strong pleiotropia and redundancy among neurotrophic factors means that CNTF expression is dispensable. However there may well be other more subtle effects of this mutation on behaviour or development.

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In reply — We have expanded the number of people genotyped for *CNTF* since our original letter (over 200 each for control and psychiatric patients). The results show that the increased mutant allele frequency among our psychiatric patients is entirely attributable to an increased proportion of heterozygotes (45%) in the schizophrenic patient subgroup (ICD-10 criteria; n=50; P<0.05). However, we have subsequently genotyped a Spanish schizophrenic sample, and found no difference in allele distribution between control and schizophrenic individuals[1]. As the same method was used in both of our studies and those of the two new reports, technical differences do not account for the discrepant nature of the Wurzburg sample[9]; this is underscored by the fact that similar allele distributions were determined in each case for the general population. Other explanations are that our result arose by chance and would disappear with larger samples, or alternatively, that the difference reflects real differences in the populations genotyped.

The notoriously broad diagnostic criteria for schizophrenia raise questions about the congruence of the classification made by different units; this is particularly true here, as different diagnostic methods were used by the various investigators. Further, it is likely that schizophrenia is a group of diseases, with differing origins, courses, clinic and prognoses. More precise categorizing of patients would allow more meaningful comparison of data from different samples, and assist the identification of subcategories for whom the mutation is relevant. Such finer classification has been proposed for the *NT3* gene, in which a polymorphism is associated with a severely affected subgroup of schizophrenia patients[10]. As the schizophrenias are unlikely to share a common aetiology, particular mutations may be associated with particular forms of the disease.

Nothen *et al.* comment that their "samples were drawn from the same population as Thome *et al.*" The German origin of both datasets does not guarantee that they represent a common psychiatric population; nor is the involvement of other factors leading to an overrepresentation of the mutation in the Wurzburg sample to be excluded. In conclusion, while we are cautious about the interpretation of our results, we remain open on the question of an involvement of *CNTF* in schizophrenia until further work is completed.

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Biotinidase mutational 'hotspot'

Sir — Last year in *Nature Genetics*, Pomponio *et al.*[1] described a 3-bp insertion coupled with a 7-bp deletion (an indel event) in the human biotinidase gene. Often this type of complex mutational event, especially one of frequent origin, is triggered by nearby DNA sequences[2] but this does not seem to be the case for the biotinidase indel. This indel is frequently found in symptomatic children (50% of whom carry the indel in at least one of their mutant alleles) from a variety of ethnic backgrounds and geographical regions. It was therefore proposed that the 7-bp region which undergoes the indel is a mutational hotspot. However, in the report[1] there was no instance of *de novo* generation of the indel event: all affected patients with the indel inherited it from a parent. For siblings 38 and 39, both of whom are heterozygous for the indel, the genotype of only the mother was given who, although being a carrier, was shown not to carry the indel. It is therefore likely that the indel was inherited from the father, since identical *de novo* indel events in both children is unlikely.

This situation of a discrete mutational event frequently being responsible for a human genetic disease is reminiscent of that found in cystic fibrosis (CF). A 3-bp deletion (ΔF508) accounts for about 70% of worldwide CF chromo-