Polymorphisms of DNA repair genes *OGG1* and *XPD* and the risk of age-related cataract in Egyptians

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**Purpose:** To analyze the association of the polymorphisms of xeroderma pigmentosum complementation group D (*XPD*) and 8-oxoguanine glycosylase-1 (*OGG1*) genes with the risk of age-related cataract (ARC) in an Egyptian population.

**Methods:** This case-control study included 150 patients with ARC and 50 controls. Genotyping of *XPD* Asp312Asn was performed by amplification refractory mutation system PCR assay and genotyping of *OGG1* Ser326Cys was carried out by PCR including confronting two-pair primers.

**Results:** The Asn/Asn genotype of *XPD* gene was significantly associated with increased risk of ARC (odds ratio [OR] = 2.74, 95% confidence interval [CI] = 1.01–7.43, p = 0.04) and cortical cataract (OR = 5.06, 95% CI = 1.70–15.05, p = 0.002). The Asn allele was significantly associated with an increased risk of ARC (OR = 1.75, 95% CI 1.06–2.89, p = 0.03) and cortical cataract (OR = 2.81, 95% CI = 1.56–5.08, p<0.001). The *OGG1* Cys/Cys genotype frequency was significantly higher in ARC (OR = 4.13, 95% CI = 0.93–18.21, p = 0.04) and the Cys326 allele (OR = 1.85, 95% CI = 1.07–3.20, p = 0.03). Moreover, the Cys/Cys genotype of the *OGG1* gene was significantly higher in cortical cataract (OR = 6.00, 95% CI = 1.24–28.99, p = 0.01) and the Cys326 allele was also significantly associated with cortical cataract (OR = 2.45, 95% CI = 1.30–4.63, p = 0.005).

**Conclusions:** The results suggest that the Asn/Asn genotype and Asn312 allele of *XPD* polymorphism, as well as the Cys/Cys genotype and Cys326 allele of the *OGG1* polymorphism, may be associated with increased risk of the development of ARC, particularly the cortical type, in the Egyptian population.

The transparent crystalline lens of the eye is composed of fibers that come from the anterior subcapsular epithelia. The lens epithelia are essential for the growth, differentiation, and homeostasis of the lens. Epithelial cells near the lens equator divide and differentiate into lens fibers at a constant slow rate throughout life, resulting in a steady growth of the lens fiber mass. The mitotically quiescent central region of the epithelium is thought to protect the underlying fibers from injury and oxidative insult [1], to transport ions to and from the deeper layers of the lens [2], and perhaps to provide nutrients to elongating lens fibers [3]. Cataract develops with opacification of lens fibers. Age-related cataract (ARC) is a leading cause of blindness worldwide. Its etiology is multifactorial and not fully understood.

Oxidation may involve various biomolecules such as proteins, membrane lipids, and DNA. DNA base modifications resulting in mutations and genomic instability are a major consequence of oxidative stress. Oxidative DNA damage is processed by cellular DNA repair mechanisms, but their efficacy decreases with age [4]. Most oxidative DNA damage is repaired by both base excision repair (BER) and nucleotide excision repair (NER) pathways [5-7].

Reactive oxygen species generate a variety of modified bases in DNA, and 8-oxoguanine is one of the major and best-characterized products of oxidative DNA modifications [5,8]. It has been used as a biomarker for cellular oxidative stress [9], and can pair with adenine in double-stranded DNA during DNA replication. If this mispairing is not repaired, a G:C to T:A transversion mutation will occur. In mammalian cells, the major defense against the mutagenic effect of 8-oxoguanine is provided by the BER pathway. The 8-oxoguanine glycosylase-1 (*OGG1*) and mutY homolog genes initiate this repair pathway by recognizing and removing 8-oxoguanine and adenine paired with 8-oxoguanine, respectively [6,10,11].

