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## *Reply to the Letter to the Editor*

# Polyomaviruses and autism: more than simple association?

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We wish to thank Carla Arpino and colleagues for their comments on our recent report of an association between autism and polyomavirus infection in postmortem neocortical brain tissue (Lintas *et al,* 2010). This study represents the first of a series of papers aimed at addressing the hypothesis of vertical viral transmission in a sizable subgroup of autistic patients. We believe this mechanism could lead to an overestimation of genetic roles in this disease by spuriously boosting heritability estimates (Freitag, 2007). Due to space constraints, we were evidently unable to fully clarify in our Discussion that we envision viral genomes as already present in parental gametes (egg and/or sperm cells) and to be passed onto the offspring already at the time of fertilization. Viral genomes would start being actively transcribed in permissive cells of the fetus only at a later stage during development. Within this framework, our study was exclusively aimed at highlighting possible viral candidates potentially involved in this process. Hence, we agree with Arpino and colleagues in predicting that vertical transmission from mother to offspring "before, during, or after delivery" should not be particularly relevant to autism, as this mechanism would not explain (a) neuropathological abnormalities pointing toward neurodevelopmental derangements occurring during the first and/or second trimester (Bauman and Kemper, 2005; Miller *et al,* 2005); (b) the association between autism and paternal age (Reichenberg *et al,* 2006; Lauritsen *et al,* 2005; Sasanfar *et al,* 2010); and (c) the low likelihood of transplacental transmission for polyomaviruses, pointed out by Arpino and colleagues.

In this study we have chosen to assess all available samples and not to apply an age-matched design as in our previous work (Lintas *et al,* 2009; Palmieri *et al,* 2010; Garbett *et al,* 2008), both for its exploratory purpose and to maximize sample size, an inevitable constraint of all postmortem studies. Regardless, as stated at the bottom of Table 3 (Lintas *et al,* 2010), mean age ± SD for 15 autistic patients was 13.36 ± 8.78, and for 13 controls was 15.23 ± 8.89 ($P = .610$). Our results clearly do not stem from age differences between cases and controls.

BK virus, JC virus, and simian virus 40 (SV40) were combined in our analysis for two reasons: (a) they belong to the same family and each was overrepresented among cases versus controls (4:0, 6:3, and 2:0, respectively); (b) gametic transmission of polyomaviruses from parents to offspring is predicted to generate not only direct damage during development, but also indirect damage mediated by an overproduction of cytokines, relatively nonspecific in reference to its viral trigger (Ashwood *et al,* 2006; Vargas *et al,* 2005; Smith *et al,* 2007). Also the trend toward an overrepresentation of infections by multiple viruses ($P = .08$) points toward nonspecific viral contributions. Nonetheless, we agree that viral infections might be the consequence of immunosuppression or tissue susceptibility rather than the cause of autism. For this reason, we have undertaken a search of polyomavirus in male gametes of fathers of autistic children and controls, which is providing very encouraging results. We sincerely hope this effort will contribute to solve the mistery of the "missing heritability" (Maher, 2008) in autism genetic research, and to explore the potential role of gametic viral infections as potential triggers of genomic instability and evolution of the species.

***Declaration of interest:*** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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