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Response to Fusco et al.

To the Editor: The authors' comments consist of two parts, to which we will reply separately.

1) The authors state that next to *GDI1*, overexpression of other genes present within the recurrent aberration should be taken into account as well to explain the MR phenotype in our families. In particular, the *IKBKG* gene is a candidate because mutations have been implicated in IP, often associated with neurological abnormalities, and because the NF-κB pathway has been linked to MR. We completely agree with a prominent role for the *IKBKG* gene and its pathway in neurological disorders and we have taken this gene seriously into account for a role in the MR phenotype of our families. However, we identified a 190 kb duplication, which overlaps our recurrent aberration, in a female patient as well as her normal father. This finding is described on page 812 of our paper[1] and the position of this polymorphic duplication is illustrated in Figure 2 (horizontal striped bar). This benign copy number variant includes, among others, *IKBKG*, which demonstrates that at least a duplication of this gene does not cause a pathological condition. Because *IKBKG* is duplicated in affected males of our family 4, we excluded it as a candidate gene. We do mention that we still have to be careful with this "rejection." We agree, however, that in the sentence on page 819 "*Moreover, the role of other genes within the aberration, such as UBL4A and FAM3A, cannot be excluded even though the apparent 190 kb copy-number polymorphism identified in a normal male individual seems to exclude a contribution of a double dosage of both genes in family 4*," the *IKBKG* gene should have been included as well. Of the remaining genes in the nonoverlapping aberrant region, we did check brain expression for all genes. For those with the highest expression (*FLNA*, *RPL10*, *ATP6AP1*, and *GDI1*), we checked their expression levels in patient-derived cell lines. So we did not focus on *GDI1* alone but proposed this gene as the most likely candidate gene, which is clearly discussed.

2) The authors would have liked us to put more emphasis on the recombination events that occur between the two oppositely oriented LCRs, L1 and L2, and the consequences these might have on the *IKBKG* gene. In our study, the aim was not to describe the NAHR events that occur between LCR partners (K1 and K2, or L1 and L2). We clearly point to the occurrence of recombination events (see page 816 "*… multiple possible NAHR-driven inversion events that could have taken place between the subunits of each set*") that probably resulted in homogeneity of the entire LCR. Because *IKBKG* was not regarded as a candidate dosage-sensitive gene for the MR phenotype, and because our male patients as well as their carrier mothers do not show characteristics features of IP, we did not further investigate the *IKBKG*

copy number, which, however, can be deduced from the oligo-array data (GEO accession numbers GPL9083 and GSE17813). Finally, in the paper of Fusco et al.,[2] the breakpoint of the *MER67B* duplication could have been cloned because of their correct assumption that the *MER67* repeat could have been involved. Moreover, the breakpoint could easily be identified because of a divergent sequence from the reference sequence resulting from the duplication. The reason why we were unable to clone their breakpoints (present somewhere within the LCRs) is because of the >99% sequence identity, their homogeneity, and because in our case we don't have any handle where to look within the 35-kb-large LCR. Moreover, we always expect to find homogeneic reference sequences, which preclude detecting the breakpoints.

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