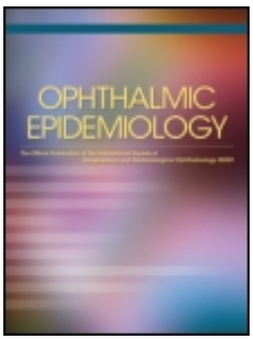

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ORIGINAL ARTICLE

Prevalence of Granular Corneal Dystrophy Type 2 (Avellino Corneal Dystrophy) in the Korean Population

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ABSTRACT

Purpose: This study investigates the prevalence of granular corneal dystrophy type 2 (GCD2; Avellino corneal dystrophy) in the Korean population.

Methods: GCD2 homozygotes were identified through a collaboration of Korean referral centers for corneal disease. The genetic status of the patients and their immediate families were verified by DNA analysis. A lower bound for the gene prevalence was calculated using a model based on the Hardy-Weinberg principle. A second population-based model was developed to correct for known underestimation in the primary model. The corrected model used population data from the 2005 Korean census and fertility rates from historical Korean census data.

Results: We identified 21 individuals homozygous for GCD2 (R124H mutation) from 16 Korean families. From this, we estimate that the overall prevalence (combining heterozygotes and homozygotes) is at least 8.25 affected persons/10,000 persons. Our corrected estimate for overall prevalence is 11.5 affected persons/10,000 persons.

Conclusion: We present the first estimate of the prevalence of GCD2. Although uncommon, the prevalence of GCD2 in Korea is greater than anticipated. We believe that our approach could potentially be applied to estimating the prevalence of other rare diseases.

KEYWORDS: Granular corneal dystrophy type 2; Avellino corneal dystrophy; Prevalence study; Korea; Mathematical model

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INTRODUCTION

The corneal stromal dystrophies are a collection of heritable disorders that cause opacifications to form in the corneal stroma. Historically, these entities were characterized by the clinical morphology of the

opacities. Molecular genetic techniques have identified specific mutations that are associated with most of these dystrophies. Granular corneal dystrophy type 2 (GCD2; Avellino corneal dystrophy; MIM 607541) shows some clinical features of both granular and lattice dystrophies.[1–3] GCD2 is strongly associated with the R124H mutation of the *TGFBI* (formerly *βIGH3*) gene.[4] The heterozygous form of GCD2 is generally mild; for many patients, their only symptoms are visually insignificant corneal opacities during their lives. In contrast, patients with the homozygous form of GCD2 have severe visual impairment from early in childhood.[5,6] While the heterozygous and homozygous forms are often viewed as distinct clinical entities, they both stem from the same specific mutation. The name "Avellino corneal dystrophy" was coined in a report of two related Italian-American families whose origin was Avellino, Italy.[1,7] Since then, GCD2 has been reported in persons of various ethnic origins,[1–3,5] including Koreans.[8–10] The prevalence of GCD2 has not yet been reported. Reports from several countries of the relative frequencies of granular corneal dystrophy type 1, GCD2, and lattice dystrophy among "corneal dystrophy" patients show that GCD2 has the highest prevalence.[8,11–15] The genetics of these corneal dystrophies was recently reviewed by Kannabiran and Klintworth.[16]

The purpose of this study is to estimate the prevalence of GCD2 in the Korean population. Because of its relatively low prevalence, a direct measurement of a population based sample would be prohibitively expensive. This study identifies homozygous patients as a measure of the frequency with which carriers marry. From that number, the Hardy-Weinberg principle lets us compute the allele frequency. Korean census data are also used to correct for "undetectable" families.

PATIENTS AND METHODS

Patients and Clinical Evaluation

This study collected data on Korean patients within the Republic of Korea. This is a geographically isolated nation with an ethnically distinct population of about 47 million. Immigration and emigration rates are low. Since homozygous GCD2 patients have a severe visual disability,[5] most homozygotes are seen by an ophthalmologist at an early age. These patients are almost invariably referred to an academic institution for diagnosis and/or treatment. The Corneal Dystrophy Research Institute of Severance Hospital at Yonsei University (Seoul, Korea) has coordinated collaboration among these academic centers to identify all GCD2 homozygotes.

Sixteen families with 21 patients homozygous for the *TGFBI* R124H mutation are the subjects of this study. These patients all have severe corneal opacification and their genetic status was confirmed by DNA analysis. Family members of GCD2 patients received a slit lamp examination (looking especially for opacities in the corneal stroma) and DNA analysis. DNA analysis was performed from peripheral blood as described previously.[9,17,18] Exons 4 and 12 were sequenced to identify the R124H and the R555W mutations. All families were from different regions and none of the study families knew of any of their relations that had corneal disease. This study was performed in accordance with the Declaration of Helsinki and was approved by the Severance Hospital Institutional Review Board (approval number CR04124). Informed consent was obtained from all subjects.

