Association of the Glutathione S-transferase Omega-1 Ala140Asp Polymorphism With Cerebrovascular Atherosclerosis and Plaque-Associated Interleukin-1α Expression

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Background and Purpose—Glutathione S-transferase omega-1 is a multifunctional enzyme. The Asp/Asp genotype of the Ala140Asp polymorphism of the *GSTO1* gene has been alleged to increase the risk of vascular dementia. The objective of this study is to address the question of whether common vessel disorders known to cause vascular dementia are modified in their severity by this polymorphism.

Methods—The severity and expansion of atherosclerosis in the circle of Willis vessels, cerebral small vessel disease, and cerebral amyloid angiopathy were studied in a sample of 79 autopsy cases. Genotyping of the *GSTO1* Ala140Asp polymorphism as well as immunohistochemistry for glutathione S-transferase omega-1 was performed.

Results—Carriers of the *GSTO1* Asp/Asp genotype presented with more severe and widespread atherosclerosis than noncarriers. However, there was no effect on small vessel disease expansion and cerebral amyloid angiopathy severity. Immunohistochemically, we detected interleukin-1α expressing macrophages in the lipid core of atherosclerosis plaques exhibiting glutathione S-transferase omega-1-positive material. *GSTO1* Asp/Asp carriers showed larger areas of atherosclerosis plaques containing interleukin-1α-positive material than carriers of the *GSTO1* Ala-allele.

Conclusions—The *GSTO1* Asp/Asp genotype presumably modulates the severity and expansion of atherosclerosis in the circle of Willis. The cellular colocalization of glutathione S-transferase omega-1 and interleukin-1α suggests a functional interaction between both proteins which in part might explain the function of glutathione S-transferase omega-1 in the pathogenesis of cerebral atherosclerosis. (Stroke. 2007;38:000-000.)

Key Words: atherosclerosis ■ cerebral arteries ■ GSTO1-1
Results

Logistic regression analysis revealed that the GSTO1 Asp/Asp genotype was associated with an increased expansion of AS (Figure 1A; power: 0.71) and an advanced histopathological type when compared with the GSTO1 Ala/Ala and Ala/Asp genotypes (Figure 1B; power: 0.8). There was no association of the GSTO1 Ala140Asp polymorphism with small vessel disease and cerebral amyloid angiopathy (Figure 1C–D).

Cryosections stained with an antibody directed against GSTO1-1 exhibited GSTO1-1 immunofluorescence in the peripheral part of the lipid core of the AS plaque (Figure 2). Double-label immunofluorescence showed colocalization of IL-1β and GSTO1-1 in macrophages (Figure 2).

Using logistic regression models controlled for age, gender, and IL1A-889 (C/T), IL1B-3954 (C/T), IL1B-511 (C/T) polymorphisms, GSTO1 Ala/Ala and Ala/Asp individuals exhibited less IL-1β/AS plaque than Asp/Asp carriers (Figure 1E; power: 0.84). Anti-2-macroglobulin/AS plaque and neutrophil elastase/AS plaque did not differ among the GSTO1 genotypes, although neutrophil elastase/AS plaque was shown recently to be associated with the expansion and type of AS (Figure 1F–G).

Discussion

Our results revealed that carriers of the GSTO1 Asp/Asp genotype exhibited AS lesions of (1) a more advanced histopathological type and (2) a higher degree of expansion of AS plaques in the circle of Willis than carriers of GSTO1
Ala/Ala and Ala/Asp genotypes. Despite the small number of cases studied, these associations showed a power of (1) 0.8 and (2) 0.71. The use of logistic regression models revealed that these effects were not caused by age or gender. A further argument for an important role of GSTO1-1 in AS was the detection of GSTO1-1 in AS plaques. An effect of GSTO1 Ala140Asp-polymorphism on either small vessel disease or cerebral amyloid angiopathy was not found within our sample. The small number of cases studied here did not allow confirmation of the reported clinicopathological correlation with vascular dementia.

A possible link between GSTO1-1 and the expression of IL-1 has already been discussed. Our results support a functional link between GSTO1-1 and IL-1 expression. Arguments favoring this hypothesis are (1) the association of the GSTO1 Ala140Asp-polymorphism with AS and the IL-1α expression and (2) the colocalization of GSTO1-1 with IL-1α in macrophages of AS plaques. Thus, our findings extend the present knowledge insofar as an interaction of GSTO1-1 and IL-1 appears to be pathogenetically relevant for the inflammatory response in AS lesions.

In summary, our findings reveal an association between the GSTO1 Ala140Asp polymorphism and the expansion and severity of AS. Furthermore, they support the notion that GSTO1-1 plays an important role in AS lesions by modulating IL-1α expression in macrophages within AS plaques.

**Figure 1.** Association of the GSTO1 Ala140Asp-polymorphism with the expansion of AS (A), the histopathological type of AS (AS type) (B), but not with the degree of small vessel disease (C) and the severity of cerebral amyloid angiopathy (D). E, The expression of IL-1α/AS plaques was associated with the GSTO1 Ala140Asp-polymorphism. F–G, Changes in neutrophil elastase/AS plaque (F) and anti-α2-macroglobulin/AS-plaque (G) were not associated with the GSTO1 genotype. *Significant difference at P<0.05.
Acknowledgments

The skillful technical assistance of Mrs N. Kolosnjaji, Mrs A. Schulz, Mrs A. Hrychyk, and Mr H.-U. Klatt is gratefully acknowledged.

Sources of Funding

This work was supported by DFG-grant No. TH 624/4-1 (D.R.T.) and BONFOR-grant Nos. O-154.0041 (D.R.T.), O-154.0043 (D.R.T.), and O-128.0055 (H.K.), and NIH-NIA AG12411 (W.S.T.G.).

Disclosures

None.

References


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Stroke. published online August 23, 2007; Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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