Recessively inherited deletion confers risk for schizophrenia and intellectual disability

Olli P. H. Pietiläinen1,2,3, Jaana Suvissari1, William Hennah2, Virpi Leppä2, Tiina Paunio2,3,4, Annamari Tuulio-Henriksson5,6, Jari Hakkar5, Teppo Varilo2,3, Karola Rehrström1, Eveliina Jakkula1, Jaana Suokas4,5, Laura Häkkinen6, Jonna Tallila7, Kati Kristiansson9, Samuli Ripatti1,2, Sirpa Ala-Mello2, Matti Isohanni8, Jaakko Kaprio9, Johan Eriksson10, Marjo-Riitta Jarvelin10, Richard Durbin1, Jouko Lönnqvist4,5, Matt Hurles1, Hreinn Stefansson1, Leena Peltonen1,2,3,14, Nelson Freimer11,13, Mark Daly14, Aarno Palotie1,2,14

1 Wellcome Trust Sanger Institute, Hinxton, Cambridge, UK. 2 Institute for Molecular Medicine Finland FIMM, Helsinki, Finland. 3 National Institute for Health and Welfare, Public Health Genomics Unit, Helsinki, Finland. 4 University of Helsinki and Helsinki University Central Hospital, Department of Psychiatry, Helsinki, Finland. 5 National Institute for Health and Welfare, Department of Mental Health and Substance Abuse Services, Helsinki, Finland. 6 University of Helsinki, Department of Psychology. 7 Helsinki University Central Hospital, Department of Clinical Genetics, Helsinki, Finland. 8 Department of Psychiatry, and Institute of Clinical Medicine, University of Oulu, Finland. 9 National Institute for Health and Welfare, Chronic Disease Epidemiology and Prevention, Helsinki, 90014, Finland. 10 Institute of Health Sciences, University of Oulu, Oulu, Finland. 11 deCODE genetics, 101 Reykjavik, Iceland. 12 University of Helsinki, Department of Medical Genetics, Helsinki, Finland. 13 Center for Neurobehavioral Genetics, Semel Institute for Neuroscience and Human Behavior, UCLA, Los Angeles, California, USA. 14 The Broad Institute of MIT and Harvard University, Cambridge, MA, USA.

Population isolates can benefit genetic studies of rare variants in complex traits
Studies of low frequency variants in complex traits are an emerging field of interest. Populations isolates demonstrating extended allelic sharing could provide a useful setting for their study. Exploiting this hypothesis, we utilized an internal isolate of Finland, enriched for schizophrenia. We studied rare deletions that would have become enriched in this isolate due to multiple recent bottlenecks and rapid population expansion, and that would in part explain the high incidence of schizophrenia observed in the population.

Schizophrenia prevalence varies regionally in Finland
Schizophrenia varies regionally in Finland as can be seen in the housing history of the country (Figure 1). The lowest relative risk for schizophrenia is met in the south and west parts with the old Finnish population (early settlement). The risk increases markedly to North and east following the internal migration from the Savo region starting in the 15th century (indicated by black arrows). The highest regional peak of schizophrenia is met in a north-eastern isolate that was populated towards the end of the internal migration movement in the 17th century (red arrows).

Enrichment of rare deletions to an internal high risk isolate of schizophrenia
A comparison between the high risk isolate (N=173) and Helsinki with low regional schizophrenia risk (N=1,586) revealed two enriched >20 kb deletions on chromosomes 4 and 22 to the isolate (p < 6x10^-8). Analysis against schizophrenia in Northern Finland (265 patients and 5,140 controls) revealed nominal association with one of these deletions on 22q11.22. (p = 0.02, OR: 1.9) and was further replicated in 9,539 patients and 15,677 controls including individuals from rest of Finland and International Schizophrenia Consortium (p=0.03, OR2.1) (Table 1).

The 22q11.22 deletion associates with poor intellectual functioning among non-schizophrenic individuals
Schizophrenia co-morbidities, were studies among non-schizophrenic carriers of the 22q11.22 deletion in Northern Finnish population cohort (N=4872). Among eight co-morbid phenotypes studied, the deletion carriers were significantly more likely to have intellectual deficit and/or milder learning difficulties compared to non-carriers (p = 0.003, OR: 3.99). (Table 2)

22q11.22 deletion has a strong recessive effect
We identified four individuals being homozygous for the deletion, all presenting with intellectual deficit and/or schizophrenia. The deletion overlaps one gene encoding for TOP3B and was found to significantly down-regulate its mRNA levels to half among heterozygous carriers and to zero among homozygous carriers (p<10^-10). The mRNA levels of other genes were not significantly affected by the deletion. (Figure 2)