Estimation of Prevalence

The simplest approach to estimating the prevalence would divide the number of homozygous patients identified (21) by the total population. While computationally simple, this treats the conception of each homozygote as an independent event. In fact, we know that several of them are siblings, so they cannot be considered independent. Thus, such an approach would be likely to overestimate the prevalence of GCD2. To avoid the problem of non-independence, we used a model based on the Hardy-Weinberg principle. This allows for a method that is unaffected by the presence of siblings in the data set, as long as the sibling status is known.

In modeling GCD2 in this population, it is appropriate to assume a Hardy-Weinberg equilibrium. We used the variable q for the prevalence of the GCD2 allele (A′) in the Korean population. The prevalence of the normal allele (A) is $(1-q)$ and for convenience we let the variable $p=(1-q)$. The Hardy-Weinberg equation says that the genotype frequencies for normals (AA), heterozygotes (AA′), and homozygotes (A′A′) are given by p^2, $2pq$, and q^2, respectively. Also, we know that the sum of the prevalence for normals, heterozygotes, and homozygotes must be exactly one ($p^2 + 2pq + q^2 = 1$).

Families of homozygous children were identified through the presentation of the children for evaluation or treatment. Each family represents a union of parents who each carry at least one GCD2 allele (that is, each parent is either AA′ or A′A′). Thus, the prevalence of the parents in these unions is given by $2pq + q^2$ and the prevalence of the unions themselves is $(2pq + q^2)^2$. Substituting $1-p^2$ for $2pq + q^2$ reduces the expression to a single variable $(1-p^2)^2$. Thus, we can estimate the prevalence of the GCD2 allele from the observed number of families with homozygotic GCD2 children by

solving the equation $(1-p^2)^2 = F$, where F is the fraction of Korean families that can produce homozygous children. We knowingly underestimate F as the observed number of families with homozygous GCD2 children divided by half the population of Korea (half the population is an upper bound on the number of families in Korea). The underestimation of F contributes to our underestimation of the prevalence. Computations were performed with Mathematica 4.0.1 (Wolfram Research, Champaign, IL).

Correcting for Undetectable Families

Unfortunately, our model has considerable sources of underestimation. Even if our homozygote detection is perfectly efficient, some couples that could potentially produce homozygotes do not. To address this source of underestimation, we have developed a corrected model based on age-based population strata and historical fertility rates for Korea.

Because families are detected through their children, families where both parents carry a GCD2 allele that do not produce homozygous children are undetectable by this method. Thus, a heterozygous couple with no children is always undetectable. Similarly, a family consisting of a heterozygous couple with a single child is only detectable with probability 0.25 (25%) because that is the probability of such a couple producing a homozygous child. Table 1 lists the probability of detection for families based on the number of children in the family.

A population model was constructed from Korean census data from 2005 to correct for the existence of "undetectable" families (the fertility rate for 2004 was used because the rate for 2005 was not available; this does not affect the estimate). As the Korean fertility rate[19,20] has changed substantially over the last 50 years, the current population was stratified on age. Strata were chosen to match publicly available census data.[19] Data on the fertility rate are not available prior to 1960, so the strata for all people over age 50 were combined. To remain conservative in our assumptions, we assumed a fertility rate of 8 for the combined strata. The fertility rate at the end of each strata was used. In each stratum, a Poisson model with a mean of the fertility rate was used to model the number of children in a family. For each possible number of children, the probability of detection (Table 1) was weighted by the probability of that number of children (given the fertility rate). These weighted probabilities were summed over all possible family sizes to get the detectable fraction for each stratum (Table 2).

The population within each age stratum was multiplied by the respective detectable fraction to give an "effective" population in each stratum (Table 3). Since detection requires that the parents have a child old enough (at least 3) to be diagnosed with GCD2, the three strata for ages 0–14 were excluded because they were too young to be detected. The effective population is the sum of the effective populations in the remaining strata. The prevalence computation was repeated using the effective population for 2005.

In developing this model, we had to draw data from multiple sources. While the sources agreed where there was overlap, this alone is reason for caution in interpreting this model and our "effective" population used in the corrected calculation.

