

## ARTICLE

# Genetic markers and population history: Finland revisited

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The Finnish population in Northern Europe has been a target of extensive genetic studies during the last decades. The population is considered as a homogeneous isolate, well suited for gene mapping studies because of its reduced diversity and homogeneity. However, several studies have shown substantial differences between the eastern and western parts of the country, especially in the male-mediated Y chromosome. This divergence is evident in non-neutral genetic variation also and it is usually explained to stem from founder effects occurring in the settlement of eastern Finland as late as in the 16th century. Here, we have reassessed this population historical scenario using Y-chromosomal, mitochondrial and autosomal markers and geographical sampling covering entire Finland. The obtained results suggest substantial Scandinavian gene flow into south-western, but not into the eastern, Finland. Male-biased Scandinavian gene flow into the south-western parts of the country would plausibly explain the large inter-regional differences observed in the Y-chromosome, and the relative homogeneity in the mitochondrial and autosomal data. On the basis of these results, we suggest that the expression of 'Finnish Disease Heritage' illnesses, more common in the eastern/north-eastern Finland, stems from long-term drift, rather than from relatively recent founder effects.

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## Introduction

As an isolated outlier population on the European genetic landscape,<sup>1</sup> the Finns have attracted a great deal of interest among the geneticists. Owing to advantageous features in its genetic architecture, for example, overall homogeneity, reduced diversity and increased linkage disequilibrium, the Finnish population is considered as a promising target for gene mapping studies.<sup>2,3</sup> Recent analyses have, nevertheless, suggested a substantial geographical structure in the genetic diversity of the Finns.<sup>4–7</sup>

The uniqueness of the Finnish genetic architecture has been explained by a series of founder effects and a subsequent drift in local subisolates. The initial founder effects are generally associated with two colonization waves c. 4000 BP (before present) and 2000 BP to southern and western Finland, commonly referred to as the 'Early settlement area' (ESA) (Figure 1).<sup>3,8</sup> Another decisive factor shaping the Finnish gene pool is, allegedly, the peopling of the northern/eastern Finland ('Late settlement area', LSA) in the 15th–16th century by small family groups from the Early settlement area of southern Finland.<sup>8</sup> The increase of autozygosity associated with these founder effects is deemed to lie behind the occurrence of the 'Finnish Disease Heritage' (FDH), more than 35 recessive monogenic illnesses more common especially in eastern Finland.<sup>8–10</sup>

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**Figure 1** The map of Northern Europe and Finland showing the assessed sub-populations. The dark grey areas show the *a priori* assumed Early settlement area and the hatched line depicts the approximate position of the first political border between Sweden and Novgorod (Russia, year 1323).

If the scenario described above holds, the founder effects and drift in local subisolates should have left distinctive signatures in putatively neutral marker gene diversity as well. In brief, the Finns should show less genetic diversity than other European populations; this reduction should be more drastic in the *LSA*, and the diversity in the *LSA* should represent a subset of the variants observed in the source that is, the *ESA*. In particular, the uniparental mitochondrial DNA (mtDNA) and Y-chromosomal markers should reflect the history more accurately because of their lower molecular effective population size. The uniparental markers should also have similar distribution of diversity, unless there are sex-specific differences in the past demography.

Several studies have indeed shown the *LSA* of eastern/northern Finland to harbour less (neutral) genetic diversity especially in the male-mediated Y chromosome.<sup>11,12</sup> Furthermore, differences in the Y-chromosomal and autosomal variation between western and eastern parts of the country have been revealed.<sup>4,5,7,13</sup> Analyses of linkage disequilibrium are also in line with the expectations based on the demographic history scenario described above.<sup>14,15</sup>

Curiously, however, the mtDNA diversity patterns found among Finns appear to be at odds with the Y-chromosomal variation and also with the proposed 'medical genetic' scenario of population history. The Finnish mtDNA pool is shown to harbour levels of diversity comparable with

other European populations, and no significant regional differences have been observed thus far.<sup>16</sup> The observed differences between marker classes in Finland are intriguing. This is especially so, if the patterns are supposed to stem at least partly from a recent event, the internal migration on the 16th century, *i.e.* roughly 15–20 generations ago. Although the Y-chromosomal variation is frequently shown to be geographically more structured,<sup>17–19</sup> the maintenance of mtDNA homogeneity in Finland would require effective female migration between all regions. This is at odds with the subisolate structure leading to an increase of autozygosity and expression of the FDH.

The controversy raises an interesting question: Does the current neutral DNA diversity support the scenario invoked to explain the medical genetic findings? Here we have analysed the genetic differences between 12 different provinces in Finland using Y-chromosomal, mtDNA and autosomal microsatellite data. The mtDNA and autosomal microsatellite data are contrasted with the Y-chromosomal data to examine the history of different regions of Finland, and the regional Finnish diversity is then contrasted with results from several European reference populations. The following basic questions are asked:

- (1) Do the regional diversity patterns of Y-chromosomal, mtDNA and autosomal markers deviate from each other?
- (2) Do the different sub-populations in Finland have differing affinities to the neighbouring populations?
- (3) Are the diversity patterns in all marker classes plausibly explained by the prevailing concept of Finnish population history, that is with bottlenecks associated

with the external and internal migration and subsequent drift in local subisolates?

Many aspects of these questions have been earlier touched by a number of studies, but to our knowledge, this is the first study specifically targeting these questions with three classes of neutral markers and geographically structured sampling covering the whole of Finland. On the basis of the obtained results, we question the previous population historical scenarios, which emphasize late founder effects as a main factor behind FDH occurrence and genetic differences within Finland. Instead, we propose an alternative model that accentuates long-term drift in eastern Finland and dissimilar patterns of gene flow into western and eastern parts of Finland.

