships with two deaf children (male:female 97:48). Although these data were collected as part of a national census and therefore should not be prone to ascertainment bias, this male excess seems rather high. Some of this excess may, as suggested by Fraser,[12] represent environmental as well as genetic causes. Hence, for the purpose of calculating the

Table 3 Breakdown by sex of families with multiple deaf children.

No of deaf children in family	No of families with this number of deaf children	No of families with males only affected	No of families with females only affected	No of families males and females affected
2	287	97	48	142
3	127	18	14	95
4	33	5	2	26
5	8	2	0	6
6	3	0	0	3
7	1	0	1	0
Total	459	122	65	272

contribution of sex linked genes to the total deafness load, deafness will be taken as definitely hereditary only in those sibships with three to seven deaf sibs. Within this group there is still a marked preponderance of male only sibships (25 male:17 female) (table 4).

Male excess has been an invariable feature of surveys of deafness. Wilde found a male:female excess of 1·3:1, Fraser 1·18:1, and a survey of deafness in EEC countries in 1980 recorded a male:female excess of 1·2:1.[13]

Consideration of data in relation to sex linked deafness

Firstly, sibships with multiple affected deaf sons of heterozygous mothers must be considered. If there are two deaf sibs in a sibship and the deafness is

Table 4 Breakdown by sex of sibships with three to seven deaf children.

No of deaf children in family	No of families	No of families with males only deaf	No with females only deaf
3	127	18	14
4	33	5	2
5	8	2	0
6	3	0	0
7	1	0	1
Total	172	25	17

independent of sex the chance that both will be male is 1 to 3. For sibships with three deaf members the ratio is 1 to 7 and, by simple formula, if there are k deaf members the chance that all the deaf will be male is $1:2^k-1$. This formula allows us to calculate the expected number of sibships in whom deafness would be exclusively male. We can then compare this figure with those obtained from Wilde's survey (table 5).

To the nearest whole number, 29 cases of sex linked deafness can be attributed to those sibships in which more than one deaf boy was found.

Sex linked deafness is not confined to sibships wherein more than one boy is deaf. The value of such restriction in the initial part of the calculation is that it enables us to prove mathematically that an excess of males exists in such sibships, which can be accounted for by a sex linked form of deafness, whose expression is confined to males only. Having thus shown that there is evidence for sex linked deafness in Wilde's survey, let us now look at that group where deafness was an isolated finding affecting one child only. Such cases accounted for 2512 deaf people in Wilde's study, the male:female sex distribution of which was 100:73. The causes of deafness in these people must be a heterogeneous group including prenatal and early postnatal infection, autosomal recessive, autosomal dominant, and sex linked deafness. From this group must be extracted those males whose deafness is the result of sex linked genes. It is not correct to suggest simply that all excess males in this group are the result of sex linked genes. The reason for this is that in such a heterogeneous group, some of the male excess

Table 5 Calculation of the number of excess deaf males over the expected number.

No of deaf children (k)	Total no of sibships with this no of deaf children other than males only deaf (n)	Expected no of males only deaf $\dfrac{n}{2^k-1}$	Observed no of males only deaf	Excess no of sibships	Excess no of cases
3	(127–18) 109	15·57	18	2·43	(×3=7·29)
4	(33–5) 28	1·87	5	3·13	(×4=12·52)
5	(8–2) 6	0·19	2	1·81	(×5=9·05)
6	(3–0) 3	0·048	0	−0·048	(×6=−0·288)
7	(1–0) 1	0·0078	0	−0·0078	(×7=−0·0546)
					=28·52 cases

results from postnatal infections, some of which are ototoxic, as such causes of acquired deafness are generally characterised by a male excess, a fact noted by Wilde in his study.[14-16]

The number of cases of male deafness determined by sex linked genes in families with multiple deaf members is 29. If the number of isolated cases and number of multiple cases which would be born to a theoretical population of normally hearing women heterozygous for a sex linked recessive gene are considered, we can accurately estimate the number of cases resulting from this gene in those sibships wherein only one boy was deaf. Ascertaining such women through their offspring, only those who have had at least one affected son can be detected. If they were each to have only one affected son, then all such cases would be isolated cases. If they have two sons, then for each sibship with both sons affected, there will be two sibships with one affected and one unaffected son and one sibship with two unaffected sons. In this case the proportion of isolated to multiple cases will be 1:1, and of isolated to total cases will be 1:2. In general, in a proportion $^nC_1 1/2^n$ of families containing n brothers, one will be affected, two in a proportion $^nC_2 1/2^n$, etc. The proportion of isolated to total cases therefore becomes $1/2^{n-1}$.

Using this formula, Fraser[12] showed that for 8304 cases of sex linked recessive deafness in families with multiple deaf members, 9438 isolated cases can be expected from the same cause. Therefore we can expect a further 33 cases (to the nearest whole number) of sex linked recessive deafness in the isolated case group to correspond to the 29 already identified in the multiple case group.

