World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.3748/wjg.v20.i16.4558

World J Gastroenterol 2014 April 28; 20(16): 4558-4565
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (8): Gastric cancer

Ethnic differences in gastric cancer genetic susceptibility: Allele flips of interleukin gene

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Received: October 28, 2013 Revised: December 12, 2013
Accepted: March 8, 2014
Published online: April 28, 2014

Abstract

Polymorphisms in promoter regions of inflammatory cytokines have been widely studied, and potentially functional polymorphisms have been discovered. Conflicting results from meta-analyses of interleukin (*IL*)-*1B* and *IL-10* polymorphisms show differences in gastric cancer susceptibilities between Caucasian and Asian populations. In particular, we note the suggestion of an allele flip in *IL-1B* and *IL-10* gene polymorphisms. In Asian populations, the *IL-1B*-1464G/-511C/-31T haplotype indicates risk for gastric cancer, while the opposite haplotype, *IL-1B*-1464C/-511T/-31C is the risk-related allele in Caucasians. Furthermore, while *IL-10*-1082G/-819C/-592C is associated with gastric cancer in Asians, *IL-10*-1082A/-819T/-592T is linked to gastric cancer risk in Caucasians. These seemingly contradictory results may be attributed to distinct carcinogenic mechanisms underlying the different gastric cancer subtypes. The allele flip observed in *IL-10* and gastric cancer appears to reflect allelic heterogeneity, similar to that observed in *IL-1B*. In this review, we focus on the allele flip phenomenon observed between different ethnic groups in an effort to resolve certain controversial results from recent studies on interleukin polymorphism. In addition, we re-emphasize the importance of stratifying gastric cancer subtypes based on anatomical site and Lauren classification to prevent false associations arising through dilution of true ones.

Key words: Allele flip; Gastric cancer; Interleukin gene

Core tip: In Asian populations, the highly expressed interleukin (IL)-1β haplotype may increase risk for gastric cancer. Abundant IL-1β expression determined by this haplotype may suppress gastric acid production in response to chronic *Helicobacter pylori* (*H. pylori*) infection, resulting in atrophic gastritis, the precursor of non-cardia gastric cancer. Conversely, the less expressive *IL-1B* haplotype associates with gastric cardia cancer in Caucasians. Only low levels of IL-1β are produced in response to *H. pylori* infection and gastric acid secretion is increased. Induction of gastroesophageal reflux disease may then promote cardia cancers.

Kim J, Kim Y, Lee KA. Ethnic differences in gastric cancer genetic susceptibility: Allele flips of interleukin gene. *World J Gastroenterol* 2014; 20(16): 4558-4565 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i16/4558.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i16.4558

INTRODUCTION

Gastric cancer is the fourth most common cancer diagnosis in men worldwide, and the mortality rate is one of the highest among cancers. The incidence rate is especially high in East Asian countries including Japan, China and Korea[1,2]. Of the various factors that contribute to

gastric cancer, including infectious, dietary, environmental and genetic factors, the chronic inflammatory state induced by *Helicobacter pylori* (*H. pylori*) infection is currently regarded as the most prevalent. Of note, however, only a small proportion of *H. pylori*-infected individuals develop gastric cancer, which implies that individual susceptibility, possibly genetic, is also involved[1,3,4].

Associations of chronic inflammation with carcinogenic processes have prompted researchers to investigate the role that *H. pylori*-related inflammation may play in gastric cancer development. Thus, it was found that inflammatory cytokines, such as interleukin (IL)-1β, also encoded by *IL-1B*, IL-1 receptor antagonist (IL-1RA), and tumor necrosis factor (TNF)-α are upregulated during *H. pylori* infection[5-8]. Interest now converges on *IL-1B, IL-1RN, IL-8* and *IL-10*, encoding IL-1β, IL-1RA, IL-8, and IL-10. The potent proinflammatory cytokine IL-1β participates in a variety of cellular activities, including cell proliferation, differentiation and apoptosis[9], in the amplification of immune response to infection, and as a potent inhibitor of gastric acid secretion[10]. Studies on single nucleotide polymorphisms (SNPs) in the *IL-1B* promoter region reveal significant associations with gastric cancer that some meta-analyses support[10,11]. Polymorphisms of *IL-10* and *IL-8* are also associated with gastric cancer risk[10].

