Am J Hum Genet 35:1241–1251, 1983

X-Linked Inheritance of Alport Syndrome: Family P Revisited

SANDRA J. HASSTEDT[1] AND CURTIS L. ATKIN[2]

SUMMARY

Likelihood analysis using two autosomal/X-linked mixed models confirmed that Alport syndrome is an X-linked dominant disease in a large Utah kindred, family P. The penetrance was estimated as .85 in females and 1.0 in males. Previously reported abnormal segregation ratios were reexamined. No excess of affected offspring of affected parents was found. Nor was the penetrance in daughters of asymptomatic carrier mothers found to be lower than in the daughters of symptomatic mothers, although the sample size was small. However, there was an unexplained deficiency of sons of affected fathers. There was no deficiency of sons of affected mothers, nor was there a deficiency of males in the kindred.

INTRODUCTION

Alport syndrome is a form of hereditary progressive glomerulonephritis and sensorineural deafness [1, 2]. Males are more severely affected. Their disease, detectable in early childhood through urinary abnormalities and audiometry, eventually results in renal failure and deafness. Affected females usually have less obvious urinary abnormalities and less frequently develop uremia or deafness.

Since Alport syndrome occurs in successive generations within families and affected individuals usually have an affected parent, it is obviously dominantly inherited. It has been controversial whether the dominant locus is on an autosome [3–8], or on the X chromosome, or somehow strongly sex determined [9–14]. Recently, the suggestion has been made that both autosomal and X-linked forms occur [15].

Family P, most members of which live in Utah, was the first large pedigree of Alport syndrome to be studied [12, 14]. Renal failure in male members of this

Received January 5, 1983; revised April 11, 1983.

This work was supported by grants AM-26627, RR-64, and HD-17463 from the National Institutes of Health, 6-213 from the March of Dimes Birth Defects Foundation, and by the Hereditary Nephritis Foundation.

[1] Department of Human Genetics, University of Utah Medical Center, Salt Lake City, UT 84132.

[2] Departments of Internal Medicine and Biochemistry, University of Utah Medical Center.

family occurs in early middle age (mean ± SD = 33.3 ± 6.7 years, no. = 19 through 1982). Most affected males develop deafness. Pedigree members have been examined numerous times by investigators in Utah, and their data have been examined several times by other investigators. The Utah investigators have consistently concluded that the disease locus is on the X chromosome; others have differed with this opinion. We present here the first analysis to compare the fit of autosomal and X-linked inheritance of Alport syndrome in family P. Likelihoods of autosomal and X-linked models were computed and compared to the likelihood of a mixed model that included each as a submodel. In the past, some investigators found evidence for abnormal segregation in family P. We reexamine the evidence in this paper.

BACKGROUND

In the original reports of family P, Perkoff et al. [12] and Stephens et al. [14] proposed partial X-linkage as the mode of inheritance, that is, a locus located on the homologous portions of the X and Y chromosomes. Haldane's test [16] supported this conclusion, which was based on the observation that two of 17 sons and 18 of 22 daughters of males in the kindred were affected. The two affected sons and four unaffected daughters were thought to represent X-Y crossovers. The recombination fraction was estimated as .154 ± .058. A positive test for the disease was defined as findings of pyuria, bacteriuria, hematuria, proteinuria, or cylindruria. In addition, males with a family history indicating death from the disease were classified as affected and unexamined males over 26 without a family history of the disease were classified as normal. Deaf family members without urinary symptoms were considered unaffected.

Following the initial publication, Morton [17] reexamined these data and suggested X-linkage with incomplete penetrance in females as the mode of inheritance. He explained the two instances of male-to-male transmission as misdiagnoses.

Perkoff et al. [13] again favored a model of partial X-linkage after a second study of family P. The two cases of male-to-male transmission were not eliminated upon reexamination. The affected offspring of males in the family consisted of two of 20 sons and 24 of 29 daughters.