## Materials and methods

### Samples and laboratory methods

Altogether, 1126 Finnish males were analysed in this study. These samples were obtained either through paternity testing conducted at the Finnish National Public Health Institute ( $N=606$ ) or collected by the authors (JUP and AS) with informed consents. The Finnish samples also include mtDNA sequences ( $N=200$ ) published earlier.<sup>16</sup>

Subsets of all samples were genotyped with 17 Y-chromosomal (Y-STR) and 9 autosomal microsatellite (aSTR) markers, and a total of 639bp of mitochondrial hypervariable segment (HVS)-I and II sequence data were obtained. The final data set consisted of altogether 907 Y-STR, 832 mtDNA and 805 autosomal microsatellite profiles, with an actual overlap between marker sets of 58% (Y-STR–mtDNA), 75% (Y-STR and aSTR) and 54% (mtDNA–aSTR). The sample sizes are shown in Table 1.

**Table 1** Basic statistics for the assessed markers

	Y-STR				mtDNA				aSTR				$F_{IS}$
	$N$	$A$	$AR$	$\hat{H}$	$N$	$A$	$AR$	$\hat{H}$	$N$	$A$	$AR$	$\hat{H}$	
HA Häme	60	54	35.3	$0.996 \pm 0.004$	81	66	35.5	$0.993 \pm 0.004$	53	6.8	6.6	$0.760 \pm 0.092$	$0.038^{NS}$
KY Kymi	52	43	32.1	$0.982 \pm 0.012$	74	62	35.7	$0.994 \pm 0.004$	43	6.6	6.5	$0.764 \pm 0.074$	$0.024^{NS}$
LMO Larsmo	82	56	29.9	$0.984 \pm 0.005$	73	41	26.6	$0.974 \pm 0.007$	74	7.3	6.8	$0.734 \pm 0.082$	$0.053^{NS}$
TU Turku	56	56	38.0	$1.000 \pm 0.003$	110	91	36.5	$0.995 \pm 0.003$	49	6.8	6.6	$0.767 \pm 0.072$	$0.004^{NS}$
UU Uusimaa	177	140	34.3	$0.991 \pm 0.003$	64	55	36.3	$0.996 \pm 0.004$	93	7.1	6.5	$0.759 \pm 0.072$	$-0.002^{NS}$
VA Vaasa	87	71	33.9	$0.993 \pm 0.004$	49	45	37.1	$0.996 \pm 0.006$	78	7.6	7.0	$0.764 \pm 0.082$	$-0.023^{NS}$
Early settlement	514	354		$0.994 \pm 0.004$	451	265		$0.995 \pm 0.001$	390	8.6		$0.759 \pm 0.084$	$0.015^{NS}$
CF Central Finland	56	47	33.0	$0.990 \pm 0.007$	64	51	33.9	$0.991 \pm 0.005$	49	6.6	6.4	$0.765 \pm 0.081$	$0.019^{NS}$
KU Kuopio	52	42	31.4	$0.985 \pm 0.009$	89	59	31.6	$0.986 \pm 0.005$	48	6.6	6.4	$0.773 \pm 0.052$	$0.000^{NS}$
LA Lappi	91	71	33.4	$0.992 \pm 0.003$	52	41	32.6	$0.987 \pm 0.007$	106	7.3	6.7	$0.750 \pm 0.082$	$0.034^{NS}$
MI Mikkeli	39	32	31.0	$0.987 \pm 0.010$	41	36	35.0	$0.993 \pm 0.008$	42	6.3	6.3	$0.767 \pm 0.065$	$-0.060^{NS}$
NC Northern Carelia	48	40	32.0	$0.983 \pm 0.011$	47	35	30.3	$0.980 \pm 0.011$	40	6.8	6.8	$0.772 \pm 0.052$	$0.008^{NS}$
OU Oulu	93	65	30.8	$0.983 \pm 0.007$	75	57	34.1	$0.992 \pm 0.004$	116	7.3	6.5	$0.762 \pm 0.069$	$-0.018^{NS}$
Late settlement	379	229		$0.988 \pm 0.003$	368	186		$0.989 \pm 0.004$	402	8.3		$0.764 \pm 0.072$	$0.003^{NS}$
AL Åland	14	14	ND	$1.000 \pm 0.027$	13	12	ND	$0.987 \pm 0.035$	13	5.9	ND	$0.765 \pm 0.062$	$-0.027^{NS}$
All combined	907	528	—	$0.992 \pm 0.001$	832	384	—	$0.993 \pm 0.001$	805	9.9	—	$0.762 \pm 0.072$	$0.003^{NS}$

$A$  = number of haplotypes/alleles;  $AR$  = haplotype/allelic richness;  $\hat{H}$  = haplotype diversity;  $N$  = number of samples; NS, not significant; ND, not determined.

Haplotypes of 17 Y-chromosomal STR loci were obtained using the AmpF/STR Yfiler kit (Applied Biosystems) as described in Palo *et al.*<sup>20</sup> For the data analyses the repeat number of DYS389I was subtracted from that of DYS389II. Multilocus profiles of nine autosomal STR loci (D3S1358, vWA, FGA, TH01, TPOX, CSF1PO, D5S818, D13S317 and D7S820) and Amelogenin were genotyped using the AmpF/STR Profiler kit (Promega). All STR products were analysed on an ABI Prism 310 automated sequencer and GeneMapper v. 3.2 software (Applied Biosystems). Concatenated mitochondrial HVS-I and HVS-II sequence data (sites 16024–16385 and 72–340, aligned length 639 bp) were obtained following Hedman *et al.*<sup>16</sup>