Other meta-analyses, however, present conflicting results with respect to *IL-1B* and *IL-10* polymorphisms and gastric cancer susceptibilities between Caucasian and Asian populations. On review of multiple meta-analyses, an "allele flip" between Asian and non-Asian groups is observed; most prominently in polymorphisms of *IL-1B* and *IL-10*. The allele flip refers to an inverse risk relationship of an allele in different groups or settings, for example, an allele found to be protective in one situation, but risk-related in another[12]. A genuine allele flipping results from variations in allele frequencies and linkage disequilibrium (LD) that produce different patterns of risk association of a marker allele or haplotype across different ethnic groups[13]. Alternatively, multiple loci may interact to create a disease phenotype[14]. Finally, the phenomenon may be caused by allelic heterogeneity and locus heterogeneity, wherein different populations exhibit associations with alleles at different loci, through differences in genetic background or environment[12]. Despite extensive review using meta-analysis, no clear explanation of allele flipping among these interleukin genes between different ethnic groups has emerged.

Here we concentrate on allele flips of *IL-1B* and *IL-10* polymorphisms in association with gastric cancer development in Asian and Caucasian groups. Of particular interest are the etiological significance of flipping in relation to genetic susceptibility and the incidence of gastric cancer at different anatomical sites.

GASTRIC CANCER EPIDEMIOLOGY AND CLASSIFICATION

Gastric cancer may be classified by histopathological criteria as proposed by Lauren *et al*[15] into two principal types, intestinal and diffuse, which differ in histology, pathogenesis, epidemiology, genetic profile, and prognosis[16]. Based on anatomical site, stomach cancer may be classified as cardia or non-cardia (fundus, antrum, pylorus lesser curvature, and greater curvature)[17]. Non-cardia intestinal gastric cancer is strongly associated with chronic inflammation related to *H. pylori* infection[3,4]. For tumors arising in the proximal region of the stomach, namely the gastric cardia/gastroesophageal junction, inflammation due to chronic gastric acid secretion may be the driving force in carcinogenesis[18,19]. Gastric cardia cancers are usually of the intestinal type[20]. As proposed by Hansen *et al*[21], the cardia cancers may comprise two distinct etiological subtypes, one non-cardia-like gastric cancer and the other resembling esophageal adenocarcinoma. The types of gastric cancer are summarized in Table 1. Diffuse-type gastric cancer is thought to arise through genetic changes in gastric cancer stem cells or epithelial precursor cells and usually lacks defined premalignant lesions[22]. Recently, Shah *et al*[20] proposed a classification of gastric cancer based on clinical and epidemiological data into three principal types: proximal nondiffuse gastric cancer, diffuse gastric cancer, and distal nondiffuse gastric cancer. These distinctions are supported by gene expression analysis.

In the United States, rates of gastric cancer at all sites decreased from 1978 to 2005, while cardia cancer rates increased in the early years and plateaued[17]. With respect to histological type, intestinal-type cancer decreased at all sites except at the gastric cardia[17]. The declining prevalence of *H. pylori* infection has most likely contributed to downward trends in intestinal-type gastric cancer at non-cardia sites, particularly in Caucasians[17]. Among Asians living in the *H. pylori* endemic region, there is ample evidence that non-cardia types outnumber cardia types, although the incidence of cardia-type gastric cancers has increased in recent years[23].

IL-1 GENE POLYMORPHISM

Non-cardia, intestinal type gastric cancer

The IL-1 family includes the cytokines IL-1α, IL-1β and IL-1RA, encoded by three genes, *IL-1A, IL-1B* and *IL-1RN* on chromosome 2q14[24,25]. Three polymorphisms in the promoter region of *IL-1B*, including *IL-1B*-1464 (G/C; rs1143623; previously known as -1476), *IL-1B*-511 (C/T; rs16944), and *IL-1B*-31 (T/C; rs1143627), are widely studied in association with gastric cancer risk. Studies of the *IL-1B* polymorphism have revealed an increased risk of gastric cancer with proinflammatory phenotype in Caucasian carriers of *IL-1B*-31C and *IL-1B*-511T[11]. In meta-analyses, however, the *IL-1B* and *IL-1RN* polymorphisms imply different levels of risk for Asians and Caucasians. A landmark meta-analysis by Persson *et al*[26] revealed a consistent negative association of *IL-1B*-31C with gastric cancer in Asians. Other data show an even more significant increase in risk for non-cardia gastric cancer related to *IL-1B*-511T and *IL-1RN**2 alleles, but

