

with the failure—up to this day—to answer even one of our detailed complaints, prompts one to ask whether the IMA is merely an executive arm of the Israeli establishment—one that works very hard to present the face of the “enlightened occupier” rather than striving for universal medical ethics. And indeed with such a view, why should they expect Palestinian doctors, detained and humiliated at every checkpoint in the Occupied Territories, to cooperate gladly with IMA, when IMA does nothing to protect them?

The ongoing joint work of PHR-Israel with our colleagues in the Palestinian medical and human rights community has engendered an alternative to the discourse of occupation, dispossession, and violence; one that is based on human rights. We believe that this different voice, which does exist locally, should be heard and used in international fora today. We urge the WMA to make its stand clear on the issue of occupation and human rights violations in our region.

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## When does exposure of children to tobacco smoke become child abuse?

Sir—We report an instance of a child aged 2·5 years, who is exposed to tobacco smoke in the home. The child is a participant in a prospective cohort study (ABIS; all babies in southeast Sweden) we are undertaking, on environmental factors affecting development of immune-mediated diseases in children.<sup>1</sup>

Exposure to environmental tobacco smoke, known to affect present and future health of children,<sup>2</sup> is one of the environmental factors being studied. Parents are asked, in questionnaires, if and how much they smoke. A subsample of smoking parents of 2–3 year-old children has been asked about their smoking behaviour at home—ie, what precautions they use to protect their child from tobacco smoke. To validate this questionnaire, we have analysed urine cotinine concentrations (the major urinary metabolite of

nicotine) in specimens provided by children of this age. We recorded that the smoking behaviour of parents at home was significantly associated with cotinine concentrations of their child. Cotinine concentrations were adjusted for creatinine.<sup>3</sup>

The child we report here had a cotinine/creatinine ratio of 800 µg cotinine/1 g creatinine, corresponding to active smoking of 3–5 cigarettes a day.<sup>4</sup> The parents reported a joint consumption of 41–60 cigarettes a day. They said they smoke in the kitchen and living room, whereas bedrooms were reported to be smoke-free. The parents reported smoking at the dinner table once a day and in front of the television set several times a day. They also said they smoke near the kitchen fan several times a day and near an open door at least once a week. These comments from the parents indicate that, in their opinion, their child was well protected from exposure to environmental tobacco smoke, since they did not smoke in bedrooms and the windows were almost always open.

Though nicotine and cotinine metabolism is independent probably due to genetic differences,<sup>5</sup> the cotinine concentration of this child is remarkably high. If active smoking in adults causes lung cancer and other serious diseases, passive smoking from the age of 2·5 years (and probably younger) must be even more deleterious. Since a child at this age cannot, by his or her own will, avoid a smoky environment, we ask ourselves when exposure to tobacco smoke should be regarded as child abuse?

We want to stress the fact that, although most parents are aware of the importance of protecting their children from tobacco smoke, and try in different ways, children can still be massively exposed to this toxic drug. Since to just forbid smoking might be ineffective, nurses and doctors should pay attention to smoking behaviour of smoking parents they meet. Until we know more about effective measures of protection, the recommendation should be never to smoke indoors in homes with children.

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## Genes for schizophrenia

Sir—In their Rapid review on genes for schizophrenia (Feb 1, p 417),<sup>1</sup> Paul Harrison and Michael Owen make omissions in their presentation of the data in support of the *PRODH* gene being a susceptibility gene for the disorder. They claim that no one has replicated the association, but this statement is incorrect. First, the original paper that described the *PRODH* gene as a susceptibility gene for schizophrenia<sup>2</sup> included a within-study replication whereby the original positive association seen with the US sample was reproduced in an independent South African sample. Although Harrison and Owen include similar supporting information for other genes (ie, *G72*) in their table, they ignore it in the case of *PRODH*.

Second, they do not mention the study by Jacquet and colleagues,<sup>3</sup> in which systematic screening of 23 genes from the 22q11 locus for individual gene deletions revealed deletions of the *PRODH* gene in one family with schizophrenia. *PRODH* was the only one of the 23 genes examined that was deleted in individuals with schizophrenia. Furthermore, the studies by Jacquet and colleagues<sup>3</sup> and Liu and colleagues<sup>2</sup> identified several mutations of conserved residues in their independent samples of patients with schizophrenia. Hyperprolinaemia was correlated with the presence of these coding mutations as well as with schizophrenia in the carrier families. Moreover, both studies presented evidence for a modest to striking (depending on the tested population) enrichment of these mutations in populations of patients with schizophrenia.

Although we understand that Harrison and Owen themselves have not been able to replicate the association between *PRODH* and schizophrenia in their own sample, there are two independent published studies with positive and consistent

evidence in support of *PRODH* as a susceptibility gene for schizophrenia.

