Recessively inherited deletion confers risk for schizophrenia and intellectual disability

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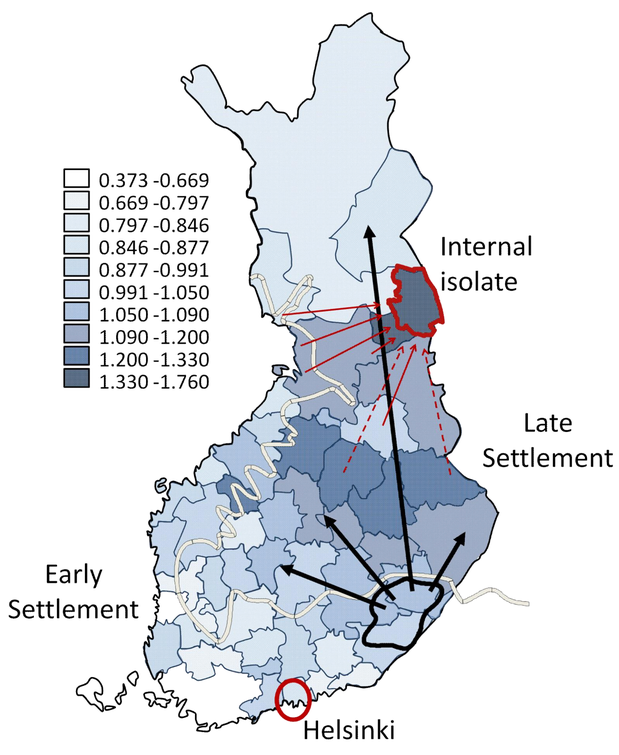
Population isolates can benefit genetic studies of rare variants in complex traits

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 an follows closely the housing history of the country (Figure 1). The lowest relative risk for schizophrenia is met in the south and west parts with the oldest 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).

Figure 1.



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 ($p < 6*10^{-8}$).

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)

Table 1.

			North Finland (265 cases , 5,140 CTRLs)			Replication sample (9,539 cases, 15,677 CTRLs)		
CHR	Start	End	Deletion Freq	P-value	OR	Deletion Freq	P-value	OR
4	59.18	59.36	0.0019	0.1381	2.687	na	na	na
22	20.66	20.90	0.0076	**0.02439**	**1.908**	0.00095	**0.029**	2.071

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)

Table 2.

	Frequency			
Trait	**Affected**	**Unaffected**	**OR**	**p-value (Fisher)**
Schizophrenia	0.0085	0.0051	1.683	0.4487
Psychosis	0.012	0.0050	2.41	0.2118
Intellectual deficit	0.025	0.0048	5.429	0.003777
Repeated grades in school	0.019	0.0045	4.325	0.000806
Epilepsy	0	0.0052	0	1
Neonatal convulsions	0.0023	0.0052	0.44	0.7355
Cerebral palsy and/or perinatal brain damage	0.015	0.0050	3.089	0.1473
Impaired Hearing at 14 years old	0.0058	0.0051	1.148	0.696

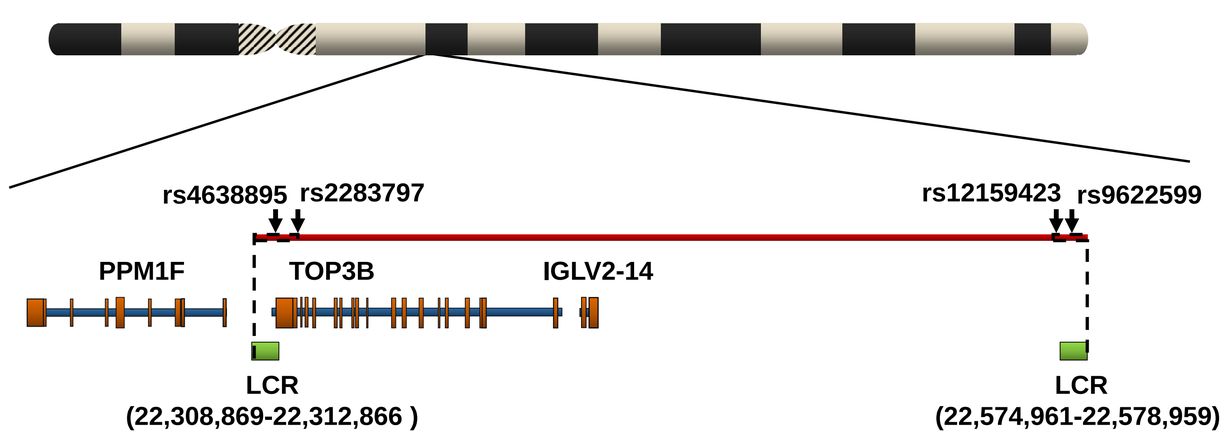
22q11.22 deletion has a strong recessive effect

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)

Figure 2



Positions according to build hg19

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