Table 1 Differing risk associations for cytokine polymorphisms according to race and tumor type

Tumor type	Non-cardia or cardia with atrophy (non-cardia-like), intestinal		Cardia (esophageal), intestinal		Diffuse	
Race	Asian	Non-asian	Non-asian	Asian	Asian	Non-asian
Direction of association						
H. pylori infection	↑	↑	↓	↓	↑	↑
Gastric acid secretion	↓	↓	↑	↑	-	-
IL-1β production	↑	↑	↓	↓	-	-
IL-10 production	-	↓	-	↑	-	-
Allele flips of IL-1B and IL-10 (risk haplotype)						
IL-1B-1464/-511/-31	GCT	CTC	CTC	-	-	-
IL-10-1082/-819/-592	-	ATA	-	GCC	-	-
Genetic factors other than IL-1B and IL-10[1]	IL-8, ZBTB20, PRKAA1	IL-1RN			MUC1, PSCA	IL-1RN, TNFA
Molecular classification by gene expression analysis[20]	Distal non-diffuse		Proximal non-diffuse		Diffuse	

[1]Information based on meta-analyses[10,26] and GWAS[69-71,81]. ↑: Increase; ↓: Decrease. *H. pylori*: *Helicobacter pylori*; IL: Interleukin; PSCA: Prostate stem cell antigen.

only among Caucasians, while the *IL-1B*-511T allele may be protective against gastric cancer among Asians[27,28]. In addition, complete LD between *IL-1B*-31 and -511 has been found[11]. In East Asian populations, *IL-1B*-31TT homozygosity may be associated with increased risk for intestinal-type gastric cancer[29].

Another polymorphism in the *IL-1B* promoter region at -1464 may be associated with gastric cancer, and -1464G is a putative risk allele in Asians[30]. Moreover, -1464G is closely linked to *IL-1B*-511C/-31T alleles previously designated as risk alleles in Asians. In contrast, -1464C, in LD with *IL-1B*-511T/-31C and a risk allele among Caucasians, is associated with decreased risk of gastric cancer in the Chinese population[31]. In atrophic gastritis, a precursor lesion in gastric cancer, -1464CC, may be associated with atrophic gastritis in the antrum among Caucasians[32]. The haplotype associated with gastric cancer risk in Asians (*IL-1B*-1464G/-511C/-31T) may imply the opposite level of risk in Caucasians, among whom the *IL-1B*-1464C/-511T/-31C is the putative risk allele.

However, in a country such as China, comprising multiple ethnic groups with diverse geographical and historical roots, allelic heterogeneity with respect to gastric cancer prevalence and *H. pylori* infection status is apparent[33]. Of note, -511TT is associated with an increased risk of gastric cancer in low-risk regions of China, an association that might be less obvious in high-risk regions[33]. This is similar to the situation wherein -511TT is associated with increased gastric cancer risk in a Caucasian population with lower gastric cancer risk and *H. pylori* infection, whereas -511CC is the risk allele among Asian population, namely China, Korea and Japan, where gastric cancer risk is high. Therefore, it is plausible that *IL-1B*-1464G/-511C/-31T are the risk alleles for gastric cancer among Asians, while the exact opposite is true for Caucasians, indicating the existence of a genuine allele flip in the *IL-1B* gene polymorphisms with respect to gastric cancer risk.

