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REVIEW

Genetic investigations on intracranial aneurysm: Update and perspectives

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Summary Detection of an intracranial aneurysm (IA) is a common finding in MRI practice. Nowadays, the incidence of unruptured IA seems to be increasing with the continuous evolution of imaging techniques. Important modifiable risk factors for SAH are well defined, but familial history of IA is the best risk marker for the presence of IA. Numerous heritable conditions are associated with IA formation but these syndromes account for less than 1% of all IAs in the population. No diagnostic test based on genetic knowledge is currently available to identify theses mutations and patients who are at higher risk for developing IAs. In the longer term, a more comprehensive understanding of independent and interdependent molecular pathways germane to IA formation and rupture may guide the physician in developing targeted therapies and optimizing prognostic risk assessment.

We still do not know why intracranial aneurysms (IA) develop. Genetic predisposition and environmental exposition are the two etiological factors explored so far. Although, there were already many specialized reviews in the specific topic of human genetics applied to IAs [1—5], we propose in a single scientific paper a very summarized and concise state of the art. It can help the neuroradiologists to realize the current status and problems of genetic research for IAs.

Introduction

Detection of an intracranial aneurysm (IA) is a common finding in MRI practice [6]. Three percent of the general population harbors an IA [7]. Nowadays, the incidence of unruptured IA seems to be increasing with the continuous evolution of imaging techniques [4,8,9]. The main issue is that it can lead to permanent neurological deficit or death if the aneurysm ruptures (incidence de 10/100,000). However, the low incidence of subarachnoid hemorrhage (SAH) —compared to the prevalence of unruptured IA— suggests that the majority of IA do not rupture [10].

Abbreviations: IA, intracranial aneurysm; SAH, subarachnoid hemorrhage; MRA, magnetic resonance angiography; DNA, desoxyribonucleic acid; SNP, single nucleotid polymorphism; VNTR, variable number tandem repeat; GWL, genome wide linkage; GWAS, genome wide association study; OR, odds ratio; NGS, next generation sequencing.

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Important modifiable risk factors for SAH include cigarette smoking (relative risk, 2.2 to 3.1), high blood pressure (relative risk, 2.5 to 2.6), and heavy (> 150 g/week) alcohol consumption (relative risk, 1.5 to 2.1) [11]. Individuals aged 40 to 60 years are at highest risk for IAs, with women affected more than men by a 3:2 ratio [12,13].

In 1999, the MARS group cleared the issue of screening healthy relatives around a patient with an IA. Indeed, among the 1st degree relatives, 149 patients should be screened with MRA to prevent 1 SAH and 298 patients to prevent one death by SAH [14]. Furthermore, familial history of IA is the best risk marker for the presence of IA [15]. For example, the risk of IA, as determined by magnetic resonance angiography (MRA) screening, is about four times greater among members of families with two or more patients presenting with IA than among the general population.

Numerous heritable conditions are associated with IA formation, including autosomal dominant polycystic kidney disease, neurofibromatosis type I, Marfan syndrome, multiple endocrine neoplasia type I, pseudoxanthoma elasticum, hereditary hemorrhagic telangiectasia, and Ehlers-Danlos syndrome type II and IV [16,17]. These syndromes account for less than 1% of all IAs in the population and therefore cannot explain the familial aggregation in most of IA cases [18]. Indeed, familial IA is supposed to represent 10% of all cases [19] and it appears that a systematic research of familial history of IA reveals familial forms more often than anticipated. Thus, ascertaining multigenerational extended pedigrees through affected index cases will likely lead to identify rapidly a sizable cohort of familial cases [18].

State of art — genetics studies

Several genetic models could explain the heritability of IAs. This condition may be attributable to the inheritance of rare genetic variation with major effect, but incomplete penetrance. This category of genetic variation can be assessed through familial investigations. Another hypothesis, which can be tested by applying population-based approaches, is that IAs are caused by common genetic variation with small effect size [18].

The collective efforts of multiple international consortiums have identified millions of common SNPs and copy number polymorphisms in DNAs from populations of various ancestries, as well as linkage-disequilibrium patterns [20]. This is the basis of the two main strategies applied for the last fifteen years to identify genetic variation causally related to IA: genome wide linkage (GWL) and genome wide association studies (GWAS) (Table 1).

Familial investigations

The availability of large families allows to test the unusual circumstance in which IAs are transmitted as a consequence of a mutation in a single gene with a major effect. Genome wide linkage analyses look for the chromosomal position (loci) containing the disease gene by interrogating genetic markers, Single Nucleotid Polymorphism (SNP) or Variable Number Tandem Repeat (VNTR). This method has permitted to identify disease-causing genes in complex disorders such as diabetes, obesity, and hypertension [21—23]. Furthermore, it has also shed light on the physiopathology of cerebral cavernous malformations [24]. To date, a number of studies have applied linkage analysis to IA. The non-parametric approaches are attractive with respect to IA because the penetrance is likely incomplete, meaning that each mutation carrier is not necessarily affected. Overall, non-parametric linkage analyses have identified multiple loci contributing to IA formation and possible rupture [25—31] but only 4 (1p34.3—p36.13, 7q11, 19q13.3, and Xp22) have been replicated in different populations [26,27,29,32].

The strongest evidence to date involves regions on chromosomal arms 7q and 19q, on which several linkage hits have been reported in independent studies [25]. Positional candidate genes were tested in the relevant regions but only moderate associations were found (*PERLECAN* gene, *ELASTIN* gene, *COLLAGEN type 1 A2* gene) [1]: no functional variant was shown as segregating with IA.

Population-based studies

GWAS provide an alternative approach to elucidate the influence of genetic variants in complex or multi-factorial disorders. This strategy is based on the identification of a number of SNPs in loci that are significantly associated with the presence of IA, independently of modifiable risk factors. Logistic regression analysis is performed to predict the probability of IA given a specific SNP. Odds ratios (ORs) and *P* values are generated to report the proportion of individuals in the case group carrying a SNP compared to the proportion in the control group. Significant SNPs are mapped to loci, which can then be scrutinized to infer which genes play a role in the pathogenesis of IAs.

GWAS on other vascular diseases, including hypertension and ischemic stroke, have already yielded insight into new disease genes and pathways [33]. Nevertheless, the amount of data on genetic associations with IAs remains much smaller than for other complex diseases and only 4 large-scale GWAS (> 3000 cases and controls) have been reported so far for IA.

GWAS identified two loci — 9p21 and 8q12 — significantly associated with IAs (P value $\leq 1 \times 10^{-7}$) [34] in case-control populations from Iceland, Netherlands and Finland [35]. At the 8q12.1 locus, *SOX17* is the main candidate. This gene required for both endothelial formation and maintenance — an important aspect when considering the predominant location of IA at arterial branch points and sites of endothelial shear stress [36]. Analyses of each dataset individually as well as jointly found that the G allele at rs10757278 is associated with an approximately 1.29-fold increase in the risk of IA [37,38]. Thus, this locus alone explains only a small fraction of the genetic risk. The number of true additional genetic risk factors and the strength of their associations with IAs remain uncertain so far.

Data pooling from all genetic association studies allows risk estimates to be determined more precisely in light of statistical heterogeneity and differences in population ethnicity between studies. One comprehensive review and meta-analysis of all published GWAS of IA was reported by Alg and al. [34]. Once again, low ORs suggest that the genetic contribution to aneurysm development is substantial but