The next challenge to the conclusion of partial X-linkage was issued by Graham [18], who claimed that there was a deficiency of males over the entire family due to a deficiency of affected sons of affected parents of both sexes. There were 121 males and 156 females in the published pedigree. He explained the deficiency as prenatal death of affected males and proposed autosomal dominant inheritance for the disease. His numbers differed from earlier reports because of his inclusion among the affected of cases of deafness without associated renal disease.

Following this, abnormal segregation was reported for family P as well as for a second pedigree by Shaw and Glover [7]. Their counts showed that heterozygous mothers, who included unaffected carriers, transmitted the gene to 41 of 74 daughters, or 55%. Their proposed mode of inheritance was autosomal dominance with nonrandom disjunction of the chromosome with the disease allele in gametes deriving from affected females and preferential segregation of the autosomal nephritis allele with the X chromosome during spermatogenesis in affected males. They concurred with Graham [18] that the abnormal sex ratio was caused by early intrauterine loss of heterozygous male zygotes.

The finding of abnormal segregation was reaffirmed by MacNeill and Shaw [19] on a set of 35 pedigrees including family P. They also reaffirmed a previous suggestion, based on another pedigree [3], that penetrance was lower in the daughters of unaffected carrier mothers than in daughters of affected carrier mothers. In family P considered alone, the penetrance was not lower. The 10 normal carrier mothers (of Perkoff's 1958 pedigree) produced 14 affected of 30 daughters, or 47%, and the 11 affected mothers produced nine

affected of 23 daughters, or 39%. One would expect the first proportion to be larger because of the ascertainment bias of selection through affected children.

When family P members were again systematically examined [9], it was found that pyuria did not occur more frequently in family members than in a control group. The urinary abnormality considered the most reliable for diagnosis of Alport syndrome was microscopic hematuria. Under this more restrictive criterion, many new cases of hematuria were found and a number of diagnoses were changed. Most of the mothers formerly considered to be clinically normal obligate carriers were shown either to have hematuria or to have normal children. Also, the two supposed instances of male-to-male transmission were disproven; according to the records of Perkoff et al. [12–14], records in our possession, and repeated subsequent studies, the two supposedly affected sons and their five living offspring have never shown hematuria. Of Perkoff's five female exceptions to X-linkage [13], three are normal sibs of supposedly affected daughters of male family members—yet neither fathers nor children are affected by present urinary criteria—and two are normal daughters of known affected males, one (daughter) of whom now has two normal sons and the other has three sons with hematuria. The latter and two other females constitute the three known instances of normal female obligate carriers in family P [9]. The count of offspring of affected males then became 0 affected of 16 examined sons and 30 affected of 36 examined daughters. On the other hand, by present criteria, there are no known affected offspring of unaffected male family members.

This seemed to provide prima facie evidence for X-linkage with incomplete penetrance in females. The renal lesion appeared to be glomerulitis due to a consistent finding of red cells and red cell casts in the urine [9]. Renal biopsies showed the ultrastructural glomerular lesions characteristic of Alport syndrome ([18]; see [2] for review of ultrastructural studies in many kindreds).

METHODS

Family P was originally ascertained in 1949 when a family member solicited help from a University of Utah physician after five male members died of renal disease. Examinations of pedigree members have been conducted three times [9, 12, 13]. Anyone designated affected in the present analysis was found to have microscopic hematuria upon urinalysis by investigators at this institution.

Family P was defined as all descendants of a man born in 1844 and his wife born in 1860. Both were Welsh immigrants to Utah. An effort was made to examine all living family members. In addition to performing urinalyses, we interviewed family members and recorded the numbers of children and miscarriages. Currently, 459 individuals have been examined. Thirty-three of 216 males and 60 of 243 females were diagnosed as having Alport syndrome based on urinalyses showing microscopic hematuria. Eleven additional males and one female were known to be affected because a diagnosis of hematuria or of renal failure was obtained from medical records. Only the five males known from medical records to be affected before the study began were designated affected in the analysis.