Thus, 62 (29+33) is a mathematical estimate of the number of cases of sex linked deafness born to heterozygous mothers and identified in Wilde's series of 4151 cases. Finally, carriers of fresh mutations must be calculated, that is, boys who are deaf because of a sex linked recessive gene, but whose mothers are not carriers of this gene. This number can be derived from the formula C=1/3 (1-f) (62+C), where f= fertility, relative to normal, of affected males. This equation assumes an equal mutation rate in male and female X chromosomes. As we do not know how many of the deaf were married we do not have an actual figure for f. However, the outcast status of deaf people in that era, as chronicled by Wilde, suggests that reproductive opportunities for deaf people were limited. A Danish study in 1892[17] calculated f for deaf males as 0·15 and we may use this estimate for f in Wilde's cohort.

Hence, C=1/3 (1−0·15) (62+C).
     C=24·5 (say 25).

The composite estimate of the total number of cases in Wilde's survey resulting from sex linked recessive deafness is 87 cases (29+33+25). Wilde tells us that 3325 congenitally deaf were reviewed and these were skewed for sex distribution with a ratio 100 males: 74·6 females. This indicates that 1905 congenitally deaf males and 1420 females were identified.

In re-evaluating Wilde's survey, deaf males were excluded from sibships wherein two brothers only were deaf. There were 97 such sibships, accounting for 194 cases of male deafness. Hence the percentage of congenital male deafness accounted for by sex linked deafness genes is 87 cases in 1711 cases of male deafness (1905–194). This represents 5·08%.

The practical application of knowing that approximately 5% of male genetic deafness is sex linked is that it enables an empirical risk figure for sex linked deafness to be calculated for genetic counselling purposes. The sister of a deaf man with no other history of deafness in the family can be shown to have a 1·3% risk of being a carrier of a gene for sex linked deafness in the following manner.

If environmental causes are ruled out, 70% of all isolated cases of deafness are genetic[18]; 5% of male deafness is sex linked, of whom approximately 25% are new mutations. Hence 75% of males deaf for this reason were born to carrier females. A sister of such a man has a 50% chance of inheriting her mother's carrier X chromosome. Therefore, the girl's risk of being a carrier is: $7/10 \times 1/20 \times 3/4 \times 1/2 = 1·3\%$.

Discussion

A figure of 5·08% represents the most conservative figure for sex linked deafness in Wilde's survey. The decision to exclude the sibships with two males only deaf is vindicated by the fact that, if included, the results would suggest that 15% of all male genetic deafness is sex linked. There is no evidence in any other published report to support so high a figure. Furthermore, personal experience in collecting pedigrees with sex linked deafness also suggests the lower figure as the more likely.

Chung *et al*[19] calculated that sex linked genes accounted for 1·3% of all cases of congenital deafness. This figure was obtained by expressing the excess number of congenitally deaf males as a percentage of the total number.

Given that their figure is based on 1248 male and 1217 female patients and that genetic deafness accounts for approximately 50% of all deafness,[20 21] it can be calculated that this approximates to 5·12% of male genetic deafness. A gene frequency of 0·8% × 10^5 and mutation rate of 2×10^{-6} was calculated.

Fraser[12] has already taken issue with the estimates of Chung *et al*.[19] Sex linked deafness was found to account for 6·2% of male genetic deafness. Gene frequency was calculated at 0·00003 and mutation rate at $7·5 \times 10^{-6}$.

In the current analysis, gene frequency may be

calculated at 0·000025 and mutation rate at $7·0 \times 10^{-6}$. The figures are calculated assuming that sex linked recessive deafness is determined by a single locus on the X chromosome.

The concordance of figures between this study and those discussed above[12][19] suggests a small but constant proportion of male deafness is determined by sex linked recessive genes. A reminder of sex linkage as a cause of deafness is especially relevant to current attempts to map the gene or genes responsible for non-syndromic sex linked deafness.[22][23]

Wilde's work also emphasises the medical and social changes with regard to deafness that the last 150 years have brought. First among these is that he identified only 400 deaf patients whose deafness was postnatally acquired. This reflects the very high mortality of meningitis and other ototoxic infectious illnesses prevalent in the 1850s. The increased social integration of deaf people into the community means that nowadays many deaf people have families, which was very exceptional in 1850. It may be argued that the figures derived above come from a group labelled congenitally deaf and so include cases whose deafness was the result of prenatal infection. This is indeed true, but the calculations are important in that they bear statistical proof that sex linked recessive deafness is an entity in the Irish population and that they allow an empirical risk figure to be derived which may be of practical value to geneticists. A recent appeal by the author to appropriate colleagues in Ireland failed to identify any cases of sex linked deafness. This must represent a failure to take a family history by clinicians or else an inability to evaluate the family history. In either case appropriate counselling of patients as to the genetic implications of their handicap for their offspring cannot be imparted. Perhaps we should remember the importance of being earnest, particularly in taking the family history.

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