The xeroderma pigmentosum complementation group D (*XPD*) is one of the DNA repair genes. Transcription factor II Human (TFIIH), containing the *XPD* helicases, is involved in local opening of DNA around a site of damage, and mediates strand separation at the site of the lesion. *XPD* is considered an essential gene because TFIIH is required for all transcription by RNA polymerase II. *XPD* codes for a protein involved in transcriptional-coupled NER, which removes and corrects oligonucleotide fragments containing a variety of lesions, such as ultraviolet (UV)-induced lesions, chemical adducts, and crosslinks [7,12]. The aim of this work was to analyze
the relationship between the OGG1 Ser^{266}Cys gene in the BER pathway and XPD Asp^{132}Asn in the NER pathway with the risk of ARC in the Egyptian population for better understanding of the pathogenesis of cataract development, with the aim of preventing or delaying the onset of this disease.

**METHODS**

**Patients:** All participants were recruited from Zagazig University Hospital and Ophthalmology Department of Zagazig University. All subjects were of Egyptian nationality. A written informed consent form was signed by each participant before participation. The study design was approved by the Ethical Committee of Faculty of Medicine, Zagazig University.

This case-control study included 150 consecutive patients with ARC (50 nuclear, 50 cortical, 50 subcapsular type). ARC was defined as lens opacity accompanied by disturbance of vision in patients over 50 years of age who did not complain of any visual disturbance before this age and had no other eye abnormalities that could explain the vision loss. Cataract status was determined by lens examination using a slit-lamp biomicroscope (Haag-Streit BQ900, Switzerland). Lens opacities were determined using the Lens Opacities Classification System (LOCS) III [13]. Only patients with ARC who had a LOCS III score ≥3 were included in the study. Patients were excluded if they had secondary cataract arising due to a local cause such as trauma, myopia, glaucoma, action of toxins, inflammation, or degenerative ocular diseases; or it was associated with systemic disease (such as diabetes) or medications inducing cataract (like steroids). In addition, patients with total or mixed-type cataract and patients with a past history of intraocular surgery were excluded.

The control group included 50 sex-matched subjects of older ages than the patients. They were selected randomly from the same population as the patients, with normal ocular examination and a LOCS III score = 0.1. They presented to the outpatient department with nonspecific ocular complaints and a LOCS III score = 0.1. They were selected randomly from the same population as the patients, with normal ocular examination and a LOCS III score = 0.1. They presented to the outpatient department with nonspecific ocular complaints and a LOCS III score = 0.1. They were selected randomly from the same population as the patients, with normal ocular examination and a LOCS III score = 0.1. They presented to the outpatient department with nonspecific ocular complaints and a LOCS III score = 0.1. They were selected randomly from the same population as the patients, with normal ocular examination and a LOCS III score = 0.1. 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Genotyping of OGG1 (rs1052133) polymorphism: Genotyping of the OGG1 (rs1052133, Ser326Cys) polymorphism was performed by PCR with confronting two-pair primers following Niwa et al. [15]. The extracted DNA was amplified with the four primers: for the C (Ser) allele: 5′-CAG CCC AGA CCC AGT GGA CTC-3′ (F1) and 5′-TGG CTC CTG AGC ATG GCG GGG-3′ (R1); for the G (Cys) allele: 5′-CAG TGC CGA CCT GCG CCA ATGG-3′ (F2), 5′-GGT AGT CAC AGG GAG GCC CC-3′ (R2). Where the bases affected by the polymorphism are underlined.

The PCR was performed in a final volume of 25 μl containing 100 ng of template DNA, 0.5 μM of each primer (Biosearch Technologies), and 12.5 μl of 2X i-Taq™ PCR Master Mix (iNtRON Biotechnology).

The amplification protocol was as follows: 95 °C for 10 min followed by 30 cycles of 95 °C for 1 min, 64 °C for 1 min, and 95 °C for 1 min, and a final extension 72 °C for 5 min using a thermal cycler PTC-100 machine (MJ Research, Inc., Watertown, MA). The OGG1 Ser326Cys polymorphism was genotyped as a 252 bp band for the C (Ser326) allele, a 194 bp band for the G (Cys326) allele, and a 406 bp common band.

The PCR products of both genes were separated in a 3% agarose electrophoresis system (Maxicell, EC 360 M E-C Apparatus Corporation, St. Petersburg, FL), then visualized with ethidium bromide staining under UV transillumination with 100-bp SiZer™ DNA marker (iNtRON Biotechnology).