Likelihoods were computed using PAP [20, 21], and the maxima were obtained with GEMINI [22]. The disease frequency was fixed at 1/5,000 for all analyses. This number was a rough estimate obtained from our observation of about 300 known cases in Utah and southern Idaho, with a population of about 1.5 million. The results varied little for any rare disease frequency. The likelihood was corrected for ascertainment through a man and four sororal nephews, two of whom were sibs. These were the family members who died of nephritis before the study began. The ascertainment correction was made by dividing the likelihood by the probability of observing this set of cases conditional on the model [23]. The data were analyzed using two different general models of mixed autosomal/X-linked inheritance. Each of these general models included X-linked inheritance and autosomal inheritance as special cases. The two general models are called the "linkage model" and the "transmission model" in the following descriptions.

Linkage General Model

The linkage model is formulated as two alleles at each of two loci, one locus determining the disease phenotype and the second locus determining sex [24]. If "*A*" and "*a*" are the disease and normal alleles, respectively, at the disease locus, and "*X*" and "*Y*" are the X and Y chromosomes, respectively, then the four haplotypes *aX*, *AX*, *aY*, and *AY* can give rise to seven genotypes: males *AX/AY*, *aX/AY*, *AX/aY*, and *aX/aY*, and females *AX/AX*, *AX/aX*, and *aX/aX*. X-linkage corresponds to a recombination fraction of zero between the two loci; autosomal inheritance is obtained when the recombination fraction is .5. For females, the penetrance for heterozygotes at the disease locus is estimated. For males, there are two classes of heterozygotes with respect to the disease locus depending on which allele at that locus is in haplotypic combination with the Y chromosome. If the disease is autosomal, both heterozygotes are affected, but if it is X-linked, only the heterozygote in which the disease allele is haplotypic with X is affected.Therefore, the second parameter that differs between the autosomal and X-linked models is the penetrance of genotype *aX/AY*. This penetrance is 0 for the X-linked model, 1.0 for the autosomal model, and is estimated for the mixed model.

X-linkage is generally considered as a possible mode of inheritance only when there exist no affected father-son pairs. Although absence of affected father-son pairs is possible if the disease is autosomally inherited, it would occur only rarely in large kindreds. Gladstien and Spence [25] present a method of correcting the likelihood of the autosomal dominant model for the absence of any male-to-male transmission. The likelihood of the autosomal model was corrected in this manner for the uniqueness of the observed pattern of disease in the pedigree if it were autosomal.

Transmission General Model

The transmission model [26] defines the transmission probabilities for each of three parental genotypes such that they depend on sex of the parent and sex of the offspring. For females in either model and for males in the autosomal model, genotype 1 is the affected homozygote, genotype 2 is the heterozygote, and genotype 3 is the normal homozygote. For males in the X-linked model, genotype 1 is not used, genotype 2 is the affected genotype, and genotype 3 is the normal genotype. The mother-child transmission probabilities are the same for the autosomal and X-linked models (1.0, .5, or 0 for transmission to children of either sex by a mother of genotypes 1, 2, or 3, respectively). The father-child transmission probabilities are the same as the mother-child transmission probabilities except for genotype 2 (the heterozygote in the autosomal model and the affected genotype in the X-linked model). If τ_m and τ_f are the probabilities of transmission from a father to a son or a daughter, respectively, $\tau_m = \tau_f = .5$ in the autosomal model and $\tau_m = 0$, $\tau_f = 1$ in an X-linked model. Since the equilibrium genotypic frequencies depend on the transmission probabilities, genotype 1 for males under X-linkage has a frequency of zero. To compare it with an autosomal model with no male-to-male transmission, the likelihood of the model with $\tau_m = 0$ and $\tau_f = .5$ was also computed. All numbers of the form $x \pm y$ represent estimates $\pm$ standard errors of the estimates.