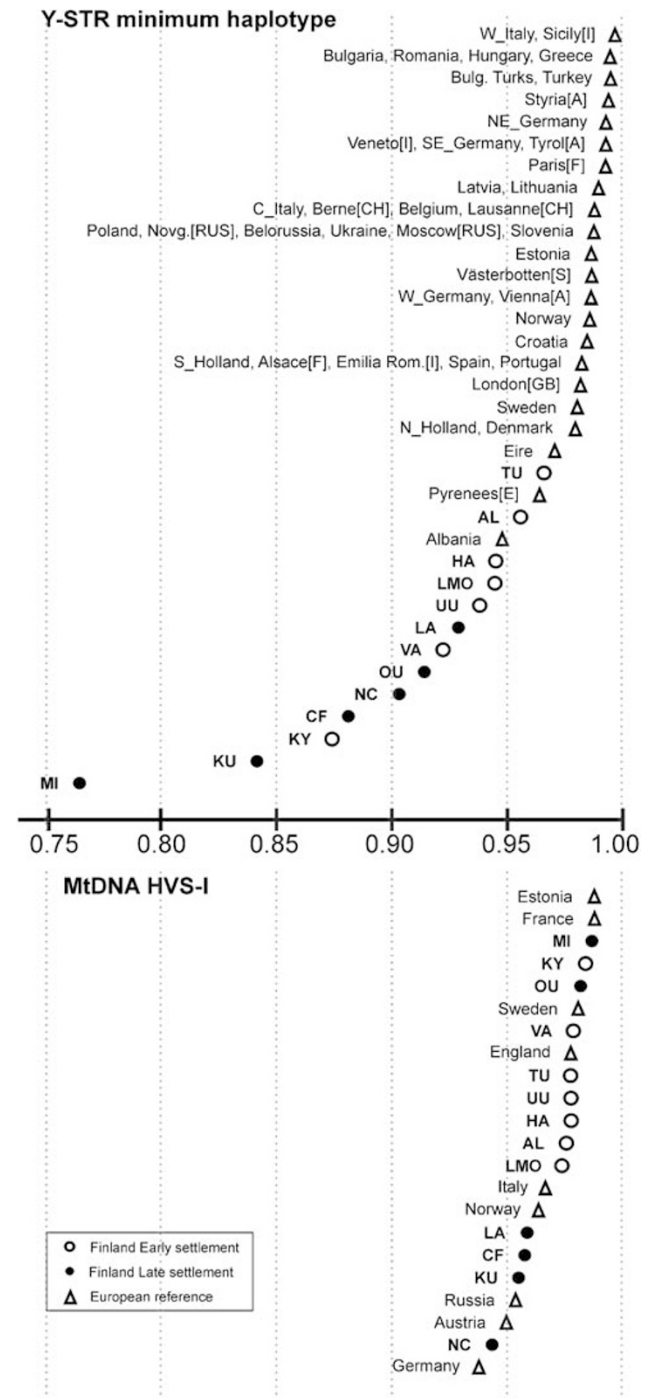
For the data analyses, the samples were assigned, according to the donor's reported place of residence, to 13 sub-populations (Figure 1; Table 1): Åland (AL), Turku (TU), Uusimaa (UU), Häme (HA), Vaasa (VA), Larsmo (LMO), Kymi (KY), Central Finland (CF), Mikkeli (MI), Kuopio (KU), Northern Carelia (NC), Oulu (OU) and Lapland (LA). These sub-populations correspond to the former Finnish provinces, except LMO, which is a part of the Vaasa province. This locality was included separately in the study as it is almost exclusively a Swedish-speaking community. Roughly 6% of present-day Finns represent the Swedish-speaking minority.

**Reference data** For the Y-STR and mtDNA comparisons, previously published data from a number of Eurasian populations were included in the analyses. The 7-locus Y-STR data for 44 population samples<sup>21</sup> were obtained through the Y-chromosome Haplotype Reference Database (YHRD).<sup>22</sup> For the analysis, the populations with pairwise  $\Phi_{ST}$  estimates not differing significantly at the 0.1% level were combined (see Figure 2 in Roewer *et al.*<sup>21</sup>), resulting in 22 metasamples. In addition, Swedish population data for 11 Y-STR loci (DYS19, DYS385a,b, DYS389I, DYS389II, DYS390, DYS391, DYS392, DYS393, DYS438 and DYS439) were kindly provided by A. Karlsson.<sup>23</sup>

A subset of the available mtDNA data was chosen to represent different parts of Europe. Data (361 bp HVS-I data; sites 16024–16385) were obtained for the following populations: Sweden ( $N=296$ , kindly provided by A. Karlsson), Norway ( $N=74$ ),<sup>24</sup> Estonia ( $N=48$ ),<sup>25</sup> France ( $N=50$ ),<sup>26</sup> Russia ( $N=174$ ),<sup>27,28</sup> Germany ( $N=200$ ),<sup>29</sup> Italy ( $N=49$ ),<sup>30</sup> Austria ( $N=101$ )<sup>31</sup> and England ( $N=100$ ).<sup>32</sup>

### Statistical analyses

**Genetic diversity** Y-STR and mtDNA diversity was assessed by calculating the number of haplotypes ( $A$ ) and by estimating the haplotype ( $\hat{H}$ ) and average gene ( $\pi$ ) diversities using the software ARLEQUIN 3.11.<sup>33</sup> To compensate the effect of unequal sample sizes, allelic (haplotype) richness ( $AR$ )<sup>34</sup> was estimated in each group using the software CONTRIB 1.02.<sup>35</sup> Unless otherwise mentioned, standard errors or statistical significance of the various



**Figure 2** Haplotype diversity point estimates in the Finnish (open and filled circles) and the European reference samples (open triangles), in a descending order. Above the axis: Y-STR (7 loci); below the axis: mtDNA HVS-I.

estimates was obtained through randomization procedures (10000 steps). Analyses of the autosomal STR data were performed using FSTAT v.2.9.3.<sup>36</sup> Genetic diversity was

estimated by calculating AR and unbiased estimates of gene diversity ( $H_s$ ).<sup>37</sup> Deviations from Hardy–Weinberg equilibrium within sub-populations, sub-population groups and total population were examined by estimating  $F_{IS}$  over all loci. Differences in average intrapopulation allelic richness and gene diversity were compared between the sub-population groups using the two-sided test and randomization procedure to assess the statistical significance.

**Sub-population differentiation** For the subsequent analyses, the sub-population AL was excluded because of its small size. The mainland sub-populations were initially grouped into regions roughly corresponding to the suggested ESA (VA, LMO, TU, UU, HA and KY) and LSA (MI, CF, KU, NC, OU and LA).