Statistical analysis: Data were processed using the Statistical Package for Social Science version 13 (SPSS Inc., Chicago, IL). The ages of the patients and the controls were compared by the Student t test. The chi-square test was used to compare the gender distribution, to test the association between the genotypes and alleles in relation to the cases and controls, and to test for deviation of genotype distribution from the Hardy–Weinberg equilibrium (HWE). The odds ratios (ORs) and their 95% confidence intervals (95% CIs) were calculated to estimate the strength of the association between polymorphism genotype alleles of patients and controls. A value of p<0.05 was considered statistically significant.

RESULTS

The ages of the controls ranged from 60 to 78 years, with a mean of 67.83±5.54 years. There were 22 males and 28 females. The ages of the cataract patients ranged from 50 to 78 years with a mean of 60.33±6.22 years. There were 56 males and 94 females. There was a statistically significant increase in the age of controls compared to cataract patients (p<0.001), but no significant difference was found as regard sex (p = 0.40). The demographic data for the study groups are shown in Table 1.

XPD (rs1799793) polymorphism analysis and age-related cataract risk: The genotype frequencies were in accordance with the HWE among the controls (p = 0.33), but not among the patients (p<0.001). In patients with ARC, the frequencies of Asp/Asp, Asp/Asn, and Asn/Asn genotypes were 44.7, 32.0, and 23.3%, respectively; in controls, the frequencies were 56.0, 34.0, and 10.0%, respectively. The frequencies of Asp and Asn alleles in cataract patients were 60.7 and 39.3%, while in controls, they were 73.0 and 27.0%, respectively. Regarding the risk of development of ARC, the Asp/Asp genotype and Asp wild allele were taken as references; the Asn/Asn genotype was significantly associated with an increased risk of ARC (OR = 2.74, 95% CI = 1.01–7.43, p = 0.04). The Asn allele was significantly associated with an increased risk of ARC (OR = 1.75, 95% CI = 1.06–2.89, p = 0.03); Table 2.

Table 3 shows the distribution of allele and genotype frequencies of XPD Asp312Asn polymorphism in controls and cataract subtypes. The genotype frequency of the Asn/Asn of XPD Asp312Asn was significantly higher in the cortical cataract (OR = 5.06, 95% CI = 1.70–15.05, p = 0.002), but not in other types. The Asn allele was significantly associated with cortical cataract (OR = 2.81, 95% CI = 1.56–5.08, p<0.001).
OGG1 (rs1052133) polymorphism analysis and age-related cataract risk: The distribution of OGG1 Ser326Cys genotypes was consistent with HWE in controls (p = 1.00), but not in patients (p = 0.009). Table 4 shows the analysis of polymorphism located at OGG1 in cataract patients. Seventy-seven patients (51.3%) were homozygous for the Ser/Ser genotype, 51 (34.0%) were heterozygous for the Ser/Cys genotype, and 22 (14.7%) were homozygous for the Cys/Cys genotype. In the control group, the frequencies of Ser/Ser, Ser/Cys, and Cys/Cys genotypes were 64.0, 32.0, and 4.0%, respectively. The frequencies of Ser and Cys alleles in cataract patients were 68.3 and 31.7%, and in controls they were 80.0 and 20.0%, respectively. Regarding the risk of development of ARC, the Ser/Ser genotype and Ser326 allele were taken as references. The occurrence of the OGG1 Cys/Cys genotype was significantly higher in cataract patients than controls (OR = 4.13, 95% CI = 0.93–18.21, p = 0.04), and the Cys326 allele was also significantly higher in cataract patients than controls (OR = 1.85, 95% CI = 1.06–2.89, p = 0.03).

Table 5 shows the distribution of allele and genotype frequencies of OGG1 Ser326Cys polymorphism in controls and cataract subtypes. When compared with controls, the genotype frequency of the Cys/Cys of OGG1 Ser326Cys was significantly increased in the cortical cataract (OR = 6.00, 95% CI = 1.24–28.99, p = 0.01), but not in other types. The Cys326 allele was significantly associated with cortical cataract (OR = 2.45, 95% CI = 1.30–4.63, p = 0.005).