RESULTS

Counts of offspring by sex and disease status of parents and offspring are given in table 1. The same individual may have been entered both as a parent and a child since all belong to one pedigree. There were no cases of male-to-male transmission within the pedigree. Affected fathers produced many fewer normal daughters than affected daughters.

Results of the likelihood analysis using the linkage model are given in table 2. Parameter estimates and relative $\log_{10}$ likelihoods for the X-linked, autosomal,

TABLE 1

NOS. OFFSPRING BY SEX AND DISEASE STATUS OF PARENT IN THE KINDRED, FAMILY P, AND BY SEX AND DISEASE STATUS OF OFFSPRING

	FATHER			MOTHER		
	Affected	Normal	Unknown	Affected	Normal	Unknown
No.	16	68	13	36	89	19
Sons:						
Affected	0	0	1	27	5	5
Normal	16	46	0	32	85	4
Unknown	4	86	20	21	89	29
Daughters:						
Affected	30	0	1	26	0	3
Normal	6	45	4	30	88	10
Unknown	2	78	17	14	94	23

and autosomal/X-linked mixed models are given. The first parameter is the disease allele frequency (q), which corresponds to a disease frequency of 1/5,000 (our estimate, see METHODS). The next parameters are penetrance probabilities for the seven genotypes in this model. The penetrance of female heterozygotes, *AX/aX*, was estimated for all models. The penetrance for the one form of male heterozygote that differed between the X-linked and autosomal models, *aX/AY*, was estimated for the mixed model as the boundary value of zero. The final parameter is the recombination fraction, θ, which was estimated for the mixed

TABLE 2

LINKAGE MODEL: PARAMETERS, PARAMETER ESTIMATES WITH STANDARD ERRORS AND LOG_{10} LIKELIHOODS FOR THE X-LINKED, AUTOSOMAL, AND AUTOSOMAL/X-LINKED MIXED MODELS

	X-linked model	Autosomal model	Autosomal/X-linked mixed model
q ($\times 10^4$)	1.48	1.03	1.44
Female penetrances for genotypes*:			
AX/AX	1.0	1.0	1.0
AX/aX	.85 ± .05	.94 ± .04	.89 ± .06
aX/aX	0	0	0
Male penetrances for genotypes*:			
AX/AY	1.0	1.0	1.0
aX/AY	0	1.0	0†
AX/aY	1.0	1.0	1.0
aX/aY	0	0	0
θ	0	.5	.06 ± .07
Log_{10} likelihood difference	9.93	0	10.11
Correction for no male-to-male transmission	...	7.36	...
Total	9.93	7.36	10.11

NOTE: Parameters without standard errors were fixed at those values except q, which was computed from a disease frequency of 1/5,000 and the penetrance of genotype *aX/AY* for the mixed model that maximized on the boundary at zero.

* "*A*," "*a*" = disease and normal alleles at nephritis locus, X and Y chromosomes.

† Maximized on the boundary.

model. A correction was made to the autosomal likelihood for the absence of male-to-male transmission in the pedigree [25]; estimates were the same with or without the correction. The mixed model maximized to parameter estimates and a likelihood very similar to those for the X-linked model. The $\log_{10}$ likelihood of the mixed model is larger by 2.76 than the $\log_{10}$ likelihood of the autosomal model corrected for no male-to-male transmission. This is sufficient to reject the autosomal model as the mode of inheritance, since there are only two more parameters in the mixed model than in the autosomal model. One cannot reject X-linkage as the mode of inheritance since the mixed model increases the $\log_{10}$ likelihood by only 0.18.

Results of a corresponding analysis using the transmission model are shown in table 3. The first parameter is again the disease allele frequency (q) corresponding to a disease frequency of 1/5,000. The next six parameters are penetrances for the three male and three female genotypes. The female heterozygous penetrance was estimated for all models. The final two parameters are the transmission probabilities from a father of genotype 2 to a son (τ_m) and daughter (τ_f). Both were estimated for the autosomal/X-linked mixed model, but τ_m was estimated as the boundary value of zero. The relative $\log_{10}$ likelihoods and parameter estimates for the X-linked and autosomal models are necessarily identical to those presented with the linkage model (table 2). The transmission autosomal/X-linked mixed model also gave results nearly identical to those for the linkage autosomal/X-linked mixed model. The biggest difference between the results from the two models is that setting $\tau_m = 0$ in this analysis did not have the same effect as making the correction for no male-to-male transmission in the previous analysis.