Differences between the sub-populations and sub-population groups were assessed by  $\Phi_{ST}$  for the haplotypic data, and by the analogous  $F_{ST}$ ,<sup>38</sup> for the autosomal diploid STRs. To account for the mutation rate heterogeneity between mtDNA control region sites,  $\Gamma$ -corrected Tamura-Nei substitution model<sup>39</sup> with shape parameter  $\alpha = 0.2$  was assumed.<sup>40,41</sup> Correlation between genetic and geographical distances between sub-populations was assessed by Mantel tests using the software ARLEQUIN. For the genetic distance matrix, transformed linear  $\Phi_{ST}' = \Phi_{ST}/(1 - \Phi_{ST})$ <sup>42</sup> was used and the geographic distances were given as kilometres separating the major towns in each province (sub-population).

The differentiation among the Finnish sub-populations in each marker class was visualized by simple UPGMA trees, constructed based on the  $\Phi_{ST}$  distances using program MEGA 4.0.<sup>43</sup> Arguably, dichotomous trees are not optimal means for representing distances between multiple populations. Here, however, UPGMA was chosen because the method allows the visualization of differences between marker sets in a way that, for instance, multidimensional scaling does not.

Analysis of molecular variance (AMOVA)<sup>44</sup> was run first assuming the ESA/LSA structure described above. AMOVA was also performed in an exploratory fashion for several different modes of clustering (see Table 2).

**Population affinities** For both the Y-STR and mtDNA sequence data, the relationships of the Finnish sub-populations and the reference populations were assessed by estimating pairwise  $\Phi_{ST}$  values as described above. The linearized  $\Phi_{ST}$  distances among populations were visualized by multidimensional scaling, constructed using the ALSCAL procedure in SPSS v. 16.0 (SPSS Inc.).

The relative contribution of neighbouring populations into the Finnish sub-populations was assessed using ADMIX 2.0.<sup>45</sup> With both the Y-STR and mtDNA data, the primarily eastern Finnish sub-populations formed genetically unique clusters, which were assumed as a parental population. However, the composition of these clusters differed

**Table 2** AMOVA designs and results

	ESA/LSA	Y1/2/3/4	MT1/2/3/4
$F_{CT}$ (P)			
YSTR	0.012 <sup>NS</sup>	0.047 <sup>***</sup>	0.033 <sup>**</sup>
mtDNA	0.004 <sup>*</sup>	0.000 <sup>NS</sup>	0.011 <sup>***</sup>
aSTR	0.000 <sup>NS</sup>	0.001 <sup>NS</sup>	0.002 <sup>*</sup>
$F_{SC}$ (P)			
YSTR	0.033 <sup>***</sup>	0.002 <sup>NS</sup>	0.013 <sup>NS</sup>
mtDNA	0.003 <sup>*</sup>	0.005 <sup>**</sup>	−0.002 <sup>NS</sup>
aSTR	0.003 <sup>***</sup>	0.002 <sup>*</sup>	0.002 <sup>*</sup>
$F_{ST}$ (P)			
YSTR	0.045 <sup>***</sup>	0.048 <sup>***</sup>	0.046 <sup>***</sup>
mtDNA	0.008 <sup>***</sup>	0.005 <sup>***</sup>	0.009 <sup>***</sup>
aSTR	0.003 <sup>***</sup>	0.003 <sup>***</sup>	0.003 <sup>***</sup>

ESA/LSA: (VA, TU, UU, HA, KY, LMO)/(CF, KU, MI, NC, OU, LA).

Y1/2/3/4: (VA, LMO)/(HA, TU, UU, LA)/(CF, KU, MI, NC, OU)/(KY).

MT1/2/3/4: (VA, UU, HA)/(TU, CF, KU, NC, KY, OU, LA)/(KU, MI)/(LMO).

\* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$ ; NS, not significant.

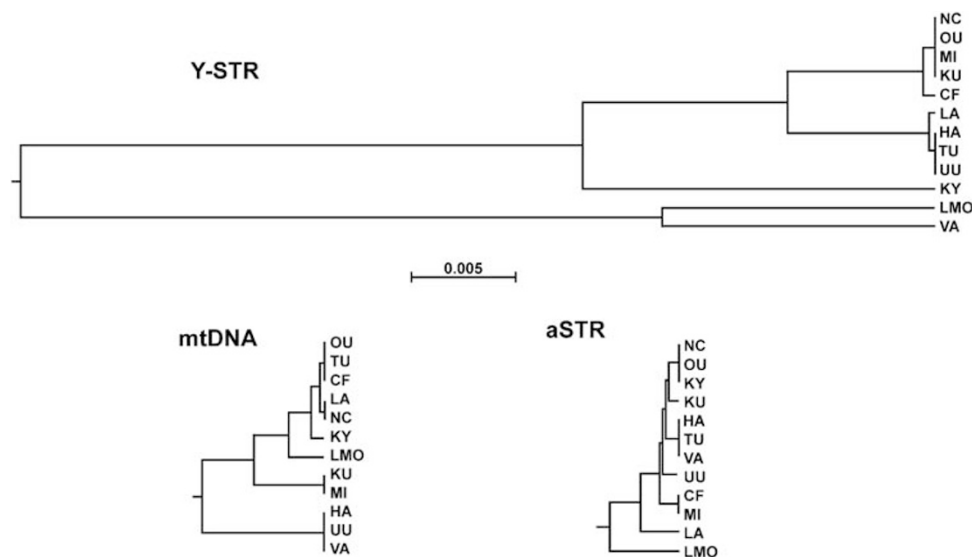
between markers. For Y-STR, the admixture was assessed in sub-populations TU, UU, VA, LMO, HA and LA. The eastern Finnish sub-population cluster, CF, KU, MI, NC and OU ( $N = 288$ ), was assumed as one parental population. The first set of Y-STR analyses was based on 11-locus haplotypes (see above) and included only the eastern Finland and Sweden as parental populations. The second set included 7-locus haplotypes deposited in the YHRD and assumed the Swedish and the Baltic (Latvia-Lithuania) as parental populations. For the mtDNA data, the admixture proportions were estimated for sub-populations UU, HA, VA, KU and MI. The Finnish parental population was formed by grouping data from CF, NC, OU, LA and TU. Again Sweden was assumed as the other parental population.

