Molecular Epidemiology of Breast Cancer: A Review

ABSTRACT

The standard paradigm providing a general mechanistic explanation for the association of estrogens, exposure to ionizing radiation, and breast cancer risk is that the proliferative stimulus provided by ER-mediated (E2) leads to the appearance of spontaneous mutations. This, the key contribution of E2, is in the stimulation of breast epithelial cell proliferation. However, emerging evidence supports a complementary pathway involving direct (hereditary) or indirect (radiation DNA damage, via indirect-acting genotoxic agents) mechanisms originating from estrogen metabolites. While mutagens in high concentrations such as 2HNE, H2O2, and H2S cause a high risk for an individual, they represent a slow overall stochastic process due to slow allele frequencies in the population. On the other hand, mutations in phases 1 and 2 enzymes genes involved in xenobiotic and endobiotic metabolism, including enzymes encoding CYPIA1, N-acetyltransferase 2, and glutathione-S-transferase (GST) isotypes M1 (m1), T1, and P1 (deactivating alleles), might identify a lower relative cancer risk for an individual. However, because these mutations seem to be rare among individuals, they appear as a high stochastic risk category of genes. The intent of this review is to present current literature on the molecular epidemiology of breast cancer with emphasis on the role of polymorphisms in high- and low-potency genes on susceptibility to breast cancer. (Tech Rep Health 2003, 7(4): 17–28)

RESUMÉ

Épidémiologie moléculaire du cancer du sein: un réexamen. Le paradigme standard qui fournit une explication mécanistique générale pour l'association de l'estrogène, l'exposition aux rayons X et le risque de cancer du sein est que le stimulus prolifératif fourni par l'estrogène (E2) conduit à l'apparition de mutations spontanées. Avec le contributio de E2, c'est la stimulation de la prolifération des cellules épithéliales du sein qui est claire et évidente. Cependant, l'évidence indique que des voies supplémentaires qui impliquent les métabolites géniques actifs (mutations d'ADN, en particulier par voie de radicaux libres) sont également responsables de ces mutations. Alors que les mutations dans les gènes à haute fréquence (telles que BRCAl, BRECt et p53), conduisent à un risque élevé au niveau individuel, elles représentent un facteur de risque de développement de cancers génétique chez l'individu. Cependant, pour ces situations, l'importance de ces connaissances chez les individus, elles sont considéré comme des gènes à faible risque de cancer. Le but de cette revue est de présenter les données actuelles sur l'épidémiologie moléculaire du cancer du sein avec une emphasis sur le rôle des polymorphismes dans les gènes à haute et faible fréquences sur la susceptibility au cancer du sein. (Tech Rep Health 2003, 7(4): 17–28)

KEY WORDS: Molecular epidemiology, breast cancer, genes

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Introduction

Breast cancer is the most common cancer in Nigerian women and the incidence appears to be rising. The actual incidence of the disease is unknown but in 1993, the estimated incidence of breast cancer in Nigeria was 35.6 per 100,000.12 This is believed to be a gross underestimation of the true incidence of the disease. Late presentation is a marked feature of breast cancer in Nigeria, with about 70% of cases reporting to hospital with advanced disease.

The actual causes of most cases of breast cancer are unknown. Most studies on the etiology of the disease have centered on the role of oestrogens. Oestrogens are a major female hormone influencing the development and maintenance of the breast, and all available evidence implicates oestrogens as the final common pathway for the initiation of mammary carcinogenesis. Oestrogen and some of its metabolites induce tumorigenesis in several models including the breast, and this has been shown to correlate with the chances of genetic mutations that can lead to the development of breast cancer. Indispensable levels of oestrogens have been correlated with the risk of breast cancer, but the result of these studies have not been consistent.23

One possible explanation for diverse results across populations may be differences in the prevalence of common inherited variants or polymorphisms in the genes that code for enzymes involved in steroid hormone production and metabolism. In this review, we highlight recent advances in the molecular biology of the cancer cell that have enabled investigators to explore the role of high and low penetrance genes and polymorphisms in genes encoding-oestrogen-metabolizing enzymes in breast carcinogenesis.

Candidate Genes

The candidate genes involved in breast cancer susceptibility studied thus far can be divided into three main groups, namely, high penetrance genes such as TP53, BRCA1 and BRCA2; genes coding for proteins with roles in steroid hormone metabolism; and genes coding for oestrogen-metabolizing enzymes.