To test the influence of haplotype on IL-1β expression, Chen *et al*[34] investigated the effect of SNPs in the *IL-1B* promoter region in terms of haplotype context. Of note, the SNPs at -1464, -511 and -31 in the promoter region expressed functional activities that were influenced by haplotype context[34]. This observation was confirmed in a subsequent study *in vivo*, by the finding of a positive association between haplotype pairs containing *IL-1B*-1464G/-511C/-31T and levels of IL-1β expression in Caucasian subjects, despite previous understanding of *IL-1B*-511T/-31C as the proinflammatory allele[35,36]. In an *in vitro* study, -31T expressed stronger promoter activity than -31C by virtue of retaining the TATA sequence, and showed greater binding affinity for transcription factors as well[36]. The haplotype consisting of *IL-1B*-1464G/-511C/-31T shows a positive association with lung cancer risk and higher *IL-1B* gene expression in Caucasians[37]. In evaluating transcriptional activities of individual SNPs, the -1464C SNP had higher transcriptional activity by itself[38]. Placing the SNPs in haplotype context, however, the G allele at -1464 in the -1464G/-511C/-31T haplotype combination expressed higher transcriptional and translational activities, underscoring the influence of other SNPs in the genetic environment on individual SNPs[38].

It is also possible that the allele flip seen in *IL-1B* polymorphisms results from allelic heterogeneity reflecting differences in clinical backgrounds between Asian and Caucasian populations, such as the prevalence of *H. pylori*-related premalignant gastric lesions and cancer arising at different anatomical sites. The presence of *H. pylori* infection is strongly associated with risk of non-cardia intestinal gastric cancer. The *IL-1B*-1464G/511C/-31T haplotype, with high mucosal IL-1β expression, is believed to be a proinflammatory allele that produces IL-1β in excess in response to *H. pylori* infection, and suppresses gastric acid secretion. Prolonged hypochlorhydria provides an environment favorable to *H. pylori* survival, leading to atrophic gastritis or intestinal metaplasia, and subsequently to non-cardia intestinal-type gastric cancer; the predominant subtype among East Asians. The direct

suppression of gastrin secretion by excess IL-1β expression in association with the -31T allele may be directly observed[39].

In non-cardia intestinal-type gastric cancer in Caucasians, *IL-1RN**2 may be an essential factor. IL-1RA, encoded by the *IL-1RN* gene, is a naturally occurring anti-inflammatory cytokine that competes with the binding of IL-1 to its receptor[40]. The second intron of *IL-1RN* includes a penta-allelic 86-bp variable number tandem repeat producing two repeats (*IL-1RN*2*) or three to six repeats (*IL-1RN*L*)[40]. As El-Omar *et al*[11] have suggested, the presumably proinflammatory *IL-1RN**2 and *IL-1B*-31C haplotypes, presenting risk factors for *H. pylori*-related gastric cancer, may be in strong LD in Caucasian populations. Accordingly, low acid secretion shows a significant positive association with *IL-1RN**2, and homozygosity for this allele increases risk of hypochlorhydria. In an *in vitro* study, *IL-1RN**2 evidently increased production of IL-1B, regardless of the allele type of *IL-1B*, indicating that *IL-1RN**2 has a decisive role, not the IL-1B polymorphisms[41]. In the Human Genome Epidemiology Network (HuGE) meta-analysis, the association of *IL-1RN**2 with gastric cancer detected appears to be confined to non-Asian populations, because overall frequency of the *IL-1RN**2 allele among Asians is low, if measurable[26,32].

Cardia, intestinal-type gastric cancer

Studies of gene associations in cardia cancer are conducted mostly with Caucasian subjects because non-cardia, intestinal-type cancer predominates among Asians. In an unusual investigation, Kamangar *et al*[42] first divided cancer into cardia and non-cardia gastric adenocarcinoma and then tested associations with *H. pylori*. *H. pylori* showed a strong positive risk association with non-cardia gastric cancer but an inverse association with cardia gastric cancer risk[42]. Some studies have found that *H. pylori* infection is associated with decreased risk of adenocarcinoma arising near the esophagogastric junction[42-47]. This may be explained by the tendency of *H. pylori* colonization to induce gastric atrophy, with reduced acid secretion, thereby reducing acid reflux into the esophagus, and reducing risk of esophageal or junction cancer[42,48]. The cardia cancers were positively associated with gastroesophageal reflux disease (GERD)[49]. The *IL-1B*-1464C/-511T/-31C allele among Caucasians is associated with low levels of IL-1β expression in response to *H. pylori* infection or other inflammatory stimuli, and could not efficiently suppress gastric acid. Increased acid production following a subsequent inflammatory response would then produce GERD-like symptoms and promote cardia cancers.

