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SHORT COMMUNICATION

Molecular Confirmation of the Causes of Inherited Visual Impairment in Northern Pakistan

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ABSTRACT

Families with inherited visual impairment were identified and examined from January 2000 to December 2005 and given a clinical diagnosis. Known genes and loci were screened for mutations or linkage at Institute of Ophthalmology and Neurosciences, University of Leeds, in order to provide molecular confirmation. Inherited retinal disease was the most common cause of inherited visual impairment in 38 of 57 families (66.6%) with Leber's congenital amaurosis, rod-cone dystrophy and cone-rod dystrophy being the most common diagnoses in 22, 8 and 3 families respectively. Anterior segment dysgenesis was diagnosed in 8 families (14%). Mutations in known genes or linkage to known loci were identified in 23 of 57 families (40%). All families had molecular confirmation of autosomal recessive inheritance or a pedigree consistent with this mode of inheritance, with evidence of first-cousin marriage. Knowledge of carrier status and genetic counseling may allow families to make an informed decision regarding marriage, and thus begin to plan a way of reducing the incidence of inherited visual impairment.

Key words: *Inherited visual impairment. Retinal disease. Blindness. Autosomal recessive. First-cousin marriage. Leber's congenital amaurosis. Rod-cone dystrophy.*

There has been a rapid escalation in the use of molecular diagnostic strategies in many areas of clinical medicine over the last few years. A molecular diagnosis for an inherited disease offers a precise diagnosis, confirms the mode of inheritance and may provide not only a mutation specific prognosis, but can also help identify a novel therapeutic strategy.[1] The strong association between consanguineous marriages and autosomal recessive diseases is well known.[2] In communities where consanguinity is a common practice, such as those in the Middle East and Pakistan, a molecular diagnosis may also allow identification of the carrier status and thus, can be used to reduce the incidence of recessive disease such as visual impairment.[2,3] The aim of this study was to describe the causes of inherited visual impairment, the most common mode of inheritance and the frequency of molecular confirmation in a selected series from Northern Pakistan.

As part of an ongoing project to identify the molecular basis of inherited retinal diseases, 57 families with inherited visual impairment in Northern Pakistan were identified and examined from January 2000 to December 2005. Families were identified from a variety of sources, including schools for the blind, support groups for the visually impaired and personal and professional contacts. A clinical diagnosis was given to all the families on the basis of history and ophthalmic examination. Families were invited to participate in the research project to identify the genetic basis of inherited visual impairment. Peripheral blood samples were taken from participants. DNA was extracted and analyzed at the Institute of Ophthalmology and Neurosciences, University of Leeds, United Kingdom, in order to identify mutations in known genes or linkage to a known or new locus. Where molecular confirmation could not be obtained, the most likely mode of inheritance was ascertained from a family tree.

Of the 57 families, 38 families (66.6%) were diagnosed as having inherited retinal disease. Within these 38 families, 22 (58%) were diagnosed as having Leber's congenital amaurosis (LCA), while 8 had a rod-cone dystrophy, 3 had a cone-rod dystrophy, 2 had achromatopsia, 2 had congenital stationary night blindness and 1 family had Biedl-Bardet syndrome (Table I).

Anterior segment dysgenesis, with a variable combination of microcornea, corneal opacification, iris coloboma and congenital cataract, was diagnosed in 8 of 57 families (14%). Primary congenital glaucoma was diagnosed in 3 families (5%) and isolated microphthalmos was diagnosed in 2 families (3.5%). Single families had one of 5 other diagnoses and no diagnosis was made in a final family (Table I).

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Table I: Clinical diagnosis and molecular confirmation of the causes of inherited visual impairment in 57 families in Northern Pakistan.

Clinical diagnosis	Number of families	Confirmed gene or locus
Leber's Congenital Amaurosis (LCA)	22	LCA5 (3 families)
		RPGRIP (4 families)
		AIPL1 (3 families)
		LCA9-linked (1 family)
		CRB1 (1 family)
		TULP1 (1 family)
		RPE65 (1 family)
		Not ascertained (8 families)
Rod-cone dystrophy	8	RP26-linked (1 family)
		CRB (2 families)
		Rhodopsin (1 family)
		Not ascertained (4 families)
Cone-rod dystrophy	3	Not ascertained
Achromatopsia	2	Not ascertained
Congenital stationary night blindness	2	Arrestin (1 family)
		Not ascertained (1 family)
Biedl bardet syndrome	1	Not ascertained (1 family)
Anterior segment dysgenesis	8	Not ascertained (1 family)
Primary congenital glaucoma	3	CYP1B1 (2 families)
		GLC3-linked (1 family)
Microphthalmos	2	Not ascertained
Lens subluxation	1	Not ascertained
Polar cataract	1	Not ascertained
Sclerocornea	1	Not ascertained
Congenital hereditary endothelial dystrophy	1	SLC4A11
Optic atrophy	1	Not ascertained
No clinical diagnosis	1	–

To date, mutations in known genes or linkages to known loci have been identified in 23 of 57 families (40%, Table I). For the remaining families, the molecular confirmation remains to be ascertained. All families had molecular confirmation of autosomal recessive inheritance or a pedigree consistent with this mode of inheritance, with evidence of first-cousin marriage.

In this series, retinal disease was the most common cause of inherited visual impairment in Northern Pakistan. This finding is in keeping with the results of a prior study from Lahore conducted in the schools for the blind, in which retinal disease was found to be the most common cause of visual impairment in children; diagnosed in 41% of the cases, followed by disorders of the globe, corneal disease, cataract and glaucoma in 24%, 19%, 7% and 6% of the cases respectively.[4] High consanguinity was also observed in the parents of these children.[4] A similar study from Karachi conducted in a blind school also reported retinal disease to be the most common cause of visual impairment in children (41%), followed by disorders of the globe (20.1%) and lens (18.1%).[5]

LCA was the most common clinical diagnosis in this series. Affected individuals present with poor visual acuity from birth or shortly after. The condition is clinically and genetically heterogeneous.[6] The clinical variability may explain the differing contributions of LCA and retinits pigmentosa (RP) to the overall picture of inherited retinal disease between this and other series. Adhi *et al.* in his hospital based study,[7] reported RP to be the most common retinal dystrophy, accounting for 48 of 75 patients (64%) with retinal dystrophies.

In summary, inherited retinal disease is the most common cause of inherited visual impairment in Northern Pakistan. At present, it is possible to provide molecular confirmation to about one-third of the families with inherited visual impairment and to about half the families with inherited retinal disease. In the future, this information may identify novel therapies but presently it provides information to families and individuals. It confirms the mode of inheritance, the identification of carrier status and could be used to provide a pre-natal diagnosis. With this information and with genetic counseling, families can make an informed decision regarding marriage and thus, can begin to plan a way of reducing the incidence of inherited visual impairment.

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