DISCUSSION

Age-related cataract has been a focus of investigators attempting to identify the causes and the pathogenesis of the disease and hoping to decrease the incidence or delay its onset. Agents such as UV light and hydrogen peroxide, to which the lens is exposed throughout life, have been suggested to compromise genomic integrity and are harmful to lens epithelial cells [16,17]. It is possible that accumulated damage from these and other agents may lead to a decrease in lens epithelial cell density, as observed by some investigators [18–20]. Accumulated damage could impair the ability

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**Table 2. Genotype distributions and allelic frequencies of XPD Asp312Asn (rs1799793) polymorphism in age-related cataract patients (n=150) and controls (n=50).**

| XPD Asp312Asn polymorphism | Cataract patients, n (%) | Controls, n (%) | Odds ratio (95% confidence interval) | P value* |
|----------------------------|--------------------------|----------------|-------------------------------------|----------|
| Genotype                   |                          |                |                                     |          |
| Asp/Asp                    | 67 (44.7)                | 28 (56.0)      | 1 (reference)                      | —        |
| Asp/Asn                    | 48 (32.0)                | 17 (34.0)      | 0.91 (0.46–1.80)                   | 0.79     |
| Asn/Asn                    | 35 (23.3)                | 5 (10.0)       | 2.74 (1.01–7.43)                   | 0.04     |
| Alleles                    |                          |                |                                     |          |
| Asp                        | 182 (60.7)               | 73 (73.0)      | 1 (reference)                      | —        |
| Asn                        | 118 (39.3)               | 27 (27.0)      | 1.75 (1.06–2.89)                   | 0.03     |

* Chi-square ($\chi^2$) test

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**Table 3. Genotype distributions and allelic frequencies of XPD Asp312Asn (rs1799793) polymorphism in controls (n=50) versus in different subtypes of age-related cataract patients (n=150).**

| XPD Asp312Asn polymorphism | Controls, n (%) | Cataract patients, n (%) | Odds ratio (95% confidence interval) | P value* |
|----------------------------|-----------------|--------------------------|-------------------------------------|----------|
|                            | cortical cataract, n=50 | nuclear cataract, n=50 | posterior subcapsular cataract, n=50 |
| Genotype                   |                |                          |                                     |          |
| Asp/Asp                    | 28 (56)        | 17 (34)                  | 24 (48)                             | 26 (52)  |
| Asp/Asn                    | 17 (34)        | 15 (30)*                 | 18 (36)*                            | 15 (30)* |
| Asn/Asn                    | 5 (10)         | 18 (36)*                 | 8 (16)*                             | 9 (18)*  |
| Alleles                    |                |                          |                                     |          |
| Asp (G)                    | 73 (73)        | 49 (49)                  | 66 (66)                             | 67 (67)  |
| Asn (A)                    | 27 (27)        | 51 (51)*                 | 34 (34)*                            | 33 (33)* |

*not significant *p=0.002; odds ratio=5.06; 95% confidence interval (1.70–15.05). *p<0.001; odds ratio=2.81; 95% confidence interval (1.56–5.08).
of the lens epithelial cells to protect underlying fibers, or the reduced epithelial cell density could diminish the protection afforded by the epithelium. Lens epithelium DNA may also be affected by different insults. Many studies have indicated the association between the oxidative or UV light DNA damage and cataract development [21-26]. Spector reported that, in most cases, photochemically induced oxidative stress in rat lenses may cause irreversible changes in the lens epithelia. The earliest detectable changes in lens cell biology are observed in the epithelial cell redox set point and at the DNA level in terms of DNA integrity and 3H-thymidine incorporation followed by decreased membrane transport and changes in gene expression. Significant modification in classical cataract parameters such as hydration and transparency occur at later times [22].

The DNA repair capacity has an important role in protecting the genome against DNA damage. The proteins involved in the DNA repair pathway function directly with damaged DNA and are involved with the genes and proteins that regulate DNA replication and progression through the cell cycle [27,28]. There is also interindividual variation in DNA repair capacity, which is likely attributable to genetic variation in DNA repair genes [29,30]. Decreased activity of repair enzymes with age may decrease the capacity to repair damaged DNA molecules. Defective antioxidant enzymes and functional variants of DNA replication and repair genes might be expected to be highly significant to cancer and aging [31,32]. We analyzed the association between two DNA repair genes, XPD Asp312Asn and OGG1 Ser326Cys polymorphisms, and the risk of ARC in the Egyptian population because these polymorphisms may alter DNA repair capacity. In addition, these enzymes play a vital role in the NER and BER pathways [33-37], and may subsequently lead to synergistic effects with other insults resulting in ARC.