Common Alleles of High Penetrance Genes

About 5-10% of cases of breast cancer occur due to genetic susceptibility resulting from inheritance of BRCA1, BRCA2 and TP53 genes. Mutations in the BRCA1, BRCA2 and TP53 genes are associated with a high lifetime risk of breast and other cancers.11,12 TP53 is a tumour suppressor gene whose protein product is produced as a response to DNA damage through activation of a genetic agent, resulting in cell cycle arrest in G1 and induction of pathways leading to DNA repair or apoptosis. Mutations in the TP53 gene result in decreased P53 activity, which may lead to failure of cells with DNA damage to arrest and thus continue to replicate with damaged DNA. In the case of BRCA1, the initial screening for germline mutations uncovered five sequence alterations in eight kindreds analyzed. Two were frameshift alterations, one was a nonsense mutation (Glu134Ser), and one was identified as a loss of mRNAS from the linked allele. A fifth alteration was an splicing mutation. Two nonsense mutations have been identified in African Americans, one (Cys664Gly) involves the final cysteine of the predicted CMGC zinc-binding XING finger located near the N-terminus of the 1268 amino acid protein and the second is due to insertion of methionine by arginine (Met775Arg).11 In one study, two African-American kindreds were found to carry the second alteration, suggesting that the might be a common mutation in that population. A single BRCA1 mutation, 1850delAG, has been found in approximately 20% of Ashkenazi Jewish women with early onset breast cancer and 0.02% of the Ashkenazi population.22 The majority of these mutations generate truncated protein resulting in loss of function or reduced activity of the protein product.

In one report of BRCA2 mutations, eight of the alterations were small deletions with the exception of one nonsense mutation, and all were predicted to interrupt the BRCA2 coding sequence and lead to a truncated protein product.12 A recent study from Taiwan found three different mutations in the BRCA2 gene (570delC, 3076delT, and 6696-7delC).13 All three mutations were predicted to result in frameshifts, leading to premature translational termination of the BRCA2 protein.
Four substitution mutations were also reported in that study. A particular deletion mutation, 617delT, has been reported in 8% of Ashkenazi Jewish women diagnosed with early onset breast cancer. Although there is scanty data on the prevalence of mutations in these high penetrance genes in indigenous African populations, we speculate that genetic mutations similar to those in African-American women will exist in these populations since they share considerable gene ancestry with African-Americans.

Steroid Hormone Metabolising Genes

Genes Involved in Oestrogen Biosynthesis

Genes involved in the metabolism of sex hormones are strong candidates for breast cancer susceptibility genes. Those in the sex hormone biosynthesis pathway may affect production of, and thus exposure to, the most active oestrogen, estradiol. Two genes in this pathway include the cytochrome P450 CYP19 (aromatase) gene and the cytochrome P450/c17 (CYP17) gene.

CYP19 (Aromatase) Gene

This gene is responsible for the rate-limiting step in the metabolism of C19 steroids to oestrogens and is expressed in most breast carcinomas. Five different alleles containing 7, 8, 9, 11 and 12-TTAA repeats have been described. A single allele, containing the longest repeat (TTAA) was found significantly more frequently in breast cancer patients than in control individuals, indicating that individuals carrying the A1 allele of CYP19 may have an increased risk of developing breast cancer, OR 3.7 (95% confidence interval [CI] 1.03 - 8.83).

CYP17 Gene

The CYP17 gene codes for the cytochrome P450C17 alpha enzyme, which mediates both 17-alpha hydroxylase and 17,20-lyase activities and functions at key branch points in steroidogenesis. Polymorphic alleles of CYP17 have been identified (A1 and A2), and the sequence present in the A2 allele creates a new Sp1 promoter site (GCACCC) that is hypothesised to enhance basal transcription of the enzyme.

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Gene

Higher serum estradiol and progesterone levels have been observed among multiparous pre-menopausal women carrying at least one A2 allele, compared to women homozygous for the A1 allele. Ferguson et al. found that among women of Asian, African-American and Latino descent, the presence of an A2 allele was significantly associated with the presence of advanced stage breast cancer but not in situ breast cancer. They also found that among controls, women with an A2 allele were more likely to experience menarche before 13 years than A1 homozygous (49% versus 39%). The protective association between later age at menarche and breast cancer was stronger in women with the A1/A1 genotype than with at least one A2 allele (OR = 0.47 versus 0.48).