RESULTS

We have identified 16 families with 21 children homozygous for the R124H mutation (CGC→CAC). The pedigrees of each family were investigated and are summarized in Table 4. All parents of homozygous patients available for examination were themselves heterozygous for the R124H mutation (CGC→CAC). Using the 2005 Korean registration-based census[19] of

TABLE 1 Probability of detection

Number of children	Probability of no homozygous child	Probability of detection
0	1.0000	0.0000
1	0.7500	0.2500
2	0.5625	0.4375
3	0.4219	0.5781
4	0.3164	0.6836
5	0.2373	0.7627
6	0.1780	0.8220
7	0.1335	0.8665
8	0.1001	0.8999
9	0.0751	0.9249
10	0.0563	0.9437
11	0.0422	0.9578
12	0.0317	0.9683
13	0.0238	0.9762
14	0.0178	0.9822
15	0.0134	0.9866

This table lists the probability of detection for a family with two heterozygous parents. The first column is the number of children in the family. The second column is the probability that there are no homozygous children. Recall that the probability of any child of these parents being homozygous is 0.25 (25%) and is independent of the status of any other child. Hence, the probability of a child not being homozygous is 0.75 (1–0.25) and the probability of n children not being homozygous is $(0.75)^n$. The third column is the probability that the family would be detected in this study (assuming perfect efficiency in detection). This is the probability that the family has at least one homozygous child and is derived by subtracting column 2 from 1 (100%). A family with no children is undetectable. The probability of detection for a family with two children is only 44%.

47,041,434, we estimate the overall prevalence (combining heterozygotes and homozygotes) of GCD2 is at least 8.25/10,000 ($q = 0.000412$). Our corrected estimate for the overall prevalence of GCD2 based on an effective population of 25,283,389 (Table 3) is 11.5/10,000 ($q = 0.000574$). Table 5 summarizes the different app-roaches to estimating the prevalence.

TABLE 2 Detectable fraction

Year	Fertility rate	Detectable fraction
1960	6.00	0.7769
1965	5.63	0.7552
1970	4.53	0.6778
1975	3.47	0.5800
1980	2.83	0.5071
1985	1.67	0.3413
1990	1.59	0.3280
1995	1.65	0.3380
2000	1.47	0.3075
2004	1.16	0.2517

The table lists the fraction of the population that is theoretically detectable by the method used in this study. These fractions are computed by weighting the probability of detection (Table 1) by the modeled distribution of number of children (Poisson model). The sum of these probabilities is the detectable fraction. An expression for this computation is:

$$1-\sum_{n=0}^{\infty}\left(\frac{3}{4}\right)^{n}\frac{\lambda^{n}e^{-\lambda}}{n!}$$

Since fertility rate data was not available prior to 1960, we assume a fertility rate of 8 for anyone born prior to 1956. This would be a strikingly high fertility rate and was chosen to remain conservative in our assumptions. For a fertility rate of 8, the detectable fraction is 0.8647.

TABLE 3 Finding the "effective" population

Age group	Population by age	Birth year range	Detectable population
0–4	2,382,350	2001–2005	
5–9	3,168,887	1996–2000	
10–14	3,434,891	1991–1995	
15–19	3,100,523	1986–1990	1,016,978
20–24	3,662,123	1981–1985	1,249,914
25–29	3,671,847	1976–1980	1,862,086
30–34	4,096,282	1971–1975	2,375,843
35–39	4,112,785	1966–1970	2,787,536
40–44	4,123,041	1961–1965	3,113,909
45–49	3,900,899	1956–1960	3,030,491
50+	11,387,806	–1955	9,846,634
Total:	47,041,434		25,283,390

This table shows the computation of the "effective" population. The "effective" population in each stratum is calculated by multiplying the population in the stratum by the appropriate "detectable" fraction from Table 2. The strata for people under age 15 are excluded because they essentially cannot contribute to the detectable population (detection requires a child old enough to be diagnosed with GCD2). The "effective" population is the sum of the "effective" populations in each stratum.

DISCUSSION

The prevalence rate is the proportion of cases in the population at a given time. Ideally, an estimate of prevalence would come from DNA analysis in a large population based sample. Practically, the cost of such a study is prohibitive. This study uses a Hardy-Weinberg model to estimate the prevalence of GCD2 in the Korean population. We also draw from Korean census data to build a model to correct some of the underestimation in our estimate based on the Hardy-Weinberg model.

We believe that we have identified almost all homozygous GCD2 patients in Korea. If we have failed to detect any homozygotes, this is another source of underestimation in our calculation of the prevalence. While genetic testing provides solid assurance that we have not falsely detected non-homozygotes, there is no way to demonstrate perfect efficiency in our detection.

Another source of underestimation deserves mention. People who are not mating (which would include essentially all children) are also undetectable by our approach. We correct for this in part by excluding children, but did not attempt to correct for the non-mating adult population. Failing to exclude non-mating adults is also a potential source of underestimation of the prevalence, a conservative error in a lower bound. That said, we think that the corrected GCD2 prevalence estimate of 11.5/10,000 persons is a more useful estimate than our base estimate of 8.25/10,000 persons.

The most serious potential source of overestimation in this study would be if any of the families were related. While this seems unlikely based on the family histories and the knowledge that the families are geographically dispersed throughout the country, it is not something that can be definitively excluded.