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Sir—Paul Harrison and Michael Owen<sup>1</sup> draw cautious positive conclusions from genetic linkage studies in schizophrenia and point to pathophysiological implications. One can review the same evidence and reach a different conclusion with respect to the genetic basis of psychosis and the direction of future research.

Harrison and Owen cite two meta-analyses<sup>2,3</sup> and claim that “replicated linkages to several chromosomal regions are accumulating”. But the striking feature of these meta-analyses is that, despite the fact they include many of the same studies, their summaries agree with respect to only one chromosomal arm (8p) of the nine they highlight. A reasonable conclusion is that the null hypothesis has not been disproved.

Why should this substantial endeavour have revealed so little firm evidence of genetic linkage to psychosis? An alternative to the view adopted by Harrison and Owen (that there are multiple genes of small effect) is that the relevant variation is epigenetic—ie, involves modifications such as methylation of the sequence rather than alterations in the DNA sequence itself. For this reason, the modification is invisible in terms of the linkage strategy.

There are already indications of epigenetic variation in the data from monozygotic twins. Whereas concordance (between 40% and 50%) is greater than that (12–15%) seen in dizygotic twins consistent with a genetic factor, it falls well short of 100%. The discrepancy is often interpreted as evidence for an environmental interaction, but no consistent differences in exposure to putative risk factors between affected and non-affected members of discordant pairs have been identified. The alternative is that discordance reflects a difference in gene expression in the course of development.

These arguments can be placed in relation to the nature of psychotic symptoms—ie, disturbances of human beings’ specific capacity for language. Hallucinations (voices), disturbances of thought processes (thoughts experienced as alien, loss of direction), and even delusions (distortions of meaning) can all be conceived as deviations in the transition of thought to speech (production) or from perceived speech to meaning. Thus the phenomena of psychosis are associated with the core characteristic of the species. The importance is that the relevant genetic variation relates to precisely those changes that distinguish *Homo sapiens* from other great ape species.

Already there is evidence from monozygotic twins that asymmetry of the planum temporale and its relation to handedness is subject to epigenetic variation,<sup>4</sup> as is the association between psychosis and asymmetry of the posterior segment of the Sylvian fissure that overlies the planum. Thus, the asymmetry that separates human beings from other species, and the substrate of language, is subject to variation within the species that is independent of the DNA sequence. This epigenetic variation transmitted between generations is dependent on an interaction between maternal and paternal genomes and perhaps stochastic processes in the course of development.

These conclusions lead to future strategies that depart from those of Harrison and Owen. Rather than concentrating resources on ever-widening searches for multiple genes of small effect, they dictate a focus on the characteristics that distinguish the course of brain development in *Homo sapiens* from that in other primates, and on the ill-understood interaction of genetic and epigenetic factors in determining the variation associated with this development.

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Authors’ reply

Sir—Maria Karayiorgou and Joseph Gogos take us to task for underplaying the evidence that *PRODH* is a schizophrenia susceptibility gene. The format of a Rapid review inevitably means that issues are covered briefly, without being able to do justice to every aspect of the data or their interpretation. Moreover, we were limited to 30 references, and had to remove mention of unpublished data concerning several of the genes. These factors all affected the way we portrayed the background to, and strength of evidence for, each of the genes. It also led us to omit other candidates worthy of mention, such as *DISC1*, *DRD3*, and *HTR2A*.

Nevertheless, Karayiorgou and Gogos correctly point out that their study<sup>1</sup> includes a within-study replication which, to be consistent with the way we summarised the *G72* data, should have been stated in the table. We apologise; the error arose when we simplified an earlier version of the table, which included more details about replications. Although we acknowledge this upgrading of the evidence, we are still cautious about the evidence for *PRODH*, since some comparisons used two-marker haplotypes whereas others used three-marker haplotypes, and the observation was not significant in a third sample ( $p=0.055$ , one-tailed)<sup>1</sup> nor in an independent family-based association study.<sup>2</sup> Lack of space and citations also led us to omit the study by Jacquet and colleagues,<sup>3</sup> which certainly provides some additional support for *PRODH* involvement in schizophrenia.

We agree with Tim Crow that epigenetic factors might well be important, and said so in our article. However, we disagree with his negative interpretation of the evidence for any of the loci, and hence for all the genes that we reviewed. The fact that two meta-analyses do not come up with exactly the same result is hardly unexpected, given the emerging methods in this specialty, and variation in the datasets used and approaches adopted. We are more impressed by the similarities than the differences in results between the two meta-analyses, and by the fact that in the larger one,<sup>4</sup> six loci met genome-wide criteria for significance (including 6p and 8p, harbouring *DTNBP1* and *NRG*, respectively). That three of the other five susceptibility genes are also situated at loci with strong, albeit less conclusive, evidence of linkage, surely increases the likelihood that they are true loci for schizophrenia. Moreover, although the evidence might be incomplete with respect to the multiple susceptibility genes model of