Genes Involved in Oestrogen Metabolism

CYP19/A1 Gene

Hydroxylations at the C-16 and C-2 positions is catalyzed by the 16-alpha- and 2-hydroxylases, and these enzymes are encoded by the CYP19/A1 gene. The CYP19/A1 gene is a critical component of the inducible phase I cytochrome P450 supergene family and is also responsible for the oxidative metabolism of 17-beta estradiol, and such toxicants as diethylbenzene and benzo(a)pyrene. Overexpression of the enzymes in the C-16 pathway has been implicated in carcinogen metabolism and breast cancer risk. The CYP19/A1 gene is located on chromosome 6p21 and is critical for breast carcinogenesis.

The frequency of each of these polymorphisms varies as a function of race. The association of the MspI polymorphism with breast cancer was negative in Caucasian but highly significant in African-American women. An increased frequency in post-menopausal breast cancer with the exon 7 polymorphism was recently demonstrated.

CYP19/B1 Gene

CYP19/B1 is expressed constitutively in the human mammary carcinoma MCF-7 cell line and the enzyme product mediates the hydroxylation of 17-estradiol.
beta-estradiol) or form catechol estrogens, a compound with demonstrable carcinogenic activity in human mammary and uterine sites.12,13 These polymorphisms have been described, a single base substitution resulting in amino acid substitutions of Arg (CAG) by Gly (GGG) and Ala (GCC) by Ser (TGC) identified at codons 48 and 159 in exon 2 respectively, and a third single base substitution of thymine by cytosine in intron 1.7 The frequency of the genotypes of Ala-Ser polymorphism in patients with breast cancer was found to be slightly but statistically significantly different from that in healthy control subjects.21

CYP2D6 (Debrisoquine Hydroxylation Gene)

The CYP2D6 gene is located on chromosome 22q and codes for debrisoquine hydroxylase,10,11 which metabolizes a variety of drugs and other xenobiotics. The CYP2D6 gene may activate procarcinogens or, conversely, directly carcinogens.11 A number of alleles have been characterized at the CYP2D6 locus. The "poor metabolizer" phenotype (CYP2D6 mutant/mutant genotype), which is rare in Asians, occurs in about 5-10% of Caucasians and 2% of African-Americans.12 Studies of the CYP2D6 genotype and the risk of breast cancer have yielded conflicting results. Laden et al.13 found that Spanish women who were poor metabolizers had about a two-fold increased risk of breast cancer, and Shum et al.14 provided some evidence of an association between the poor metabolizer phenotype and the risk of breast cancer. However, the studies of Shiah et al.15 and Duchesne et al.16 reported no increased risk of breast cancer among carriers of the various alleles of the CYP2D6 gene.

CYP3A4 Enzyme Activity

Several recent studies17-20 have shown that CYP3A4 plays a major role in the 4- and 16-alpha hydroxylations of estrone, particularly estriol, the predominant type of estrogens in postmenopausal women.20 CYP3A4 is also involved in the activation of many environmental carcinogens such as polycyclic hydrocarbons, heterocyclic amines, aromatic and nitrosamines.17-20 Furthermore, CYP3A4 is present in human mammary epithelial cells,21 suggesting that these enzymes may be involved in the in vivo activation of many mammary carcinogens in these target cells. A polymorphism in the 5'-flanking region (298 A/G) of the CYP3A4 gene has recently been described and this polymorphism was shown to be related to the risk of prostate cancer22 and treatment-related leukemias.23 Zheng et al.24 recently described two additional allelic variants of the CYP3A4 gene. They also reported a positive association between urinary 6-beta-OH cortisol ratio and breast cancer risk, and the association was stronger in postmenopausal women in whom oestrone is the major form of oestrogen.

Genes for Phase II Enzymes

The phase II enzymes consist of different classes of enzymes that are involved in the conjugation and inactivation of oestrogens and enzymes involved in the metabolism of oestrogens and various carcinogens.