TABLE 3

TRANSMISSION MODEL: PARAMETERS, PARAMETER ESTIMATES WITH STANDARD ERRORS, AND LOG_{10}-LIKELIHOOD DIFFERENCES FOR THE X-LINKED, AUTOSOMAL , AUTOSOMAL WITHOUT MALE-TO-MALE TRANSMISSION, AND THE AUTOSOMAL/X-LINKED MIXED MODELS

	X-linked model	Autosomal model	Autosomal model ($\tau_m = 0$)	Autosomal/ X-linked mixed model
q ($\times 10^4$)	1.48	1.03	1.39	1.44
Female penetrances for genotypes*:				
1	1.0	1.0	1.0	1.0
2	.85 ± .05	.94 ± .04	.94 ± .04	.89 ± .06
3	0	0	0	0
Male penetrances for genotypes*:				
1	1.0	1.0	1.0	1.0
2	1.0	1.0	1.0	1.0
3	0	0	0	0
τ_m*	0	.5	0	0†
τ_f*	1.0	.5	.5	.94 ± .07
Log_{10}-likelihood difference	9.93	0	4.81	10.12

NOTE: Parameters without standard errors were fixed at those values, except q, which was computed from a disease frequency of 1/5,000 and τ_m for the mixed model that maximized on the boundary at zero.

* See METHODS for definition.

† Maximized on the boundary.

TABLE 4

NOS. MALE AND FEMALE OFFSPRING BY GENERATION

Generation	Males	Females	Proportion
II.....	1	9	.10 ± .09
III.....	23	32	.42 ± .07
IV.....	124	116	.52 ± .03
V.....	291	278	.51 ± .02
VI.....	31	36	.46 ± .06
Total....	470	471	.50 ± .02

However, the inference is the same as before: the autosomal model can be rejected because the $\log_{10}$ likelihood increased by 5.31 and the X-linked model cannot be rejected since the increase was only 0.19.

Counts of male and female pedigree members by generation are given in table 4. Of the 941 live-born descendants of the original couple, 470 were male and 471 were female. The male proportion, .50 ± .02, was not significantly different from the estimated proportion at birth in Utah of .51 [27]. The only generation with a proportion significantly different from .51 is generation II, which consists of the nine daughters and one son of the original couple ($P = .02$). However, when correction is made for the performance of five tests for generations II–VI, this is no longer significant. When categorized by parental sex and disease status (table 5), only affected fathers produced a low proportion of sons among their offspring. This proportion of .34 ± .06 is significantly different ($P < .001$) from the expected proportion. The low proportion of sons is apparent in all generations except perhaps the final one which is incomplete (table 6).

This low proportion of males has been explained previously by prenatal death of affected sons of affected fathers and autosomal dominant inheritance [18]. The miscarriage and stillbirth rate for affected fathers, shown on line 5 of table 5, is significantly higher ($P < .05$) than the rate for normal parents of either sex and higher, but not significantly so ($P > .05$) than that for affected females, who produced a normal proportion of males.