In addition, the admixture proportions were estimated for the pooled Finnish ESA and LSA sub-populations, assuming Swedish and Russian data as parental populations. Here, the ESA and LSA grouping refers to the sub-population clusters defined above (ESA<sub>Y</sub>: TU, UU, VA, LMO, HA and LA; LSA<sub>Y</sub>: CF, KU, MI, NC and OU; ESA<sub>MT</sub>: UU, HA, VA, KU and MI; LSA<sub>MT</sub>: CF, NC, OU, LA, TU). The analyses were based on 7-locus Y-STR and HVS-I mtDNA data.

## Results

### Y-STR data

Altogether, 528 haplotypes were observed among the 907 Finnish samples analysed with 17 Y-STR markers. There were statistically significant differences in the haplotype diversities between sub-populations (Table 1). The Y-STR haplotype diversities in the Finnish sub-populations and in the European reference populations are presented graphically in Figure 2.



**Figure 3** UPGMA clustering of sub-populations based on  $F_{ST}$  distances. The trees are drawn in the same scale.

The differentiation estimates between the 12 sub-populations in mainland Finland (AL excluded) ranged from  $\Phi_{ST}=0.000$  (14 pairs of populations) to  $\Phi_{ST}=0.210$  (KY–LMO). After Bonferroni adjustment,<sup>46</sup> 17 pairwise values out of the 66 comparisons were significantly larger than zero (nominal  $P<0.05$ , adjusted  $P<0.0008$ ). The Mantel test showed no significant correlation of genetic and geographic distances over all sub-populations ( $r=0.109$ ,  $P=0.193$ ). However, when analysed separately, the correlation was significant among sub-populations within both the *ESA* and *LSA* ( $r_{ESA}=0.741$ ,  $P=0.005$ ;  $r_{LSA}=0.719$ ,  $P=0.030$ ).

Focusing on the *a priori* defined *ESA* ( $N=514$ ) and *LSA* ( $N=379$ ), the southern and western regions of Finland hold significantly more Y-chromosomal diversity ( $\hat{H}_{ESA}=0.994\pm0.001$  vs  $\hat{H}_{LSA}=0.988\pm0.003$ ; Table 1). AMOVA analysis assuming the *ESA* and *LSA* groups showed notably higher within-region ( $F_{SC}=0.033$ ,  $P<0.001$ ) than among-region variation ( $F_{CT}=0.013$ ). The UPGMA tree (Figure 3) suggests clustering into four groups: a loose group of VA, LMO (*Y1*); the sub-populations TU, UU, HA and LA (*Y2*); the sub-populations NC, OU, MI, KU and CF (*Y3*); and finally KY on its own (*Y4*). In the AMOVA, this grouping renders the within-group variation indistinguishable from zero ( $F_{SC}=0.002$ ,  $P=0.194$ ) and increases the among-group variation ( $F_{CT}=0.047$ ,  $P<0.001$ ).

### Mitochondrial DNA

Mitochondrial HVS-I and HVS-II data were obtained for 832 individuals. Altogether, 384 haplotypes were observed, with an estimated haplotype diversity of  $\hat{H}=0.993\pm0.001$  and a gene diversity of  $\pi=0.012\pm0.006$  in the total data. There were small but significant differences between the

mtDNA diversities in different sub-populations (Table 1). The HVS-I haplotype diversities in the Finnish sub-populations and in the European reference populations are presented in Figure 2.

The level of among-sub-population differentiation was substantially lower than that observed in the Y-STR data (arithmetic means Y:  $\Phi_{ST}=0.036$ , mtDNA:  $\Phi_{ST}=0.007$ ). In the mtDNA, the estimates ranged between  $\Phi_{ST}=0$  (17 pairs) to  $\Phi_{ST}=0.030$  (KU–VA), with six estimates significant after the Bonferroni correction. No significant correlation was observed between the mtDNA and geographic distances in Finland ( $r=0.049$ ,  $P=0.356$ ), nor within the *ESA* ( $r=0.239$ ,  $P=0.199$ ) or *LSA* ( $r=0.051$ ,  $P=0.323$ ).

As with the Y data, the *ESA* held more mtDNA diversity ( $\hat{H}_{ESA}=0.995\pm0.001$  vs.  $\hat{H}_{LSA}=0.989\pm0.003$ ). The inter-regional differentiation was also significant, yet lower than that with Y-STRs ( $\Phi_{ST}=0.005$ ,  $P<0.001$ ). AMOVA revealed low, but significant, among-region and within-region differences ( $F_{CT}=0.004$ ,  $P=0.002$ ;  $F_{SC}=0.003$ ,  $P<0.050$ ).

The tree (Figure 3) suggests clustering into four groups, but the compositions differ from those obtained with the Y-STR data: *MT1*: HA, UU and VA; *MT2*: KU and MI; *MT3*: OU, TU, CF, LA, NC and KY and *MT4*: LMO. The *F*-statistics obtained assuming this structure were  $F_{CT}=0.011$  ( $P<0.001$ ) and  $F_{SC}=-0.002$  ( $P=0.906$ ). Notably, the mtDNA data suggest closer affinity between LMO and the Late settlement area sub-populations than the Y-STR data.