IL-10 GENE POLYMORPHISM

IL-10, encoded by the *IL-10* gene at chromosome 1q31.1, is an anti-inflammatory cytokine. Three polymorphisms in the *IL-10* promoter, namely *IL-10*-1082 (G/A; rs1800896), -819 (C/T; rs1800871), and -592 (C/A; rs1800872), are shown to influence inflammation in response to infection at the transcriptional level[50-52]. An allele flip in *IL-10* polymorphisms with respect to gastric cancer risk is also observed. In Caucasian populations, risk for non-cardia gastric cancers in association with the -1082AA genotype may be increased twofold, while the -1082G allele is the risk allele in cardia gastric cancer in studies of Asians, independent of *H. pylori* infection[53-55]. In a meta-analysis, *IL-10*-1082G carriers showed a significant increase in risk of developing gastric cancer, especially for cardia-type gastric cancer among Asians[56,57]. A recent meta-analysis by Yu *et al*[58] showed a significantly negative association of *IL-10*-819TT with gastric cancer risk in Asians, in accordance with the previous finding that *IL-10*-819CC is a risk allele[59]. Furthermore, identification of *IL-10*-592AA as a protective allele for total gastric cancer incidence in Asians supports *IL-10*-1082G/-819C/-592C as the risk haplotype[60,61].

Evidence indicates that selection mechanisms operating on the *IL-10* region differ among ethnic groups. In Asian populations, with relatively high prevalence of chronic *H. pylori* infection, *IL-10*-1082A, is found more frequently than in Caucasian populations. Relatively low IL-10 expression by *IL-10*-1082A promotes elimination of *H. pylori* infection, and this may exert positive selective pressure on the haplotype. In Caucasian populations *H. pylori* infection is less prevalent, and greater IL-10 production would be advantageous in defense against infectious and inflammatory diseases[55]. This may explain the relatively high frequency of the *IL-10*-1082G allele in Caucasian populations[55]. Evidence for balancing selection within the IL-10 promotor region is consistently reported in studies of European populations[62,63].

In Caucasian populations with low rates of *H. pylori* infection and premalignant lesions, the -1082A allele imposes risk for gastric cancer through low IL-10 production and consequent excess of proinflammatory cytokines. This promotes inflammation of the gastric mucosa, which may increase frequency of the mutation[55,64]. These findings are consistent with observations of carcinogenesis in non-cardia cancer. In Asian populations, wherein *H. pylori* infection and premalignant lesions such as atrophic gastritis and intestinal metaplasia are more common, high-expression *IL-10*-1082G may suppress cytotoxic anti-tumor T-cell activity and thereby promote tumor progression[55,65]. In high-risk populations, IL-10 may play an essential role in advanced stages of gastric cancer[55]. In the Taiwanese population, *IL-10*-1082G may be linked to gastric cancer risk and advanced cancer, and cardia location of gastric cancer may be associated with a high-producing *IL-10* genotype[66]. Carriers of the *IL-10*-1082G/-819C/-592C haplotype may be susceptible to virulent *H. pylori* strains with a high capability to colonize and adapt, and also to gastric cancer development[67]. As compared to carriers of the *IL-10*-1082A/-819T/-592A haplotype, those with the *IL-10*-1082G/-819C/-592C carriers show higher mucosal levels of IL-10 mRNA,

which may result in a diminished proinflammatory response and capacity to control *H. pylori* infection[67]. Actually, it appears that the *IL-10* genotype at -1082 is sufficient to establish a risk relationship with gastric cancer, because the *IL-10*-1082 genotype correlates well with mucosal IL-10 mRNA levels, and *IL-10*-1082G fully represents the high-expression *IL-10*-1082G/-819C/-592C haplotype[55,67]. Consequently, the allele flip of *IL-10* observed in gastric cancer represents allelic heterogeneity, similar to that observed in *IL-1B*.