TABLE 5

NOS. LIVE-BORN CHILDREN, SEX RATIOS, AND NOS. MISCARRIAGES AND STILLBIRTHS BY PARENTAL DISEASE STATUS

	FATHER			MOTHER		
	Affected	Normal	Unknown	Affected	Normal	Unknown
No.	16	68	13	36	89	19
No. live-born children	58	255	43	150	361	74
Male proportion.....	.34 ± .06	.52 ± .03	.49 ± .08	.53 ± .04	.50 ± .03	.51 ± .06
No. miscarriages and stillbirths	11	25	0	23	36	4
Miscarriage and stillbirth proportion ...	.16 ± .04	.10 ± .02	0	.13 ± .03	.09 ± .01	.05 ± .02

TABLE 6

NOS. MALE AND FEMALE OFFSPRING OF AFFECTED MALES BY GENERATION

Generation	Sons	Daughters	Proportion
III.....	1	3	.25 ± .22
IV.....	10	19	.34 ± .09
V.....	7	15	.32 ± .10
VI.....	2	1	.67 ± .27
Total....	20	38	.34 ± .06

Segregation ratios are given in table 7. Also given are ratios expected assuming X-linked dominant inheritance with 85% penetrance in females. None of the proportions is significantly different from the expectations. Also shown in table 6 are the segregation ratios for offspring of female carriers whose heterozygous genotype was inferred from at least one affected offspring. Three unaffected obligate carrier women produced eight affected sons, two normal sons, and three normal daughters. Two unexamined carriers produced five affected sons, four normal sons, three affected daughters, and seven normal daughters. The segregation ratios with both sexes grouped were estimated as the ratio of affected to total offspring after subtracting one affected offspring for each mother [28]. The observed proportions are not statistically different from the expected proportions, although the sample sizes are very small.

DISCUSSION

Likelihood analysis of Alport syndrome in family P supported X-linked dominant inheritance of the disease. The penetrance estimates were .85 for females and 1.0 for males. There may also be an autosomal dominant form of the disease since other reported pedigrees show cases of male-to-male transmission [3–8, 15]. However, no cases of male-to-male transmission have been found in 23 unrelated Utah pedigrees ascertained through probands with the more general diagnosis of hereditary nephritis and the analysis gives little evidence of an autosomal dominant subgroup [29]. Alport syndrome may also be heterogeneous based on variation between pedigrees in the age at which renal insufficiency begins [30] and whether or not deafness also occurs [9, 31].

TABLE 7

SEGREGATION RATIOS (AFFECTED OFFSPRING/TOTAL OFFSPRING) ACCORDING TO PARENTAL TYPE

	AFFECTED FATHERS		AFFECTED MOTHERS		NORMAL CARRIER MOTHERS	UNEXAMINED CARRIER MOTHERS
	Sons	Daughters	Sons	Daughters		
Observed.....	0	.83 ± .06	.46 ± .06	.46 ± .07	.58 ± .14	.39 ± .11
Expected.....	0	.85	.50	.425	.4625	.4625

NOTE: Observed ratios from data in table 1. Expected ratios calculated for X-linked dominant inheritance with 85% penetrance in females.

The two autosomal/X-linked mixed models used in this analysis gave surprisingly similar results although they represent different processes biologically and are not simply algebraic permutations of one another. The $\log_{10}$ likelihood at the maximum differed by only .01, and the female heterozygous penetrance estimates were the same. Also, θ (from the linkage model) $= 1 - \tau_f$ (from the transmission model). Therefore, the limited information obtained from this one example indicates that the two models work equally well.

None of the other anomalies reported through the years to justify other modes of inheritance in this pedigree have stood the tests of rediagnosis and reanalysis. There is no deficiency of males in the kindred [18], no excess of affected offspring [7, 19], and no evidence that the penetrance in daughters is lower when the mother is asymptomatic [19].

The only anomaly found is the low proportion of sons among the offspring of affected fathers. This finding has not been explained. Excess prenatal death of affected sons of affected fathers and autosomal dominant inheritance as previously suggested [18] is inconsistent with two observations: (1) the reported miscarriage rate for affected fathers is not higher than for affected mothers, and (2) 83% of the daughters of affected males are affected when 50% or less would be expected. Also, the autosomal model with no male-to-male transmission that corresponds to this hypothesis was rejected by likelihood analysis.

