Arch Toxicol (2016) 90:883–889
DOI 10.1007/s00204-015-1501-1

TOXICOGENOMICS

Determination of NAT2 acetylation status in the Greenlandic population

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Received: 22 December 2014 / Accepted: 5 March 2015 / Published online: 21 March 2015

Abstract *N*-acetyltransferase 2 (NAT2) is a well-studied phase II xenobiotic metabolizing enzyme relevant in drug metabolism and cancerogenesis. NAT2 activity is largely determined by genetic polymorphisms in the coding region of the corresponding gene. We investigated NAT2 acetylation status in 1556 individuals from Greenland based on four different single nucleotide polymorphism (SNP) panels and the tagging SNP rs1495741. There was good concordance between the NAT2 status inferred by the different SNP combinations. Overall, the fraction of slow acetylators was low with 17.5 % and varied depending on the degree of Inuit ancestry; in individuals with <50 % Inuit ancestry, we observed more than 25 % slow acetylators reflecting European ancestry. Greenland has a high incidence of tuberculosis, and individual dosing of isoniazid according to NAT2 status has been shown to improve treatment and reduce side effects. Our findings could be a first step in pharmacogenetics-based tuberculosis therapy in Greenland.

Keywords Greenland · Inuit ancestry · Isoniazid · *N*-acetyltransferase 2 · Tuberculosis treatment

Electronic supplementary material The online version of this article (doi:10.1007/s00204-015-1501-1) contains supplementary material, which is available to authorized users.

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Introduction

One of the first examples of genetic variation in drug metabolism was the *N*-acetylation of the anti-tubercular agent isoniazid, and it later turned out that NAT2 is mainly driving this variation (Sim et al. 2008). Enzyme activity is divided into three main categories as slow, intermediate and rapid acetylation, with some studies combining intermediate and rapid acetylation. Furthermore, NAT2 plays an important role in *N*-acetylation of carcinogenic aromatic amines, and slow acetylation status is a risk factor for urinary bladder cancer (Hein 2002).

The coding exon of *NAT2* is polymorphic, and the frequencies of the identified mutations are highly variable across the world (Sabbagh et al. 2011). A common genetic variant tagging NAT2 acetylation status, rs1495741, had several findings in genome-wide association studies in recent years; the allele representing slow acetylation status was associated with risk of urinary bladder cancer (Figueroa et al. 2014; Rothman et al. 2010), lower lipid levels (Teslovich et al. 2010; Willer et al. 2013) and increased skin fluorescence (Eny et al. 2014).

The first humans arrived in the North American Arctic around 6000 years ago, and Greenland was populated by Eskimos in several migration waves (Raghavan et al. 2014). Today the Greenlandic population is characterized by this Inuit ancestry and European ancestry introduced by immigration mainly from Denmark and Norway over the last 300 years. Comparing Greenlandic genomes with genomes from the three major global population groups (Africans, Asians and Europeans) showed that they are quite distinct (Pereira et al. 2015).

Greenland has a high incidence of tuberculosis with annually more than 100 new cases per 100,000 individuals (Statistics Greenland 2014), and isoniazid is widely used in

both prevention and treatment of tuberculosis. Individual differences in drug metabolism result in substantial variation of isoniazid blood levels (Mitchell and Bell 1957). Slow NAT2 acetylation status is a risk factor for anti-tuberculosis drug induced liver injury (Wang et al. 2012), a severe side effect of treatment. A study on the pharmacokinetics of isoniazid suggested that standard doses are only appropriate for intermediate acetylators, while a 50 % decrease for slow acetylators and a 50 % increase for rapid acetylators could improve both the safety and the efficacy of treatment (Kinzig-Schippers et al. 2005), and a subsequent clinical trial was able to prove these effects (Azuma et al. 2013). We therefore decided to determine the NAT2 acetylation status of 1556 Greenlandic individuals based on genetic data from the *NAT2* region to investigate the potential of *NAT2* screening in Greenlandic tuberculosis patients.

Materials and methods

Subjects

In 2013, we recruited individuals from seven of the twelve largest towns in Greenland, with populations ranging from 1181 (Upernavik) to 16,454 (Nuuk) (Statistics Greenland 2013). Together, more than 31,000 individuals of the total population of 57,000 were living in these seven towns. Participants had to be born in Greenland and had to be older than 16 years. Individuals were identified through the Greenlandic Civil Registration System and received a letter inviting them to participate. This study was based on 1556 individuals with genotype information available. Basic demographic information of the participants is given in Table 1. The Commission for Scientific Research in Greenland (approval No. 2013-17) and the Danish Data Protection Agency approved the study. Written and informed consent was given by all participants and by parents for participants under 18 years.