We believe that our approach could potentially be applied to estimating the prevalence of other diseases. For our approach to be helpful, the disease should meet the following four criteria: (1) the disease is genetic and its genetics are known, (2) the disease has complete penetrance, (3) there is a direct confirmatory test for the disease, and (4) the disease has a severity that leads most patients to seek medical attention. The population of interest should meet two additional criteria: (1) it must be in a Hardy-Weinberg equilibrium and (2) its healthcare infrastructure for the disease of interest should be able and willing to collaborate in the identification of patients. This last criterion may be the most challenging.

The greatest clinical significance of our findings is in the area of refractive surgery. We have previously reported the exacerbation of GCD2 in seven heterozygous patients as a complication of Laser-Assisted In

TABLE 4 Summary of GCD2 families identified

Family	Father	Mother	Sibling	Sex	Age	Genotype
1	Not examined (deceased)	Not examined (deceased)	I	M	58	**Homozygote**
			II	F	53	Heterozygote
			III	M	49	Heterozygote
			IV	F	43	**Homozygote**
			V	F	40	Unaffected
2	Heterozygote	Heterozygote	I	F	16	Unaffected
			II	F	12	**Homozygote**
			III	M	10	Unaffected
3	Not examined (deceased)	Not examined (deceased)	I	F	60	Not examined
			II	M	58	**Homozygote**
			III	M	55	**Homozygote**
			IV	F	53	Unaffected
			V	M	51	**Homozygote**
			VI	M	45	Not examined
			VII	F	43	Heterozygote
			VIII	M	41	**Homozygote**
4	Heterozygote	Heterozygote	I	M	32	**Homozygote**
			II	M	30	Unaffected
			III	F	28	Heterozygote
5	Heterozygote	Heterozygote	I	F	10	**Homozygote**
			II	M	7	Unaffected
			III	M	6	Unaffected
6	Heterozygote	Heterozygote	I	F	21	Heterozygote
			II	F	19	**Homozygote**
7	Not examined (deceased)	Not examined (deceased)	I	F	36	**Homozygote**
			II	F	34	**Homozygote**
8	Heterozygote	Heterozygote	I	F	27	**Homozygote**
			II	M	26	Unaffected
9	Heterozygote	Heterozygote	I	M	6	**Homozygote**
			II	F	4	Unaffected
10	Heterozygote	Heterozygote	I	F	13	**Homozygote**
11	Heterozygote	Heterozygote	I	M	4	**Homozygote**
12	Heterozygote	Heterozygote	I	M	28	Unaffected
			II	M	25	Heterozygote
			III	F	23	**Homozygote**
13	Heterozygote	Heterozygote	I	F	30	**Homozygote**
			II	F	27	Not examined
			III	M	24	Heterozygote
14	Not examined (deceased)	Not examined (deceased)	I	F	71	**Homozygote**
			II	F	66	Unaffected
			III	F	63	Heterozygote
			IV	M	61	Heterozygote
			V	M	59	Heterozygote
			VI	F	52	Heterozygote
			VII	M	50	Unaffected
15	Not examined (deceased)	Not examined (deceased)	I	M	52	Unaffected
			II	M	49	Heterozygote
			III	M	45	**Homozygote**
			IV	F	43	Unaffected
16	Heterozygote	Heterozygote	I	M	25	**Homozygote**

This table summarizes the 16 families with children homozygous for GCD2. Genetic testing was done on all living parents and all but three siblings (the exceptions are listed as "Not examined"). The only abnormal mutation identified was R124H (CGC→CAC).

TABLE 5 Prevalence estimates

	H-W model	Corrected H-W model
Homozygous	0.00170	0.00317
Heterozygous	8.24603	11.24700
Total	8.24773	11.25017

This table lists our prevalence estimates (per 10,000) for homozygotes and heterozygotes in the Korean population. The first column is a conservative estimate based on our Hardy-Weinberg model. The second column is based on our corrected Hardy-Weinberg model that additionally attempts to exclude persons from the population that are undetectable by this study (see "Correcting for undetectable families" in the Patients and Methods section).

Situ Keratomileusis (LASIK),[10] a popular type of corneal surgery used to reduce refractive error. We are now aware of 130 additional Korean heterozygous patients seen in our clinical practices (unpublished data) and two Caucasian heterozygous patients (USA)[21,22] who have had a severe exacerbation of their GCD2 following LASIK. With the continued popularity of LASIK, these reports suggest that the number of GCD2 patients at risk for severe vision loss as a complication of LASIK is greater than previously thought. It is crucial that refractive surgeons do a careful pre-operative examination of candidates for LASIK surgery (or similar procedures).

Our estimate for the prevalence of GCD2 in Korea is the first for this disease. While our base estimate of the prevalence is conservative, it is relatively large in comparison to other genetic diseases. As ophthalmologists are likely to be the healthcare providers that diagnose GCD2, they should be prepared to make appropriate referrals for genetic counseling.

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The first two authors (Lee and Cristol) contributed equally to this work.

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