There is some evidence of more fetal wastage among the offspring of affected parents. However, since miscarriage data tends not to be very reliable, the higher miscarriage rate for affected parents than for normal parents may be due to more complete data collection, as compared to that of other family members, because of repeated examination and questioning of diseased individuals. The segregation ratio for affected mothers does not reflect a selective loss of affected male fetuses.

An observation of excess segregation in a pedigree may often result from sampling bias. The first opportunity for bias to occur is in the ascertainment of the pedigree. Because of a chance occurrence of excess segregation, a pedigree may have a distinctive disease cluster, which leads to its ascertainment. Since the ascertainment criterion may not be well defined, it is difficult to make an appropriate correction in likelihood analysis, let alone when computing segregation ratios. This pedigree is large enough so that the original cluster seems not to have affected the segregation ratios. Second, although sequential sampling rules [32] specify that the decision of whom to sample next should be based only on family members already seen, unsolicited information is frequently given regarding branches with the disease. To eliminate that sampling bias, an effort was made to examine all descendants of the original couple. The third possible source of bias results because affected individuals are generally more willing to cooperate with disease studies than are normal individuals.

In addition to the possibility that sampling biases (as well as misdiagnoses) in the original published version of family P led to hypotheses of oversegregation, some previous studies also miscalculated the segregation ratios by including the affected offspring of carriers, in computing the segregation ratio, without correction for ascertainment of the carriers.

It should be emphasized that our conclusion that Alport syndrome is inherited as an X-linked dominant applies only to this pedigree. Since many cases of male-to-male transmission have been reported in the literature, an autosomal form of the disease must occur in some families. This observed genetic heterogeneity has implications for genetic counseling in a particular family [33].

ACKNOWLEDGMENTS

We thank Drs. Lynn Jorde and Mary Dadone for comments and Drs. W. M. O'Neill, Jr., H. A. Bloomer, D. P. Duffy, R. L. Siegler, and A. C. San Juan, Jr., for clinical studies.

REFERENCES

1. GUBLER M, LEVY M, BROYER M, ET AL.: Alport's syndrome. A report of 58 cases and a review of the literature. *Am J Med* 70:493–505, 1981
2. HABIB R, GUBLER M-C, HINGLAIS N, ET AL.: Alport's syndrome: experience at Hôpital Necker. *Kidney Int* 21, Suppl 11:S20–S28, 1982
3. PREUS M, FRASER FC: Genetics of hereditary nephropathy with deafness (Alport's disease). *Clin Genet* 2:331–337, 1971
4. CHAZAN JA, ZACKS J, COHEN JJ, GARELLA S: Hereditary nephritis. Clinical spectrum and mode of inheritance in five new kindreds. *Am J Med* 50:764–771, 1971
5. CRAWFURD MD'A, TOGHILL PJ: Alport's syndrome of hereditary nephritis and deafness. *Q J Med* (N.S.) 37:563–576, 1968
6. CASSADY G, BROWN K, COHEN M, DEMARIA W: Hereditary renal dysfunction and deafness. *Pediatrics* 35:967–979, 1965
7. SHAW RF, GLOVER RA: Abnormal segregation in hereditary renal disease with deafness. *Am J Hum Genet* 13:89–97, 1961
8. PURRIEL P, DRETS M, PASCALE E, ET AL.: Familial hereditary nephropathy (Alport's syndrome). *Am J Med* 49:753–773, 1970
9. O'NEILL WM JR, ATKIN CL, BLOOMER HA: Hereditary nephritis: a re-examination of its clinical and genetic features. *Ann Intern Med* 88:176–182, 1978
10. MULROW PJ, ARON AM, GATHMAN GE, YESNER R, LUBS HA: Hereditary nephritis. Report of a kindred. *Am J Med* 35:737–748, 1963
11. PATTON RB: Chronic hereditary nephritis with nerve deafness. A Nebraska kindred. *Ann Otol Rhinol Laryngol* 79:194–202, 1970
12. PERKOFF GT, STEPHENS FE, DOLOWITZ DA, TYLER FH: A clinical study of hereditary interstitial pyelonephritis. *Arch Intern Med* 88:191–200, 1951
13. PERKOFF GT, NUGENT CA, DOLOWITZ DA, STEPHENS FE, CARNES WH, TYLER FH: A follow-up study of hereditary chronic nephritis. *Arch Intern Med* 102:733–746, 1958
14. STEPHENS FE, PERKOFF GT, DOLOWITZ DA, TYLER FH: Partially sex-linked dominant inheritance of interstitial pyelonephritis. *Am J Hum Genet* 3:303–313, 1951
15. EVANS SH, ERICKSON RP, KELSCH R, PEIRCE JC: Apparently changing patterns of inheritance in Alport's hereditary nephritis: genetic heterogeneity versus altered diagnostic criteria. *Clin Genet* 17:285–292, 1980
16. HALDANE JBS: A search for incomplete sex-linkage in man. *Ann Eugen (Lond)* 7:28–57, 1936
17. MORTON NE: Further scoring types in sequential linkage tests with a critical review of autosomal and partial sex linkage in man. *Am J Hum Genet* 9:55–75, 1957
18. GRAHAM JB: Hereditary chronic kidney disease: an alternative to partial sex-linkage in the Utah kindred. *Am J Hum Genet* 11:333–338, 1959
19. MACNEILL E, SHAW RF: Segregation ratios in Alport's syndrome. *J Med Genet* 10:23–26, 1973