### Autosomal microsatellites

In total, 82 alleles were encountered at nine autosomal STR loci genotyped for 805 individuals. The gene diversity over all samples and loci was  $H_s=0.762\pm0.072$ ; the observed

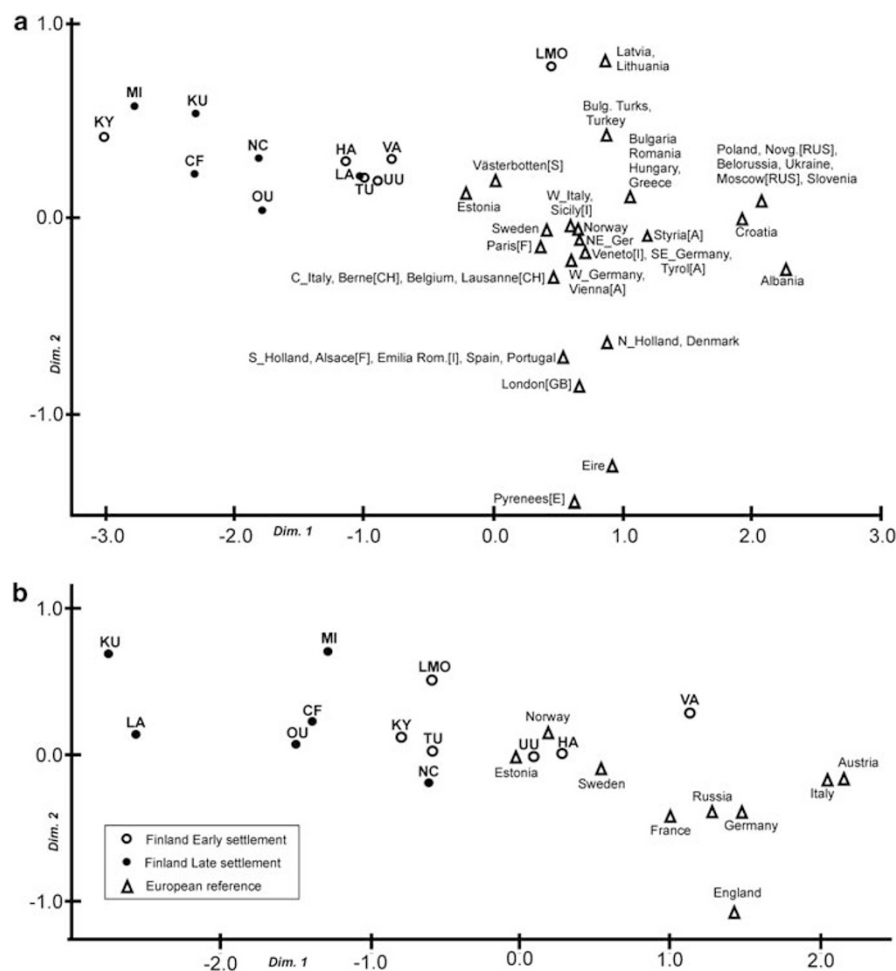
$F_{IS} = 0.006$  did not deviate significantly from zero (95% CI:  $-0.003$  to  $0.016$ ; Table 1). Concordant with this, no significant differences in the allelic richness (based on 39 samples) nor in the expected gene diversities between the sub-populations were observed. There were no significant differences in the allele richness or expected heterozygosity between the Early and Late settlement areas, either ( $AR = 5.63$  vs  $5.56$ ,  $P = 0.213$ ;  $H_s = 0.757$  vs  $0.762$ ,  $P = 0.498$ ).

The genetic differentiation in the autosomal STRs between the 12 sub-populations in Finland is an order of magnitude lower than that in the Y-STR variation. The pairwise values stretch from  $F_{ST} = 0$  (18 out of 66 comparisons) to  $F_{ST} = 0.015$  (LMO–KU). Only three pairwise  $F_{ST}$  estimates, all involving the LMO sub-population, remained statistically significant on the nominal 95% level after the Bonferroni adjustment. However, AMOVA results showed a significant variation among groups within regions ( $F_{SC} = 0.0028$ ,  $P < 0.001$ ), but not among regions ( $F_{CT} = 0.0003$ ,  $P < 0.268$ ).

As with all other markers, the Mantel test revealed no significant correlation between genetic and geographical distances within Finland ( $r = 0.131$ ,  $P = 0.216$ ), nor within LSA ( $r = -0.022$ ,  $P = 0.505$ ). In contrast, among the ESA sub-populations, a significant correlation was observed ( $r = 0.681$ ,  $P = 0.009$ ).

### Population affinities

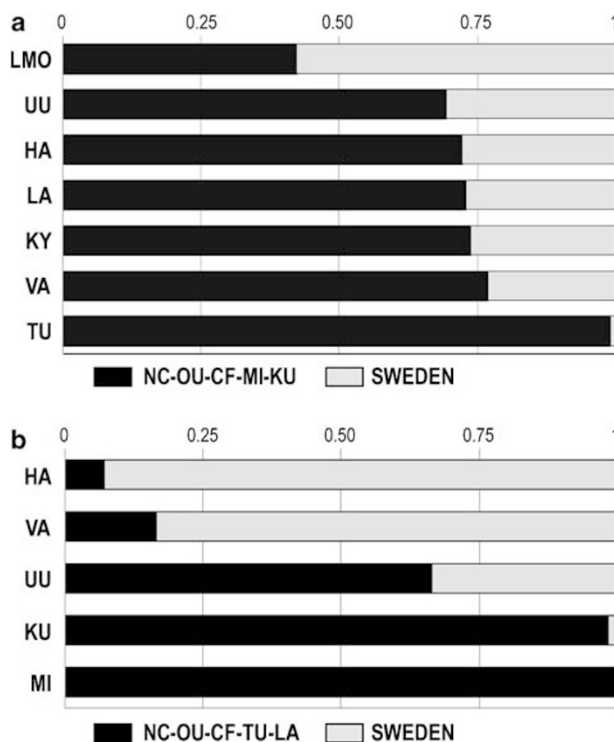
As within Finland, the distances among the Finnish and the European reference populations were an order of magnitude higher in the Y-STR (average  $\Phi_{ST} = 0.129$ ) than in the mtDNA data (average  $\Phi_{ST} = 0.011$ ). The MDS plots based on the linearized distances are shown in Figure 4. Although the patterns differ depending on the marker type, the Early settlement area sub-populations are generally placed closer to the European references, especially Sweden and Estonia. The KY population, however, is an exception clustering with the eastern sub-populations in the Y-STR (Figure 4a). In case of the LMO sub-population, the Y-chromosomal and mitochondrial data reveal



**Figure 4** MDS scatterplot based on the linearized  $\Phi_{ST}$  estimates. (a) Seven-locus Y-STR haplotypes. (b) mtDNA HVS-I sequence data.

contradictory affinities. The mtDNA data suggest loose clustering among Finnish sub-populations, but the Y-STR data place this sample in the vicinity of the Baltic populations, Latvia and Lithuania, in the MDS. Nevertheless, based on the pairwise Y-chromosomal  $\Phi_{ST}$  estimates, the LMO sample is clearly closer to Sweden ( $\Phi_{ST}=0.020$ ) than the two Baltic states ( $\Phi_{ST}=0.158$ ).