Catalytic O-Methyltransferase Gene

The catalytic oestrogen(s) are the major metabolites of oestrogen in humans and animals. The 2-catalysed oestrogens have been reported to be active in both prostate-predominant and cancer-exhibiting activities through interactions with xenobiotics (cellular proteins and DNA). The catalytic O-methyltransferase is involved in the conjugation and inactivation of the catalysed oestrogens. An amino acid change (valine to methionine) at position 138/108 in the threonine-bound/resolved form of the protein has been linked to decreased methylation activity of the enzymes.21 This amino acid change is believed to be closely associated with the observed twofold distribution of CPT2 enzyme activity in the population associated with high COMT (Val/Val), intermediate COMT (Val/Met) and low COMT (Met/Met) activity.22 Thompson et al.23 showed that genetic polymorphism in the enzyme and was differentially associated with breast cancer risk among pre-menopausal and postmenopausal women.

GSTs (Glutathione-S-Transferase Genes)

The GST family are phase II enzymes that detoxify carcinogens and their reactive intermediates such as 1,3-dithiol-2-one.24-25 GSTs are encoded by a superfamily of genes.
those produced by GVP11, by facilitating their conjugation to glutathione and subsequent excretion. To date, four polymorphic families of cysteolic sulfhydryl GSTs (κ, π, μ, and θ) have been identified in humans. For both GSTM1 and GSTT1, a high percentage of the Caucasian populations are homozygous for null alleles (up to 50 and 20% respectively) and have no detoxifying GST activity. About 23–35% of African-Americans are also homozygous for the null GSTM1 and GSTT1 alleles. Levels of DNA adducts, intercellular exchange and somatic genetic mutations may be increased in carriers of GSTM1 and GSTT1 null genotypes, and these individuals may have a higher risk of cancer of the breast and other sites because of their impaired ability to metabolize and eliminate carcinogens.

The GSTM1 genotype has been related to the individual breast cancer risk in several recent studies, some of which suggested an association between GSTM1 null genotype and breast cancer risk in postmenopausal women, whereas others found no association.

**GSTP1 Gene**

For GSTP1 gene, two variant alleles, GSTP1*B and GSTP1*C, have been detected in addition to the wild-type allele GSTP1*A. In both variants, a point mutation at nucleotide 133 results in a single amino acid change from phenylalanine (Phe) to valine (Val) at codon 105. This residue lies in close proximity to the hydrophobic binding site for electrophilic substrates, and the Val variant allele has been demonstrated to exhibit altered specific activity and affinity for electrophilic substrates. In contrast to GSTT1, there is little data on the potential role of GSTP1 and GSTT1 genotypes in breast cancer risk. Two recent studies revealed no significant association between the GSTP1 genotypes and breast cancer predisposition, although one study suggested a trend for increasing risk with higher numbers of GSTP1 Val alleles.

Unlike Diphospho-Glucuronosyltransferase 1A1 Gene (UGT), catalyze the glucuronidation reaction, which represents a major route for the detoxification of a diverse range of molecules including carcinogens and biologically active endogenous compounds such as steroids. An additional role of UGT enzymes is to maintain intracellular steady-state levels of steroids including estrogens in target tissues. Various polymorphisms in the UGT1A1 gene have been described. Lower expression of UGT1A1 might lead to an increase in the level of estradiol and exposure to a higher local concentration of active estrogen, and therefore, have considerable impact on tumour initiation and growth. The low-activity UGT1A1 allele has been observed to be positively associated with invasive breast cancer in women of African ancestry. This association was negative for Caucasian women.

**N-Acetyltransferases**

The N-acetyltransferases, NAT1 and NAT2, are also phase 1 enzymes and they participate in the detoxification of the arylamines, some of the main carcinogenic components of tobacco smoke and the amine produced during cooking of meat.

However, the action of NATs on these carcinogens can produce electrophilic forms that may induce point mutations in DNA. Polymorphisms in both genes result in two phenotypes: slow acetylators who are homozygous for low activity alleles and fast acetylators who carry one or more high activity alleles.

**N-Acetyltransferase 1 Gene**

The association between NAT1 phenotypes and the risk of breast cancer has been investigated in various studies with some demonstrating a relationship between these genotypes and breast cancer risk. Zheng et al. found that the NAT11 allele was associated with a five-fold increased risk of breast cancer. The risk was particularly increased among women who smoked cigarettes, consumed high levels of red meat, or had a preference for consistently well-done meat. The NAT110 allele was related to a slightly elevated risk of breast cancer, and this association was primarily confined to Caucasion or light smokers.

