# UGT1A1*28 polymorphism and acute lymphoblastic leukemia in children: a Danish case–control study

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**BACKGROUND:** Oxidative stress is a possible risk factor in the development of acute lymphoblastic leukemia (ALL) in children. Bilirubin is a potent endogenous antioxidant, and the UGT1A1*28 polymorphism is the main genetic cause of variation in plasma bilirubin in Western Europe.

**METHODS:** In a case–control study of 665 incident cases of ALL in childhood in Denmark 1982–2010 and 1,379 controls, associations between UGT1A1*28 genotypes and ALL in childhood were estimated as odds ratios by logistic regression with adjustment for sex and birth decade. Subgroup analyses were carried out by age at onset in three groups, and on the ALL subtypes precursor B-cell, T-cell, and t(12;21) positive status. Cases were identified in The Danish Registry of Childhood Cancer, and genotypes were estimated from dried blood spots stored in The Danish Neonatal Screening Biobank. Controls were newborns with blood spots taken right before and after a case.

**RESULTS:** We found no association between ALL in childhood and UGT1A1*28 genotypes. The odds ratio was 1.01 (0.88–1.17) for heterozygotes and 1.03 (0.78–1.36) for homozygotes. Also, no associations were found in the subgroup analyses.

**CONCLUSION:** We found no association between the UGT1A1*28 genotypes and ALL in children.

Development of acute lymphoblastic leukemia (ALL) in children is believed to involve at least two genetic "hits." The nature of these presumed "hits" and the factors associated with them have not yet been adequately described, but the first "hit" is assumed to often take place *in utero* (1). Furthermore, sex, birth weight, and birth order have been suggested as risk factors (2,3). A possible risk factor for the development of ALL is oxidative stress because previous studies have shown a relationship between neonatal oxygen supplementation and later development of ALL (4,5).

Bilirubin is a potent endogenous antioxidant with documented antioxidative effects *in vitro* and *in vivo* (6,7). The possible clinical relevance of bilirubins antioxidative effects has been explored in adults, were observational studies of pulmonary function, cardiovascular disease, cancer and all-cause mortality have indicated protective associations (8–10). *In vitro* studies, observational data and a single interventional trial suggest that bilirubin may be particularly important as an antioxidant in the neonatal period and in the preterm population. However, outside the first months of life bilirubin as an antioxidant has not been investigated in the pediatric population (11–13).

A challenge to the interpretation of observational studies on bilirubin is the possibility of reverse causation and potential confounding by sex, body mass index, diet, and smoking (14,15).

A way of addressing possible confounding and reverse causality in observational studies is by employing genes as instrument variables for the phenotype of interest (Mendelian randomization) (16). If a genotype has a well-characterized relationship with a phenotype, this can be utilized to estimate the effect of the phenotype upon an exposure of interest. As the genotype is assigned randomly from parental genotypes at birth the estimate will be un-confounded by external factors and reverse causality will not be an issue (16). For bilirubin, such a study design is possible utilizing a common genetic variant—the UGT1A1*28 allele.

The rate limiting enzyme in the metabolism of bilirubin is hepatic uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1). In the common genetic variant, the UGT1A1*28 allele, a thymine-adenine base pair has been inserted into the TATAA box of the promoter region of the *UGT1A1* gene, resulting in seven TA pairs instead of the usual six. The TATAA box controls expression of the *UGT1A1* gene, and UGT1A1*28 reduces the expression of hepatic UGT1A1 in a risk allele dose-response manner. UGT1A1*28 is the genotype behind Gilbert-Meulengracht's syndrome and the main known genetic cause of variations in plasma bilirubin in Western European populations accounting for ~18% of all variations (17–21). The allele frequency and high correlation to plasma bilirubin variations make UGT1A1*28 a possible instrument variable for bilirubin. This has been used in previous studies on the possible importance of bilirubin in association with cardiovascular disease, inflammatory bowel disease and colorectal cancer (18,22,23).

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Hence, we investigated the relation between UGT1A1*28 genotypes and the development of ALL in children in a case–control study, encompassing incident cases in Denmark 1982–2010.

## RESULTS

Between 1982 and 2010, 903 incident cases of ALL in children 1–14 y old were present in the two databases; 679 could be identified in the biobank and had a dried blood spot deemed suitable for further analysis. For 14 of these, either DNA amplification or genotyping failed, making genotypes for 665 cases available for the study. In all, 1,419 controls had a blood spot drawn from the biobank for the study. In 40 of these, DNA amplification or genotyping failed; consequently a genotype was available in 1,379 controls. Baseline characteristics of cases and controls are shown in **Table 1**.