The male genetic contribution of two parental populations, the LSA sub-population cluster and Sweden, was evaluated in the remaining sub-populations VA, LMO, TU, UU, HA, KY and LA. The LA was included here because of its proximity with the ESA sub-populations (Figure 3), which altogether show closer Scandinavian affinity (Figure 4). The analysis based on 11-locus Y-STR haplotypes suggests a substantial 20–30% Swedish contribution in most ESA sub-populations and LA (Figure 5a). In the LMO, the Swedish contribution exceeds the Finnish. The TU sub-population does show only negligible Swedish contribution, but the analysis with 7-locus haplotype data and three parental populations suggests c. 30% contribution from the Latvia-Lithuania metasample into this region. In all other sub-populations, the Baltic contribution was low (c. 4% in UU) or came up as negative (rest of the sub-populations). The pairwise  $\Phi_{ST}$  estimates, however, suggest somewhat closer affinity between TU and Sweden ( $\Phi_{ST}=0.111$ ) than between TU and Latvia-Lithuania ( $\Phi_{ST}=0.161$ ).



**Figure 5** The magnitude of the Scandinavian gene flow in several primarily western Finnish sub-populations estimated from (a) the Y-STR data and (b) the mtDNA HVS-I + II data.

The admixture analysis of mtDNA haplotypes followed the same logic, although a different clustering was assumed based on the sub-population differentiation. A notable Scandinavian influence was observed in three sub-populations, HA, VA and UU, whereas it was negligible in the KU and MI. These latter two populations are situated in the *a priori* defined LSA, despite their intermediate position in the mtDNA tree (Figure 3). However, one must note that the relative uniformity of mtDNA variation in Europe may not allow the identification of the Scandinavian gene flow as clearly as the Y chromosome. The relative contribution of Slavic (Russian) and Swedish populations in both the Y-chromosomal and mtDNA gene pools was estimated separately for the Finnish sub-population clusters. In all analyses, the Slavic contribution came up as negative (data not shown).

## Discussion

Recent analyses have convincingly shown the distinctiveness of the Finnish gene pool among the European populations, for example in autosomal SNP markers<sup>1</sup> or in uniparental markers.<sup>47,48</sup> Regional differences in Finland have also been reported.<sup>4–7,12,49</sup> This study, a rather straightforward haplotype-level population genetic analysis, corroborated this picture. However, the degree of segregation and diversity varies between different regions of Finland, as well as between different marker classes; we believe that the observed geographical patterns in the genetic diversity of the uniparental markers have notable corollaries for the population history of Finns.

## Different markers – different picture

Compared with the European reference populations, the Y-chromosomal diversity is low, reduced further in the Late settlement area sub-populations and show substantial regional differences. In contrast, the mtDNA diversity does not display marked reduction and shows less, albeit significant, inter-regional variation (Figure 2). The latter observation is at odds with some of the earlier studies.<sup>16</sup> No significant structure was detected in the small 9-locus autosomal STR data within Finland, which at first appears to be in contrast with the recent results from genome-wide SNP data.<sup>7</sup> However, even with 250 000 SNP markers, the differentiation between eastern and western Finland remains low in absolute terms ( $F_{ST}=0.0032$ )<sup>7</sup> and not drastically different than the estimates obtained here with a small set of autosomal markers.

The markers revealed widely varying differentiation measures between sub-populations and regions. In the Y-STR data, the average differentiation among all sub-populations is c. 10 and 5 times higher than that in the autosomal and mtDNA data (see Figure 3), respectively. The ratio between mtDNA and autosomal STR differentiation is



roughly 3, fitting to the expectations based on the effective (molecular) population sizes.

### Gene flow from Scandinavia

In contrast to the findings of Lappalainen *et al*,<sup>4</sup> which in the Y-chromosomal data suggest a clear separation between the Finnish and Swedish gene pools, the admixture analyses suggest substantial Scandinavian contribution that is gene flow into the western and northern parts of the country from the west. In the Y-chromosomal data, the Scandinavian influence was the highest in the coastal sample of Larsmo (LMO) and substantial in most Early settlement area sub-populations as well as in the Lapland (LA; Figure 5). Notably, the Scandinavian gene flow explains the proximity of the northern LA sub-population to the southern and western Finnish sub-populations TU, UU, VA and HA. Unlike the southern parts of Finland, Lapland is not separated from Scandinavia by the Baltic Sea. The regional differences in the Y-chromosomal diversity in Sweden are also small,<sup>23</sup> and gene flow from Sweden could thus homogenize the Y-chromosomal diversity between south-western and northern Finland. The large Y-STR differences between the western and eastern parts of Finland are thus plausibly explained by regionally restricted gene flow, extending to the south-western and northern Finland. The Late settlement area in turn, would seem to retain more of the Fenno-Ugric genetic composition originating from the regions east of Finland. This is reflected in the haplogroup distribution: the Scandinavian haplogroup I occurs with frequencies >30% only in western Finland.<sup>4</sup> Haplogroup N3, typical for Fenno-Ugric populations of north-eastern Europe,<sup>48,50</sup> is observed in all parts of Finland but reaches high frequencies (~79%) only in eastern Finland. The inter-regional dichotomy results in large  $\Phi_{ST}$  estimates between eastern and western Finland and, consequently, in the clustering of populations (Figures 3 and 4).