Table 1 Demographics of 1556 Greenlandic individuals in the study

Variable	*N*	Percentage
Sex: female	964	61.0
Age (years)	Mean 33.7 (SD 10.1)	
	Median 32.0 (range 16–69)	
Recruitment site		
Upernavik	85	5.5
Uummannaq	86	5.5
Sisimiut	374	24.0
Nuuk	480	30.8
Qaqortoq	196	12.6
Nanortalik	168	10.8
Tasiilaq	167	10.7

Genotyping, quality control, imputation and haplotype estimation

All 1556 individuals were genotyped on the Illumina Human Omni Express Exome chip. A total of 640,842 SNPs passed quality control; the other SNPs were excluded based on a missing rate >2 %, deviation from Hardy–Weinberg equilibrium ($P < 1 \times 10^{-6}$), minor allele frequency <1 % or discrepancies ($P < 1 \times 10^{-6}$) in allele frequencies between sexes. Subsequently, we imputed unobserved genotypes using phased haplotypes from the integrated phase I release of the 1000 Genomes Project (http://www.1000genomes.org/) with the software packages SHAPEIT (Delaneau et al. 2012) and IMPUTE2 (Howie et al. 2009). This study focused on imputed variants on chromosome 8p22. Accuracy of the estimated allele counts was assessed by SNPTEST (Marchini and Howie 2010), and all reported SNPs had average maximum posterior probabilities of 1 (indicating that there was no uncertainty) and an information measure of 1 (indicating perfect information). Haplotype frequencies were estimated with the expectation–maximization algorithm implemented in PLINK (Purcell et al. 2007).

Assessment of NAT2 acetylation status

We studied acetylation status based on previously described *NAT2* SNP panels (Hein and Doll 2012). For the 2-, 3- and 4-SNP panels and the tag-SNP rs1495741, acetylation status was determined by directly counting the number of slow haplotypes/alleles per individual. For the 7-SNP panel, we retrieved acetylation status probabilities for the 21 observed genotype combinations from reference data (Kuznetsov et al. 2009). All slow and intermediate acetylators were assessed with a probability of at least 99.6 %; for rapid acetylation status, all probabilities were >97.9 %.

Determination of Inuit ancestry

The Greenlandic population has become genetically admixed over the last centuries after Northern European visitors settled on the island. Therefore, we investigated admixture with the software tool ADMIXTURE (Alexander et al. 2009) based on a genome-wide set of 43,336 independent SNPs. The results confirmed admixture with two major components referring to Inuit and European ancestry. We estimated the proportions of Inuit and European ancestry of all individuals to investigate differences in NAT2 acetylation status between groups with different levels of Inuit ancestry.

Table 2 Imputed allele frequencies for 14 *NAT2* SNPs imputed with high accuracy based on 1000 Genomes reference data

Base-pair change	rs name	Position*	Frequency**	*N****
70T>A	rs45477599	18,257,583	0.000	–
191G>A	rs1801279	18,257,704	0.000	1556
282C>T	rs1041983	18,257,795	0.163	1555
341T>C	rs1801280	18,257,854	0.243	1554
403C>G	rs12720065	18,257,916	0.000	–
481C>T	rs1799929	18,257,994	0.240	1555
578C>T	rs79050330	18,258,091	0.000	–
590G>A	rs1799930	18,258,103	0.150	1556
609G>T	rs45618543	18,258,122	0.000	–
683C>T	rs45518335	18,258,196	0.000	–
766A>G	rs55700793	18,258,279	0.000	–
803A>G	rs1208	18,258,316	0.246	1551
857G>A	rs1799931	18,258,370	0.012	1556
+14 kb G>A	rs1495741	18,272,881	0.406	1552

* Position given according to the 19th version of the human reference genome from the Genome Reference Consortium (hg19)

** Frequency is given for the variant (second) allele in the base-pair change column

*** Number of individuals with genotype calls, "–" indicates SNPs not on the chip

Results

Coverage of *NAT2* variants

The current *NAT2* nomenclature describes human *NAT2* alleles/haplotypes based on combinations of 38 exonic variants (Arylamine *N*-acetyltransferase Gene Nomenclature Committee 2013). Imputation provided high-accuracy information for 13 of the described SNPs and the tagging SNP rs1495741 (Table 2); seven SNPs were monomorphic in our study group. Genotype frequencies for the 14 SNPs are given in Supplementary Table 1.