We chose control subjects with higher ages than the patients. Recruiting subjects from this age group had the merit of maximizing the probability that they were unaffected by cataract, that is, to avoid including younger subjects who might develop cataract in later life. The distributions of genotypes of XPD and OGG1 were in accordance with the

| OGG1 Ser326Cys polymorphism | Cataract patients, n (%) | Controls, n (%) | Odds ratio (95% confidence interval) | P value* |
|-----------------------------|-------------------------|----------------|-----------------------------------|---------|
| Genotype                    |                         |                |                                   |         |
| Ser/Ser                     | 77 (51.3)               | 32 (64.0)      | 1 (reference)                     | —       |
| Ser/Cys                     | 51 (34.0)               | 16 (32.0)      | 1.09 (0.55–2.17)                  | 0.8     |
| Cys/Cys                     | 22 (14.7)               | 2 (4.0)        | 4.13 (0.93–18.21)                 | 0.04    |
| Alleles                     |                         |                |                                   |         |
| Ser                          | 205 (68.3)              | 80 (80.0)      | 1 (reference)                     | —       |
| Cys                          | 95 (31.7)               | 20 (20.0)      | 1.85 (1.07–3.20)                  | 0.03    |
| * Chi-square test           |                         |                |                                   |         |

Table 4. Genotype distributions and allelic frequencies of OGG1 Ser326Cys (rs1052133) polymorphism in age-related cataract patients (n=150) and controls (n=50).

| OGG1 Ser326Cys polymorphism | Controls, n (%) | Cataract patients, n (%) |
|-----------------------------|-----------------|--------------------------|
|                             | cortical, n=50  | nuclear, n=50            | posterior subcapsular, n=50 |
| Genotype                    |                 |                          |                           |
| Ser/Ser                     | 32 (64)         | 22 (44)                  | 27 (54)                   | 28 (56) |
| Ser/Cys                     | 16 (32)         | 18 (36)*                 | 17 (34)*                  | 16 (32)*|
| Cys/Cys                     | 2 (4)           | 10 (20)*                 | 6 (12)*                   | 6 (12)* |
| Alleles                     |                 |                          |                           |         |
| Ser                          | 80 (80)         | 62 (62)                  | 71 (71)                   | 72 (72) |
| Cys                          | 20 (20)         | 38 (38)*                 | 29 (29)*                  | 28 (28)*|

*not significant * p=0.01; odds ratio, 6.00; 95% confidence interval, 1.24–28.99. * p=0.005; odds ratio, 2.45; 95% confidence interval, 1.30–4.63.
HWE among controls, but not among patients, indicating the possible association of these polymorphisms with the disease. The absence of deviation from the controls indicates absence of selection bias. Deviation from HWE in patients with ARC was also found in the Indian population [38].

In this study, the frequency of variant allele Asn312 of XPD gene was 27%, while in the Indian population it has been reported to be 36% [38]. We found a possible risk for XPD Asn/Asn genotype and cataract development. There was a significant increase in the frequencies of XPD Asn/Asn genotype in cataract patients as compared to controls (OR = 2.74). In addition, there was a significant increase in the frequencies of XPD Asn312 variant allele in cataract patients as compared to controls (OR = 1.75). Regarding cataract subtypes, there were significant increases in the frequencies of the Asn/Asn genotype and Asn312 in cortical cataract only, but not in other subtypes. Padma et al. were the first to report the association of XPD Asp112Asn polymorphism and ARC. They found a significant increase in the frequencies of the XPD Asn/Asn genotype in cataract patients as compared to controls, but they did not find a significant difference related to the Asn312 allele [38]. They also observed a significant increase in the frequencies of XPD Asn/Asn genotype in cortical cataract, but not in other subtypes. These results can possibly be explained by the decreased activity of the enzyme of XPD Asn312 allele in DNA repair with age, promoting cataract development.

Hou et al. reported that the XPD Asn112 variant allele may be associated with the reduced repair of aromatic DNA adducts [39]. Different XPD alleles have been associated with chromosomal aberrations, frequency of sister chromatid exchanges, DNA adducts, and reduced efficiency of DNA repair as measured by the host cell reactivation assay and increased UV-induced DNA strand breaks detected by the alkaline comet assay [40,41].