GENETIC FACTORS OTHER THAN IL-1B AND IL-10

Diffuse-type gastric cancer

Intestinal-type gastric cancer follows a multistep progression that usually initiates in chronic gastritis, whereas diffuse-type gastric cancer lacks defined premalignant lesions; diffuse-type gastric cancer is therefore suspected to be more influenced by genetics factors[22,68]. Genome-wide association studies (GWASs) reveal some additional gastric cancer susceptibility loci[69]. Detected in a Japanese GWAS, an SNP (rs2976392) in the prostate stem cell antigen (*PSCA*) gene, which encodes a glycosylphosphatidylinositol-anchored cell surface antigen, shows a significant association with diffuse-type gastric cancer[70]. Two SNPs (rs2070803 and rs4072037) in mucin 1 (*MUC1*) also show positive risk associations with diffuse-type gastric cancer in Asian populations[69-71]. We found that normal T cell expressed and secreted (*RANTES*)-403A presents a significant increase in risk for diffuse-type gastric cancer in an Asian male population, when stratified by Lauren classification and sex[72].

Non-cardia, intestinal-type gastric cancer

The chemokine IL-8 participates in the initiation and amplification of acute inflammatory reactions as well as in the maintenance of chronic inflammatory processes[73]. Evidence now links IL-8 to tumorigenesis, angiogenesis and metastasis[74-76]. A meta-analysis has shown an increased risk of *IL-8*-251A (T/A; rs4073) allele in several cancers, including gastric cancer, among Asians, but no such correlations among Europeans, suggesting racial differences in disease susceptibility with respect to *IL-8* polymorphisms[77]. A case-control study has also shown no significant association between *IL-8*-251 polymorphism and increased risk of gastric cancer, whereas the association remains in Asians[78]. In gastric cardia adenocarcinoma (non-cardia like), but not esophageal squamous cell carcinoma, the AGT/AGC haplotypes of *IL-8* polymorphisms showed a fourfold increase in relative risk in a high-risk Chinese population[79]. Unfortunately, most association studies on *IL-8* polymorphisms have focused on a single polymorphism at -251, without considering its haplotype structure. The *IL-8*-251A allele resides on two different haplotypes, and only one of these is associated with disease[80]. In other words, information regarding the *IL-8* haplotype structure is essential in determining the true relationship between *IL-8* polymorphisms and gastric cancer development.

Finally, the rs13361707 SNP in the first intron of protein kinase, AMP-activated, α1 catalytic subunit (PPKAA1) and rs9841504 in the intron of zinc finger and BTB domain containing protein 20 (ZBTB20) emerge as susceptibility loci from GWAS analysis[81].

CONCLUSION

Here, we aimed to summarize our rapidly evolving understanding of polymorphic structure in the interleukin promoter region and the involvement of *IL-1B* and *IL-10* polymorphisms in gastric cancer development. Analysis of these polymorphisms offers possible explanations for the allele flip observed in associations of *IL-1B* and *IL-10* with gastric cancer risk. The epidemiology of gastric cancer subtypes suggests a difference in genetic background between Asian and Caucasian groups. Among Asians, the *IL-1B*-1464G/-511C/-31T haplotype presents a risk allele for gastric cancer. This corresponds physiologically to increased IL-1β expression in response to chronic *H. pylori* infection, which may inhibit gastric acid production and promote atrophic gastritis and non-cardia gastric cancer. Then, what about the gastric cardia cancer, which affects only a minority of Asians? In Asians, the highly expressive *IL-10* allele may serve to augment the inflammatory response to colonization by virulent strains of *H. pylori*, and, following malignant transformation high IL-10 production, may tend to suppress anti-tumor cytotoxic T-cell response, thereby contributing to tumor progression. IL-1β expression influences the initiation of cancer in response to *H. pylori* infection, whereas IL-10 influences tumor progression after malignant transformation. Conversely, the less-expressive haplotype of *IL-1B* is associated with gastric cancer risk in Caucasians, specifically cancer of the gastric cardia. In this setting, low levels of IL-1β produced in response to *H. pylori* infection may increase gastric acid secretion, promoting gastric cardia cancers through induction of GERD. Concerning non-cardia gastric cancers in Caucasians, the less expressive *IL-10* haplotype may promote metaplasia in the distal portion of the stomach by augmenting inflammatory response, while the *IL-1RN**2 polymorphism contributes by activating IL-1β production. In conclusion, stratifying gastric cancer subtypes according to both anatomical site and the Lauren histological classification is essential in establishing genetic risk factors, because different subtypes follow different pathways of development and failure to consider this may produce false associations.

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ISSN 1007-9327
9 771007 932045 16>