Tagging of NAT2 acetylation status and comparison of different SNP panels

We investigated the accuracy of several previously studied *NAT2* SNP combinations (Hein and Doll 2012) in assessing NAT2 status, i.e., the tag-SNP rs1495741 and the panels comprised of two SNPs (rs1041983 and rs1801280), three SNPs (rs1799929, rs1799930 and rs1799931), four SNPs (rs1801279, rs1801280, rs1799930 and rs1799931) and seven SNPs (rs1801279, rs1041983, rs1801280, rs1799929, rs1799930, rs1208 and rs1799931). The SNP rs1801279 was monomorphic in our samples, but we kept the naming 4-SNP and 7-SNP panel. Supplementary Table 2 provides the linkage disequilibrium between the seven polymorphic SNPs in all Greenlandic samples.

Table 3 lists inferred slow, intermediate and rapid acetylation status for the 1556 individuals. Concordance between the different panels was high; the 2-SNP and 4-SNP panels agreed perfectly with the reference 7-SNP panel, while slow acetylation status agreed in 98.9 and 97.8 % of individuals for the tag-SNP rs1495741 and the 3-SNP panel, respectively. Supplementary Table 3 additionally provides estimated haplotype frequencies for the six polymorphic SNPs of the 7-SNP panel.

Variation of NAT2 acetylation status in Greenland

Overall, we observed 17.5 % slow acetylators in the study group. The Greenlandic population is admixed with two major components: an Inuit part reaching back to the first migration waves from North America and a Northern European part resulting from interaction with Denmark and Norway in the last 300 years (Table 4). We split the study group in three parts according to the percentage of Inuit ancestry and observed a frequency of 12.2 % slow acetylators among individuals with a high percentage of

Table 3 Inferred NAT2 acetylation status of 1556 Greenlandic individuals based on different tagging SNP panels and concordance between status determined by the 7-SNP set and the other sets

Panel	NAT2 status			Concordance*		
	Slow	Intermediate	Rapid	Slow	Intermediate	Rapid
7-SNP	273 17.5 %	716 46.0 %	567 36.4 %	Ref.	Ref.	Ref.
4-SNP	273 17.5 %	716 46.0 %	567 36.4 %	100 %	100 %	100 %
3-SNP	267 17.2 %	718 46.1 %	571 36.7 %	97.8 %	99.4 %	100 %
2-SNP	273 17.5 %	716 46.0 %	567 36.4 %	100 %	100 %	100 %
rs1495741	273 17.5 %	716 46.0 %	567 36.4 %	98.9 %	99.3 %	99.6 %

* Percentage of individuals with specific NAT2 status based on the 7-SNP set who are grouped in the same category by the other SNP set

Table 4 NAT2 acetylation status of 1556 Greenlandic individuals based on the 7-SNP set in relation to Inuit ancestry

Inuit ancestry mean (SD)	*N*	NAT2 status		
		Slow	Intermediate	Rapid
High (>70 %)	574	70	231	273
87.8 % (11.1 %)		12.2 %	40.2 %	47.6 %
Medium (50–70 %)	506	81	248	177
60.0 % (5.5 %)		16.0 %	49.0 %	35.0 %
Low (<50 %)	476	122	237	117
36.1 % (11.3 %)		25.6 %	49.8 %	24.6 %
All (0–100 %)	1556	273	716	567
63.0 % (23.4 %)		17.5 %	46.0 %	36.4 %

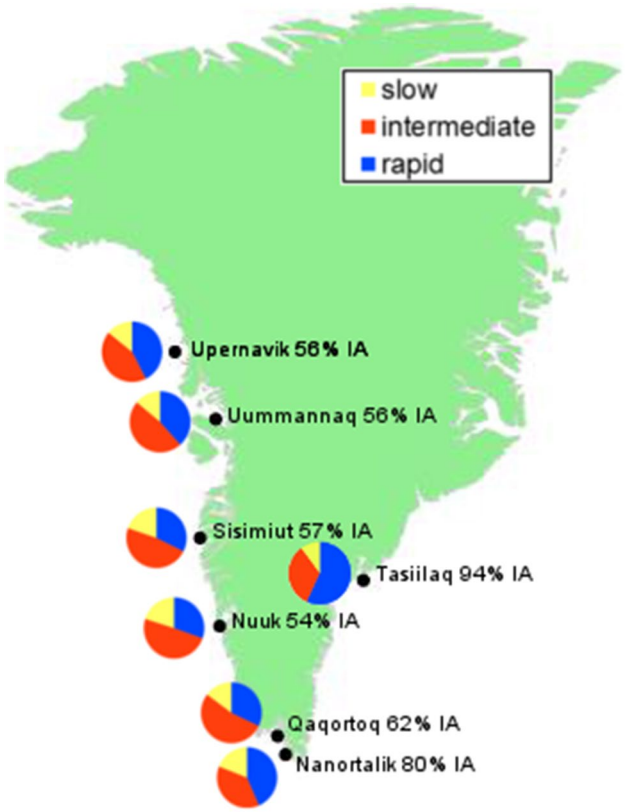

Fig. 1 Pie charts with frequencies of slow, intermediate and rapid acetylation status at the different recruitment sites, and the respective percentage of Inuit ancestry (IA). Figure generated with R (www.r-project.org)

Inuit ancestry, which is substantially lower than the 25.6 % observed in individuals with <50 % Inuit ancestry.