The dissimilarity in the differentiation patterns between Y-chromosomal and mtDNA/autosomal markers, together with the admixture analysis results, further suggests that the Scandinavian gene flow has been male biased. One example of this is the Larsmo (LMO), which shows proximity with the eastern sub-populations in the mtDNA, but strong Scandinavian affinity in the Y-STR data.

The detection of genetic admixture is, obviously, sensitive to the parental populations assumed in the analysis, as well as to the time of the gene flow from the (true) parental populations and subsequent drift. These factors are hard to circumvent and the obtained admixture estimates cannot probably be considered more than qualitatively correct.

### Finland revisited

The scenario often invoked to explain the lower genetic diversity, and the prevalence of Finnish disease heritage illnesses especially in the eastern parts of Finland

emphasizes founder effects associated with two major immigration waves c. 4000 BP and 2000 BP.<sup>3</sup> This early settlement population has formed a homogeneous source population for the relatively recent inhabitation of the eastern parts of the country.<sup>7,8,51</sup> The patchy occurrence of the FDH in the eastern part of the country is explained by numerous separate founding events from homogeneous source, randomly distributing the disease alleles into the subisolates. The differences between the Early and Late settlement areas thus allegedly stem from this 15th–16th century internal migration.<sup>4,7</sup>

There is in fact little support in the archaeological data for immigration waves into Finland around 4000 BP and 2000 BP. Instead, archaeological evidence suggests that Finland was colonized rather rapidly after the deglaciation c. 10 500 BP.<sup>52–54</sup> The initial colonization has been followed by major immigration waves c. 7500 BP (comb-ceramic culture) and 4500 BP (corded-ware culture). Second, there are no indications that the eastern parts of the country have been uninhabited until the late medieval times as proposed earlier. Model-based approaches predicting the number of inhabitants from the archaeological remains indeed propose a slow overall population growth from c. 10 500 BP onwards (P. Pesonen and M. Tallavaara, unpublished results), although significant reductions of population sizes between c. 6000 BP and 3000 BP in the western and eastern parts of the country are also suggested.

The scenario proposed earlier is also at odds with the current results. First and foremost, it would entail that the LSA diversity is a subset of the ESA diversity. However, as shown above, the differences especially in the Y-chromosome are not attributable solely to loss of diversity, but show distinctive haplotype and haplogroup distributions, which are more plausibly explained by gene flow into western Finland. The recent bottleneck associated with the settlement of the eastern/northern Finland should have affected both Y-chromosomal and mtDNA diversity relatively similarly. Unlike the Y-chromosomal variation, the mtDNA does not show any sign of reduction and displays fairly homogeneous haplogroup distribution over Finland.<sup>16</sup> The relative uniformity of the mtDNA diversity in Finland has been explained to be because of higher mutation rate in the mtDNA.<sup>11</sup> This appears unlikely. As the mtDNA haplogroups are defined by old mutations and should be rather stable, it is difficult to understand how mutation could produce a haplogroup distribution that is more similar than, for example, that in the Central European populations<sup>55</sup> in only 20 generations. Reversed, the same argument could be used for Y-chromosomal haplogroup distribution: the dichotomous patterns of I and N3 occurrence are not likely to arise because of neutral chance processes such as drift. Therefore, an alternative explanation – male-biased gene flow from Scandinavia to western parts of Finland – appears as more likely in the light of the current results.

The results propose Scandinavian gene flow as a source of inter-regional differences in Finland. As the whole of Finland has been continuously inhabited since the early Holocene,<sup>52</sup> it may be assumed that these early populations have also contributed to the present-day gene pool. It is possible that, at some stage, the majority of the males in this prehistoric population carried the Y chromosomes of haplogroup N3.<sup>48</sup> The subsequent Scandinavian gene flow has then affected the genetic composition of the south-western as well as the northernmost parts of Finland only, creating the large Y-chromosomal differences between western and eastern parts of the country. In other words, the Scandinavian influence can be seen as an additional genetic element in the ESA region (and Lapland), whereas the Finno-Ugric genetic component remains still more prominent in the east of Finland. It also fits to the notion of slight yet significant substructure observed in autosomal SNP markers.<sup>7</sup> If this gene flow has been male biased, it could also credibly explain the large differences between the Y-chromosomal and mtDNA/autosomal diversity patterns. Under the model proposed here, the patchy occurrence of FDH diseases, especially in eastern Finland, is better explained by long-term drift, more acute in the sparsely inhabited eastern Finland, rather than by relatively recent founder effects. The distances observed between the LSA sub-populations also support high drift in this area (Figure 4). Alleviated by the Scandinavian gene flow, the drift has been less severe in the western parts of the country.

This model is, to our opinion, well supported by other evidence. Already in the prehistoric times, there has been a close tie between south-western Finland, Sweden and Estonia.<sup>56</sup> The south-western parts of Finland were brought under the Swedish rule between c. 1150 and 1300, which led to the emergence of Finland's Swedish-speaking population (today comprising ca. 6%). Another Scandinavian political power, the Danes, were also actively operating along the Baltic coast in the medieval times.<sup>57</sup> Markedly, in the early medieval period, the Swedish reign was not extended further than in the south-western Finland, roughly corresponding to the ESA. This has been traditionally explained by the opposing force of Russia (Novgorod); however, ecological factors may also have had an influence on the agricultural population. The current area of south-western Finland, having a distinctive Y-chromosomal variation, correlates conspicuously with the southern boreal ecological zone (thermic growth period maps: [http://www.fmi.fi/saa/tilastot\\_72.html#7](http://www.fmi.fi/saa/tilastot_72.html#7)) and with the first political border between Sweden and Novgorod (year 1323, Figure 1).

The model for the settling of Finland proposed earlier emphasizes founder effects, both in the initial phases and during the internal immigration in the historical era. On the basis of the current results and other evidence, we have proposed an alternate model that emphasizes long-term

drift and gene flow as factors behind the regional differences. The fact that many and grave objections may be advanced against this model of Finnish population history cannot be denied. Nevertheless, the model proposed presented here most plausibly explains the genetic differences observed between the western and eastern parts of Finland and also offers justification for the dissimilarities observed between the marker classes.

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