CORRESPONDENCE

The M2 haplotype of ANXA5 gene in the context of unexplained recurrent miscarriages

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Received: 11 May 2017 / Accepted: 9 October 2017 / Published online: 14 October 2017
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A recent review, a meta-analysis of the literature, discussed the roles of genetic polymorphisms in the pathology of recurrent miscarriage, RM (Shi et al. 2017). Among variations in other genes, this review identified single nucleotide polymorphisms (SNPs) in the promoter region of the annexin A5 (*ANXA5*) gene and listed them as significantly associated with RM (Table 3, “Meta-analysis of genetic polymorphisms related to thrombophilia”). In this table, rs28651243 in *ANXA5* is wrongly identified as T-442C, whereas the correct genetic designation of this particular polymorphism should be “T-422C” (c.-422T>C). According to this table, the *ANXA5* promoter polymorphisms c.-467G>A, rs112782763; c.-448A>C, rs28717001; and c.-422T>C, rs28651243 are indicated as significantly associated with RM ($p = 0.02$) in “overall” populations. It is of importance that together with c.-373G>A, rs113588187, these three polymorphisms are building the M2 haplotype of *ANXA5*, referred as *RPRGL3*, third predisposition gene to recurrent pregnancy loss, OMIM entry 614391 (OMIM—Online Mendelian Inheritance in Man). In Table 6, “Meta-analysis results of special genetic polymorphisms”, and in the relevant discussion paragraph (Shi et al. 2017), the authors state that the M2 haplotype is not significantly associated with RM. It is impossible to trace the studies that this conclusion is based on, apparently, four association

reports according to Table 6, because the reference list does not contain them (Shi et al. 2017).

The M2 haplotype of *ANXA5* was initially defined physically through molecular cloning of both major and minor alleles comprising it (Bogdanova et al. 2007). Since the time of this initial research, the association of M2/*ANXA5* with RM was confirmed in a variety of ethnic origins through prevalence comparisons of relevant patient groups to random population resources and to healthy selected controls (Rogenhofer et al. 2017 and references therein). In Germany alone, the RPL risk attributed to M2 carriers of retrospective and prospectively recruited clinical cohorts was estimated in altogether 800 recurrent miscarriage patients and 1100 control individuals.

A query of the Genome Aggregation Database (gnomAD) on 15,496 genomes from unrelated individuals confirms the interdependent prevalence of all four minor alleles comprising the M2 haplotype, so it is not clear how the authors of the meta-analysis arrived at the conclusion that M2 is not associated with RM, when according to their analysis, the M2/*ANXA5* SNPs, c.-467G>A, rs112782763; c.-448A>C, rs28717001; and c.-422T>C, rs28651243 are significantly associated with RM, but c.-373G>A, rs113588187 is apparently not, although, a part of the haplotype.

Acknowledgements The authors thank the numerous women contributing DNA samples for cited M2 association studies. AM was supported by a PI grant of the German Research Community, DFG, MA-6288/1-1.

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Compliance with ethical standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of interest The authors declare that they have no conflict of interest.

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