Figure 1 illustrates the distribution of NAT2 acetylation status in Greenland. Slow acetylation status was less frequent in East Greenland, where there was also a larger fraction of Inuit ancestry. This can be explained by the fact that East Greenland was more isolated over the last 300 years, with European visits concentrating on the West Coast; especially, Tasiilaq stood out with an Inuit ancestry of 94 % and only 10 % slow acetylation status.

Discussion

Greenland has an admixed population with a dominating Inuit and an additional European component. The frequency of specific genetic variants in Greenland cannot easily be inferred from public databases of the major human populations. The global variation in NAT2 acetylation status has important implications for the metabolism of the anti-tuberculosis drug isoniazid, and the high Greenlandic incidence of tuberculosis motivated us to investigate *NAT2* gene variants. The fraction of 17.5 % slow acetylators observed in Greenland is one of the lowest frequencies in the world, driven by the Inuit ancestry. The observed NAT2 acetylation frequencies were close to figures from North-East Asia (Sabbagh et al. 2011), which fits with the current opinion that Greenland was populated from North America and the first humans coming to North America originally came from Siberia (Raghavan et al. 2014).

Even though substantial individual differences in isoniazid metabolism related to NAT2 acetylation status are known for more than 15 years (Parkin et al. 1997) and *NAT2* genotypes explain 88 % of the variability in isoniazid clearance (Kinzig-Schippers et al. 2005), assessment of NAT2 status is not routine clinical practice yet. Increased dosages for individuals with rapid acetylation could reduce treatment failure rates. On the other hand, a meta-analysis found a 4.7-fold increased risk of liver injury after anti-tuberculosis treatment in slow acetylators compared with rapid acetylators (Wang et al. 2012), and a lower dosage for these individuals could be indicated. A recent clinical trial investigated a *NAT2* genotype-guided treatment of tuberculosis (Azuma et al. 2013) and found that accounting for NAT2 status reduced the rate of early treatment failures in rapid acetylators compared with standard treatment (15 vs. 38 %). In the slow acetylation group, none of the seven patients with genotype-guided lower dosage experienced liver injury during the 6 month of follow-up, whereas there were seven cases of liver injury among the nine patients on standard therapy. The clinical trial was carried out in Japan, and the study group showed a distribution of NAT2 status comparable to Greenland.

Our study relied on a good characterization of NAT2 acetylation status based on the established 7-SNP panel. Additional rare variants associated with slow acetylation are known (Arylamine *N*-acetyltransferase Gene Nomenclature Committee 2013), and we cannot rule out that these variants and maybe even Inuit-specific variants are present in Greenland. Therefore, the agreement between the inferred NAT2 acetylation status and actual enzyme activity

has to be studied before treatment regimens based on genotypes can be introduced. Several methods are available for measuring enzyme activity directly (Hein and Doll 2012), and the results showed good concordance with genetically determined NAT2 acetylation status (Cascorbi et al. 1995; Chen et al. 2006; Grant et al. 1984; Hein and Doll 2012; Kinzig-Schippers et al. 2005; Parkin et al. 1997; Selinski et al. 2011; Smith et al. 1997).

Overall, we provide a first overview of NAT2 acetylation status in Greenland. The frequency of rapid acetylation is particularly high in East Greenland, where the incidence of tuberculosis is highest. Both clinical trial simulations (Gumbo et al. 2007) and an actual clinical trial provided evidence that increased doses of isoniazid can reduce treatment failure. At the advent of personalized medicine, the optimizing of isoniazid dosage based on *NAT2* genotypes in Greenland might be a practicable example.

Acknowledgments We thank all study participants for their cooperation in this study, as well as all individuals involved in collecting and handling of data and samples. We thank Mikael Andersson (data management), Poul Berger, Henrik Hjalgrim, Mikkel Koch, Jacqueline M. Mistry, Helle Møller and Johan E. Navne (all field-work). Sascha Wilk Michelsen and Karen Bjorn-Mortensen are both supported by Commission for Scientific Research in Greenland/Danish Research Council scholarships, and Bjarke Feenstra is supported by an Oak Foundation fellowship. The study was conducted with support from: The Danish Research Council, The Greenlandic Ministry of Education, Church, Culture and Gender Equality, the Maersk foundation (Fonden til lægevidenskabens Fremme), and the Aase and Ejnar Danielsens Foundation.

Conflict of interest None.

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