**N-Acetyltransferase 2 Gene**

Studies on the relationship of breast cancer risk and interactions between NAT2 genotypes and polymorphisms
Other Genes

Oestrogen Receptor (ER) Polymorphisms

Mutations in the coding region of the oestrogen receptor gene have been described in only a small percentage of breast cancer patients. More common are genetic polymorphisms of the ER gene that do not alter the encoded amino acid. As mentioned, some studies have reported that the allele frequency with the Xbal restriction site (in exon 2) is flanked in the ER gene in a 1:4 ratio among breast cancer patients as well as in controls (95% CI, 1.0-1.9). Among breast cancer patients, there was a borderline association between the Xbal restriction site and older age at onset. Several neutral polymorphisms in codons 10, 87, 243, 325, and 504 have been described in both ER positive and ER negative tumours. However, a statistically significant association was found between the polymorphism in codon 325 and a reported family history of breast cancer (OR, 4.3; 95% CI, 1.8-10.1). 17

XRCC1 Gene

One of the DNA repair genes exhibiting polymorphism variation is XRCC1, which is located on chromosome 19q13.2 and encodes a 607,000 protein. XRCC1 has no known catalytic activity but appears to play a pivotal role in BER by bringing together DNA polymerase beta, DNA ligase III and PARP at the site of DNA damage. BER targets endogenous DNA damage induced through hydrolysis, oxidative stress and alkylation as well as adducts and fragmented sites caused by exogenous agents such as ionizing radiation and alkylating or oxidative agents. Thus, XRCC1 may participate in the removal of 'non-bulky' DNA adducts, the repair of oxidative DNA damage, and the repair of DNA damage attributable to ionizing radiation. While some studies have demonstrated some association between polymorphisms in this gene and breast cancer risk, others have reported contrary findings. 18, 19

Manganese Superoxide Dismutase (MnSOD) Gene

Oxidative stress, resulting from the imbalance between pro-oxidant and anti-oxidant species damages DNA, proteins, cell membranes and mitochondria and seems to play a role in human breast carcinogenesis. Dietary sources of anti-oxidants (chemical) and endogenous anti-oxidants (enzymes), including the polymorphic manganese superoxide dismutase (MnSOD), can act to reduce the load of oxidative stress. Ambrozovic et al. 29 found a positive association between MnSOD genetic polymorphism and breast cancer risk.

Promoter Hypermethylation of DNA Repair Genes

Methylation is the main epigenetic modification in mammalian and abnormal methylation of the CpG islands located in the promoter region of the genes leads to transcriptional silencing. Examples include the p16, p15, p14, Von Hippel-Lindau (VHL), the oestrogen and progesterone receptors, E-cadherin, death-associated protein (DAP) lactate and the breast tumour suppressor gene described, retinoblastoma (RB) gene. Recent investigations of promoter hypermethylation of DNA repair genes have shown that loss of BRCA1 mRNA and protein does occur in sporadic breast and ovarian cancer. Studies have demonstrated that BRCA1 hypermethylation is leading to loss of BRCA1 function in breast and ovarian primary tumour cell lines. Bis-allclic methylation of BRCA1 is achieved in many cases by retention of one allele silenced by methylation in association with loss of the other allele by genomic deletion in this region.

Conclusion

The search for the aetiologic factors for breast and other cancers has intensified in the past decade due to advances in molecular biology and ongoing efforts to map the more than 80,000 genes in man. There is no doubt that carcinogenic metabolism of oestrogen and other carcinogens play a central role in complex cellular mechanisms, gene expression enzymes and care-giver individual differences. Environmental and genetic breast cancer can interact and an understanding of the interaction may help to reduce breast cancer risk.

Notes


cellular mechanisms resulting in cancerogenesis. Polymorphisms in genes encoding the various enzyme systems involved in metabolism of various carcinogenic compounds influence risk and inter-individual variation in cancer susceptibility. It is obvious that interactions between genes and environmental factors such as diet, cigarette smoking, and heterocyclic and aromatic amines contribute to breast cancer susceptibility, but the nature of these interactions are complex and not completely understood. These gene-environmental interactions may help to explain the differences in breast cancer risk between women of different racial/ethnic backgrounds. In particular, it may account for differences in breast cancer risk between African-American women and West African women since both populations share considerable genetic ancestry.

