Hereditary Chronic Kidney Disease: An Alternative to Partial Sex-Linkage in the Utah Kindred

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A LARGE KINDRED residing in Utah and containing many persons with chronic kidney disease was first described in 1951 (7, 11). The unusual distribution of affected persons appeared consistent with dominant partial sex-linkage, a mode of inheritance postulated to occur in humans by Haldane (4). This kindred has been studied again after a 5 year interval, and the second report has recently been published (8). The authors re-affirm their earlier belief that they are dealing with an example of dominant partial sex-linkage.

The kindred, as originally described, was analyzed by the method of sequential analysis by Morton (6), who was unable to reject partial sex-linkage in this kindred with the same assurance as in Haldane's original group of diseases. However, he obviously felt strongly that the disorder was inherited in some other fashion, because he suggested an alternative which is highly unlikely on *a priori* grounds, i. e. dominant complete sex-linkage for most of the kindred and some other disease altogether to account for the several examples of father-son transmission. As my title suggests, I agree with Morton that all possible alternatives should be excluded before partial sex-linkage is accepted, because, like him, I doubt that partial sex-linkage occurs. In the course of examining the alternatives, I believe that I have discovered the correct mode of inheritance. While my explanation is somewhat complex, the *a priori* probability that it is correct is probably greater than that of Morton's suggestion, and it is, like his, not impossible on cytological grounds.

The alternative which I am proposing is attractive, because it explains certain features of the kindred which partial sex-linkage will not explain. Specifically, the data are consistent with an autosomal, dominant trait, more severe in males. There is a deficiency of males over the entire kindred, due to a deficiency of affected males among the children of affected parents of *both* sexes. This deficiency results, presumably, from a significantly higher death rate of affected males very early during intrauterine life, because the kindred as reported does not mention frequent abortions, miscarriages or neonatal deaths. The fact that the mutant gene is pleiotropic and incompletely penetrant in addition to having an expression which varies with the sex of the affected person makes it easy to understand why partial sex-linkage has been mistakenly proposed.

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INHERITED CHRONIC RENAL DISEASE IN OTHER KINDREDS

A considerable amount of literature on inherited chronic "Bright's disease" has accumulated since about 1875. The earlier reports are listed in the bibliographies of Alport (1) and Eason and others (2). These earlier kindreds will not be summarized, because important persons in the kindreds were not studied and methods of study varied widely. When the kindreds reported by Alport (1), Reyersbach and Butler (9), Sturtz and Burke (12), Hamburger and others (5), Goldbloom and others (3), and Robin and others (10), are collated, however, certain recurring features become apparent. These may be summarized as follows:

1. Inherited chronic renal disease has usually been associated with nerve deafness, occasionally with eye lesions.
2. The renal disease has been more severe in males than females; the males usually have died young without issue, while the females often have lived to a ripe age and have had many children.
3. Few females with renal disease have also been deaf, but many males have shown both defects.
4. A few persons have shown only deafness.
5. Rarely, persons who have appeared completely normal, and occasionally persons who have shown only deafness, have transmitted the kidney disease.
6. Male-to-male transmission of the disorder has been observed, but only in Robin's kindred (only one other of the 51 affected males in this group of kindreds had a son, and he was normal).
7. The severity of the disorder has varied from kindred to kindred (see Robin).
8. The clinical and pathological picture in some kindreds has appeared to be

TABLE 1. OFFSPRING OF AFFECTED PERSONS (FROM LITERATURE, EXCLUSIVE OF KINDRED REPORTED BY PERKOFF AND OTHERS)

Source of data	Affected Males							Affected Females						
				Sons		Daughters					Sons		Daughters	
	Total males	No. deaf	No. of fathers	Affected	Normal or unknown	Affected	Normal or unknown	Total females	No. deaf	No. of mothers	Affected	Normal or unknown	Affected	Normal or unknown
Alport	7	3	0	0	0	0	0	12	5	6	7	4	10	5
Reyersbach	15	12	1	0	1	0	0	9	1	8	15	8	8	14
Sturtz	8	8	0	0	0	0	0	5	1	5	4	7	3	7
Hamburger	7	4	0	0	0	0	0	6	0	3	7	3	5	3
Goldbloom	3	2	0	0	0	0	0	1	0	1	3	1	0	0
Robin	11	?	6	3	4	5	4	6	?	1	3	3	1	0
Totals	51	>29	7	3	5	5	4	39	>7	24	39	26	27	29
Sex ratios				8		9					65		56	
Total children				17							121			

that of "chronic pyelonephritis" while in others it has appeared to be "chronic glomerulonephritis". Nerve deafness has been observed in persons with both "types" of chronic renal disease.