In this study, the frequency of variant allele Cys326 in controls was 20%. The Cys326 allele frequency ranges from 23% to 41% in Caucasians and 40% to 60% in Asians [42]. We found that OGG1 Ser286Cys polymorphism may be associated with an increased risk of ARC. The statistical analysis revealed a possible deleterious effect of the OGG1 Cys/Cys genotype (OR = 4.13) and Cys326 allele (OR = 1.85) in the development of cataract. Moreover, the genotype frequency of the Cys/Cys of OGG1 gene was significantly increased in the cortical cataract (OR = 6.00). The Cys326 allele was significantly associated with cortical cataract (OR = 2.45). It has been hypothesized that this could be due to the OGG1 Cys326 protein having an impaired repair activity, allowing 8-oxoguanine to accumulate in the DNA with a consequent increase in mutation rates. Our results are consistent with the results of Zhang et al., who first reported comparable findings in Harbin, China [43].

The OGG1 Ser286Cys polymorphism has been shown to diminish the 8-oxoguanine glycosylase-1 DNA (hOgg1) activity in vitro, suggesting that the Cys326 allele may pose a higher risk of 8-oxoguanine formation in DNA [44,45]. The effect of endogenous hOgg1 activity in human cells by the 326 allele status remains controversial. No allele-specific differences due to gender or smoking behavior have been found by Janssen et al. [46], whereas Chen and colleagues found a significant age-dependent decrease in hOgg1 activity in the lymphocytes of homozygous Cys326 allele carriers [47]. Several hypotheses have been proposed for the mechanism underlying a potential deficiency in the DNA repair capacity of the OGG1 Cys326 allele form. This variant, or its mRNA, could be less stable, causing the steady-state level of the hOgg1 enzyme in the cell to decrease [48]. Following this, subnuclear localization may be brought about by a phosphorylation of the Ser286, which is important for the localization of the protein and has potential catalytic efficiency [49]. Bravard et al. supported the idea that individuals homozygous for the OGG1 Cys326 variant could more readily accumulate mutations under conditions of oxidative stress [48]. Their results established that the intrinsic hOgg1 activity, and therefore repair capacity, of cells carrying the OGG1 Cys326 variant is particularly sensitive to the cellular redox status.

The association of XPD Asp112Asn and OGG1 Ser286Cys polymorphisms with cortical cataract observed in the present study may be supported by results of some epidemiological studies. Family epidemiological investigations have shown that hereditary factors play an important role in the occurrence of ARC [50-54]. Moreover, it is known that cortical cataract is highly heritable among other subtypes of ARC [53,54]. Previous studies have already reported an association between the UV light exposure and the development of cortical cataract. A review of 22 epidemiologic studies by McCarty and Taylor revealed that there is a well-documented risk for the development cortical cataract and UV-B exposure [55].

The results of this study cannot be generalized for several reasons. First, ARC is a multifactorial disease and its pathogenesis is complicated. The lens is exposed throughout life to a large number of possibly injurious agents that come through the aqueous humor, such as hydrogen peroxide and UV light, which result in oxidative damage. Second, ethnic differences may be an important factor that may affect genetic studies of this type. Third, the interaction of other genes participating in
DNA damage recognition repair and cell cycle regulation may have altered the effect of \textit{OGG1} and \textit{XPD} polymorphisms.

As with other candidate gene studies, there are some limitations in our study. First, as the power to detect disease susceptibility genes is influenced by the number of sample size, the size of the sample in our study seems to be relatively small. Second, the patients were recruited only from the town of Zagazig, and not from other areas in Egypt.

In conclusion, this is the first study to identify a possible association between the \textit{XPD} Asp\textsuperscript{132}Asn and \textit{OGG1} Ser\textsuperscript{326}Cys polymorphisms of the DNA repair enzyme genes and ARC in an Egyptian population. The present data support the importance of DNA repair gene polymorphisms and DNA repair genes as potential pharmacologic targets to promote DNA repair and maintain genome stability. Manipulating these targets may provide a strategy to prevent, delay the age at onset, or slow the progression of ARC. However, larger studies in multiple ethnic groups would be required to establish such relationships.

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