Future research efforts should focus on improving our research designs to overcome some of the biases of current molecular epidemiologic studies. It should be recognized that breast cancer is a heterogeneous disease with differences in relevant risk factors depending on tumour subtype. Pooling of data from large cohorts is necessary to enhance sub-group analysis. In addition, efforts should be directed at continued identification of functionally significant candidate genes and the incorporation of platforms to rapidly investigate the associations between allele variability, exposure and risk. The introduction of high throughput, DNA-based methodologies such as DNA microarrays and multiplex analysis on fluorescent microscopes, which provide simultaneous assessment of tens to hundreds of allelic variants in large numbers of samples, promises rapid, accurate and cost-effective predictive hypothesis testing for gene-based complex diseases.

Molecular epidemiology has tremendous role to play in the ongoing efforts to unravel clinical differences in breast cancer susceptibility as well as fine-tuning strategies for breast cancer prevention. Present risk assessment tools for breast cancer such as the Gail Model and the Newton-Gail Model are based on established risk factors for breast cancer such as age at menarche, parity, family history and biopsy history. Although these tools have been shown to significantly predict a woman's risk of breast cancer, there are some drawbacks in the use of the current models in different population groups. For example, the Gail model was developed from largely white populations and has been found to significantly underestimate breast cancer risk in blacks. Recently, Weisburger and colleagues evaluated and revised the Gail Model's risk factor and baseline risk (population attributable risk (PAR) component in a mixed ethnicity data set. The revised model (Gail-Newman) uses the same risk factors (age at menarche, parity, family history and biopsy history) and relative risks as those in the current standard model. However, the updated calculations of population attributable risk fractions for these risk factors has resulted in markedly different estimates for the ethnicity and age stratified baseline risks that are entered into the prediction model. Specifically, use of the revised PARs yields higher baseline risk estimates for African-American women. The Gail-Newman model was retrospectively validated on evaluations of a multicentre case-control population of 3,283 African-American women and 1,794 white women. The risk identification rate for African-American women in the Gail model is 5.6% while the Gail-Newman model identifies 19%. This is equivalent to the risk identification rate in white women evaluated by the Gail model. Molecular epidemiological research has the potential of improving current risk assessment tools by identifying susceptibility genes for breast cancer in different sub-groups of women in different population groups. Such women with, high susceptibility for breast cancer will benefit from current prevention strategies such as tamoxifen chemoprevention.

There are currently no reports in literature on the use of risk assessment tools for breast cancer susceptibility in women in sub-Saharan Africa. While earlier reports indicated that breast cancer is a rare disease in women in the region, recent observations seem to suggest otherwise. For populations in sub-Saharan Africa to benefit from these recent advances in breast cancer risk assessment and prevention efforts, we recommend the following strategies. First, there is urgent need to ascertain the true incidence of breast cancer in the region through the establishment and adequate funding of population-
based cancer registries in various countries in sub-Saharan Africa. Secondly, there is need to establish breast cancer screening programmes. Mammographic screening in the developed countries of Europe and North America has demonstrated a 25% reduction in breast cancer mortality in women aged 40–69 years. The screening programmes should be integrated into the current health care delivery systems existing in these countries. As a matter of urgency, public health practitioners and other health care providers should embark on extensive culturally sensitive health education programmes to create awareness of the disease in the population. Nurses working in the primary health care centres should be trained to conduct periodic breast examination in addition to teaching women within their locality the techniques for breast self-examination (BSE). Individuals at risk should be referred to local hospitals and tertiary institutions for screening mammography. These screening programmes should be funded by appropriate agencies in the health insurance scheme.

Developing countries in sub-Saharan Africa are currently not investing adequately in the area of molecular and genetic epidemiologic studies. Unfortunately, the burden of breast and other cancers is increasing and is likely to become major public health problems in this region in this millennium. Efforts should be made to encourage both basic scientists and clinicians working in these regions to engage in collaborative research with invisiogists in the developed countries. In addition, more funding and better focused health policies will enhance capacity for the evaluation of molecular and genetic epidemiologic research in these regions.

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