Table 1 shows the marked difference in fitness between affected males and affected females in these kindreds. It will be noted that only 7 of 51 affected males had children, producing only 17. On the other hand 24 of 39 affected women had children, a total of 121. Also, Table 1 demonstrates that deafness has been more common among affected males (29/51) than females (7/39). Finally, it should be noted that the various ratios are not markedly abnormal among the progeny of affected persons, although there has been an excess of affected children and also an excess of males.

ANALYSIS OF THE RE-EXAMINED UTAH KINDRED

The re-evaluation of the Utah kindred (8) is notable in several respects. This kindred is far and away the largest yet reported, and it has been studied very extensively. Considerably more people have been examined (168) than 5 years ago, and 97 persons have been re-examined. Also the kidneys of 4 living patients and 1 dead patient have been biopsied, and another affected person has been autopsied.

It is interesting to note that the kidneys at the most recent autopsy suggested "chronic glomerulonephritis", because the published pictures from an earlier autopsy clearly showed the changes of "chronic pyelonephritis" (7). The occurrence of both forms of chronic renal disease in a single kindred also having nerve deafness is an interesting observation, because in each of the kindreds reported earlier nerve deafness had been associated with only one type of chronic renal disease.

The sex-limited nature of the deafness is shown in Table 2. Here it can be seen that 19 of 20 cases of deafness were in males, and that deafness was inherited by these men from affected parents of both sexes. Furthermore, deafness is associated with renal disease too frequently for this combination to represent the coincidence of independent double heterozygosity. It is more reasonable to assume that deafness and renal disease are manifestations of the same pleiotropic gene. The additional evidence for pleiotropy is that some persons who are deaf alone have transmitted renal disease (III-7, III-43), and some who have had only renal disease have transmitted deafness (II-16, II-17, III-1, III-36).

The really peculiar nature of the Utah kindred begins to appear in Table 3 where the sex ratios are listed by generations, all persons considered. The ratios are reversed in generations II, III and IV, where the females considerably outnumber the males. The excess of females is statistically significant when the entire kindred is considered and unity expected ($\chi^2 = 4.41$, $p < .04$).

It is important to emphasize at this point my definition of an affected person as

TABLE 2. DISTRIBUTION OF DEAFNESS AMONG AFFECTED OFFSPRING IN THE UTAH KINDRED

Transmitting Parents	Deafness Alone		Deafness Plus Kidney Disease		Totals
	Males	Females	Males	Females	
Mothers	4	0	11	1	16
Fathers	3	0	1	0	4
Totals	7	0	12	1	20

TABLE 3. SEX RATIOS AMONG OFFSPRING IN THE UTAH KINDRED, BY GENERATIONS

Generation No.	Males	Females	Unknown	Total	Ratio M:F
I	1	1	0	2	1.0
II	1	9	0	10	0.11
III	25	34	1	60	0.74
IV	86	104	0	190	0.73
V	8	8	0	16	1.0
Totals	121	156	1	278	0.78

TABLE 4. DISTRIBUTION OF GRANDCHILDREN OF THE SEVEN AFFECTED FEMALES IN GENERATION II OF THE UTAH KINDRED

Affected Parents in Gen. III	Grandsons in Gen. IV				Granddaughters in Gen.IV				Totals
	Normal	Affected	Unk.	Total	Normal	Affected	Unk.	Total	
13 Males*.....	15	5	3	23	10	21	2	33	56
13 Females†.....	16	8	5	29	22	16	5	43	72
26 Parents.....	31	13	8	52	32	37	7	76	128

* 12 of 13 males show clinical effects of abnormal gene.

† 4 of 13 females show clinical effects of abnormal gene.

this may be at variance with that of the authors and is crucial to the scoring procedure. I define an affected person as:

1. A member of the kindred who shows either deafness or renal disease or both, or
2. A member of the kindred who has had at least 1 child showing either deafness, renal disease or both.

Table 4 records the phenotypes of the grandchildren of the 9 affected women in Generation II when affected persons are scored by my criteria. The grandchildren have been tabulated separately for affected fathers and affected mothers. If complete sex-linkage were the mode of inheritance, the affected fathers of Generation III should have had only normal sons and affected daughters. Complete sex-linkage is rejected, because there was male-to-male transmission in 5 instances, and 10 normal daughters were observed. The former is the more important observation, because some of the "normal" daughters might well represent asymptomatic carriers (9 of the 10 asymptomatic carrier parents of Generation III were female).

If partial sex-linkage were the mode of inheritance (and some crossing-over had occurred), it would be expected that the affected grandchildren from affected fathers would be predominantly female, and the affected grandchildren from affected mothers would be equally divided between males and females.