20. HASSTEDT SJ, CARTWRIGHT PE: PAP: *Pedigree Analysis Package*. Technical Report No. 13, Department of Medical Biophysics and Computing, University of Utah, Salt Lake City, 1979
21. HASSTEDT SJ, CARTWRIGHT PE, SKOLNICK MH, BISHOP DT: PAP: A FORTRAN program for pedigree analysis. *Am J Hum Genet* 31:135A, 1979
22. LALOUEL J-M: GEMINI—*A Computer Program for Optimization of General Nonlinear Functions*. Technical Report No. 14, Department of Medical Biophysics and Computing, University of Utah, Salt Lake City, 1979
23. THOMPSON EA, CANNINGS C: Sampling schemes and ascertainment, in *Genetic Analysis of Common Diseases: Applications to Predictive Factors in Coronary Disease*, edited by SING CF, SKOLNICK M, New York, Alan R. Liss, 1979, pp 363–382
24. HASSTEDT SJ, SKOLNICK M: A general autosomal/X-linked model. In preparation
25. GLADSTIEN K, SPENCE MA: Counseling for dominant traits: a correction for the ascertainment bias due to referral for analysis. *Clin Genet* 15:171–175, 1979
26. DEMENAIS FM, ELSTON RC: A general transmission probability model for pedigree data. *Hum Hered* 31:93–99, 1981
27. UTAH STATE DEPT. OF HEALTH: *Utah Vital Statistics. Annual Report*. Salt Lake City, 1979
28. LI CC, MANTEL N: A simple method of estimating the segregation ratio under complete ascertainment. *Am J Hum Genet* 20:61–81, 1968
29. HASSTEDT SJ, ATKIN CL, SAN JUAN AC JR: An investigation of genetic heterogeneity among pedigrees with hereditary nephritis. In preparation
30. TISHLER PV, ROSNER B: The genetics of the Alport syndrome. *Birth Defects: Orig Art Ser* 10:93–99, 1974
31. O'NEILL WM JR, MENNEMEYER RP, BLOOMER HA, ATKIN CL: Early pathologic features of hereditary nephritis: a clinicopathologic correlation. *Pathol Res Pract* 168:146–162, 1980
32. CANNINGS C, THOMPSON EA: Ascertainment in the sequential sampling of pedigrees. *Clin Genet* 12:208–212, 1977
33. TISHLER PV: Healthy female carriers of a gene for the Alport syndrome: importance for genetic counseling. *Clin Genet* 16:291–294, 1979