Examination of the first line in Table 4 (offspring of affected males) appears at first glance to support partial sex-linkage with some crossing-over, because there is not a 1:1:1:1 ratio, but an excess of affected females and a deficiency of affected males. It should be pointed out, however, that there is also a total deficiency of males from affected fathers, the male: female ratio being 23:33.

The 2nd line of Table 4, children of affected mothers, is disturbing from the standpoint of partial sex-linkage, because here also there is an abnormal sex ratio (29M:43F) caused by a deficiency of affected males.

TABLE 5. TESTS OF SIGNIFICANCE OF RATIOS IN TABLE 4, ASSUMING INHERITANCE TO BE SIMPLE AUTOSOMAL DOMINANCE WITH FULL PENETRANCE (1:1:1:1)

Ratios Tested	Adjusted χ^2	P, 1 d.f.
Total males v. total females (52:76)	4.49	$<.04$
Affected v. normal persons (50:63)	1.51	$>.20$
Affected females v. normal females (37:32)	0.33	$>.50$
Affected males v. normal males (13:31)	7.40	$<.01$
Normal males v. normal females (31:32)	0.03	$>.80$
Affected males v. affected females (13:37)	11.52	$<.01$
Heterogeneity (1:1:1:1 ratio)		
a. Actual (31:13:32:37)	5.38	$<.03$
b. With 24 additional affected males (31:37:32:37)	0.0062	$>.90$

TABLE 6. SEX RATIOS AMONG OFFSPRING OF PRESUMABLY NORMAL PARENTS IN THE UTAH KINDRED

Parents	Sons	Daughters	Unk.	Total	Ratio M:F
13 Mothers	27	22	0	49	1.22
3 Fathers	3	6	0	9	0.50
16 Parents	30	28	0	58	1.07

It is clear in the last line of Table 4 that there is a sizeable deficiency of male progeny when all persons are considered (76 − 52 = 24). This deficiency of 24 males can be seen to be in the category of affected males, because the addition of 24 males in this category creates an almost perfect ratio for an autosomal dominant (31:37:32:37). It should be emphasized that this deficiency of affected males is the sum of separate deficiencies from *both affected fathers and affected mothers.*

Table 5 contains χ^2 tests of significance of the various categories of children of affected persons, assuming that the disorder is actually transmitted as a fully penetrant autosomal dominant. The deficiency of affected males is clearly seen to be the factor which has caused the significant disturbances in the various ratios. The heterogeneity becomes insignificant, for example, in the last line when the deficiency of 24 affected males is replaced. It is important to emphasize that the deficiency is of *affected males not affected females.* If a deficiency of affected females were observed, lack of penetrance in the asymptomatic carriers might be suspected. However, the fact that the deficiency has occurred in the sex with the more severe clinical disease suggests that the deficiency has resulted from a significantly higher death rate at some point in gestation among the affected males.

Table 6 records the sex ratios among the presumably unaffected members of the kindred. The usual slight excess of males over females is found in this part of the kindred. Thus it becomes very difficult to attribute the reversed sex ratio among affected persons to some tendency in the kindred not related to the kidney disease.

SUMMARY

Analysis of the Utah kindred with chronic kidney disease and nerve deafness shows it to be comparable in most respects to other pedigrees in the literature. It is, however, incomparable in extent and thoroughness of study. This kindred thus provides unique insights into the nature of hereditary chronic renal disease.

The kindred appears to be abnormal in several respects not emphasized by the authors, i. e.

1. There is a significant deficiency of males in the entire kindred, and

2. There is a deficiency in Generation IV of affected grandsons but not affected granddaughters from the affected grandmothers of Generation II. The deficiency has occurred, because *both the affected fathers and affected mothers of Generation III failed to produce the expected numbers of affected sons.*

I suggest the following hypothesis as more satisfactory than dominant partial sex-linkage for explaining the inheritance of the syndrome in this family.

1. It is transmitted as a sex-influenced, dominant trait, much more severe in males (to the point that 50% of affected males are never seen, presumably because of death *in utero*). Sex limitation is not complete, however, because some transmitting females show the defect.

2. The mutant gene is pleiotropic, incompletely penetrant (penetrating less frequently in females than males) and resides on an autosomal chromosome.

This complex hypothesis of autosomal transmission fits the observations better than does dominant partial sex-linkage. For example, the deficiency of affected sons from affected fathers is explained by either hypothesis. Only the autosomal hypothesis with the added modifications, however, explains also the discrepancy of sex ratio and the deficiency of affected grandsons from both affected mothers and affected fathers. The most appealing feature of the hypothesis, of course, is that it is consistent with the cytological observations regarding the X and Y chromosomes in humans.

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