**Table 1.** Baseline clinical characteristics for controls ($N = 1,379$) and cases ($N = 665$) (column statistics)

| Characteristic | | Controls | Cases |
|---|---|---|---|
| Sex | Boys | 51.5% (710) | 56.4% (375) |
| | Girls | 48.5% (669) | 43.6% (290) |
| Birth decade | 1981–1989 | 34.5% (476) | 34.4% (229) |
| | 1990–1999 | 41.0% (565) | 40.8% (271) |
| | 2000–2009 | 24.5% (338) | 24.8% (165) |
| ALL type | T-cell ALL | – | 12.3% (82) |
| | Pre–B-cell ALL | – | 86.3% (574) |
| | t(12;21) positive | – | 7.7% (51) |
| Age at onset | 1–4 y | – | 61.5% (409) |
| | 5–9 y | – | 25.9% (172) |
| | 10–14 y | – | 12.6% (84) |

**Table 2.** Sex and birth decade adjusted odds ratios (95% confidence intervals) of acute lymphoblastic leukemia in children for UGT1A1*28 allele genotypes

| Genotype | Controls ($n = 1,379$) | Cases ($n = 665$) | OR[a] | 95% CI |
|---|---|---|---|---|
| 6/6 | 658 (47.7%) | 320 (48.1%) | Ref. | Ref. |
| 7/6 | 589 (42.7%) | 276 (41.5%) | 1.01 | (0.87–1.16) |
| 7/7 | 132 (9.6%) | 69 (10.4%) | 1.01 | (0.77–1.34) |

UGT1A1*28 allele is referred to as 7, common genotype as 6.
[a]Adjusted for sex and birth decade.

The genotypes amongst the controls were in Hardy-Weinberg equilibrium ($P = 0.94$).

No association was found between ALL and UGT1A1*28 genotype. Using participants with the common genotype as a reference group, the odds ratio (OR) of ALL per UGT1A1*28 allele was 1.01 (0.88–1.17), making the OR for heterozygotes 1.01 (0.88–1.17) and 1.02 (0.77–1.36) for homozygotes. Treating genotype as a categorical variable gave similar estimates (data not shown). There was no evidence of an effect modification by sex or birth decade (data not shown), and adjusting for these by logistic regression left point estimates and confidence intervals almost unchanged. Fully adjusted ORs of ALL in childhood for genotypes are presented in **Table 2**.

For the pre–B-cell ALL, the T-cell ALL, the t(12;21) translocation positive, and age at onset in the predefined intervals no association between genotype and outcome was found for unadjusted and adjusted estimates. Fully adjusted ORs for secondary outcomes are presented in **Tables 3** and **4**.

## DISCUSSION

In this study, the UGT1A1*28 genotype was not associated with the risk of ALL in childhood.

The UGT1A1*28 genotype has drawn considerable attention in adult studies in recent years, primarily because of its influence on plasma bilirubin levels and the possibly associated increased antioxidative capacity (24). That the genotype is not associated with risk of ALL in children points toward bilirubin not having a relevant protective effect against this disease. However, some studies indicate that in the first days of life, UGT1A1 enzyme activity is very low, and correspondingly UGT1A1*28 genotype seems to have limited effect on serum levels of bilirubin at this age (25–28). Thus, if oxygen is primarily a risk factor for childhood ALL in the first minutes of life and/or in levels above atmospheric pressure, examining allele status will not be a relevant test of bilirubin's potential protective effect. A recent Danish register-based study with Apgar score as exposure does seem to suggest that the first minutes of life could be a particularly vulnerable period for the later development of some childhood cancers (29). Umbilical cord concentrations of bilirubin may be a more relevant measure of bilirubin exposure during the first days of life (30).

A main strength of our study is the completeness and nationwide coverage. Furthermore, the existence of a unique biological resource, the Danish Neonatal Screening Biobank, gave us

**Table 3.** Sex and birth decade adjusted odds ratios (95% confidence intervals) of acute lymphoblastic leukemia with age at onset in the intervals 1–4 y, 5–9 y, and 10–14 y for UGT1A1*28 genotypes

| Genotype | Controls ($n = 1,379$) | Age at ALL onset 1–4 y ($n = 409$) | OR[a] | Age at ALL onset 5–9 y ($n = 172$) | OR[a] | Age at ALL onset 10–14 y ($n = 84$) | OR[a] |
|---|---|---|---|---|---|---|---|
| 6/6 | 658 (47.7%) | 195 (47.7%) | Ref. | 88 (51.2%) | Ref. | 37 (44.1%) | Ref. |
| 7/6 | 589 (42.7%) | 173 (42.3%) | 1.01 (0.85–1.20) | 61 (35.5%) | 1.01 (0.79–1.28) | 42 (50.0%) | 0.99 (0.71–1.40) |
| 7/7 | 132 (9.6%) | 41 (10.0%) | 1.02 (0.73–1.43) | 23 (13.4%) | 1.01 (0.63–1.63) | 5 (5.9%) | 0.99 (0.50–1.96) |

UGT1A1*28 allele is referred to as 7, common genotype as 6.
[a]Adjusted for sex and birth decade.

**Table 4.** Sex and birth decade adjusted odds ratios (95% confidence intervals) of pre–B-cell acute lymphoblastic leukemia (ALL), T-cell ALL, and the t(12;21) translocation positive ALL for UGT1A1*28 genotypes

| Genotype | Controls (*n* = 1,379) | Pre–B-cell ALL (*n* = 574) | | T-cell ALL (*n* = 82) | | t(12;21) positive (*n* = 51) | |
|---|---|---|---|---|---|---|---|
| | | | OR[a] | | OR[a] | | OR[a] |
| 6/6 | 658 (47.7%) | 276 (48.1%) | Ref. | 42 (51.1%) | Ref. | 27 (52.9%) | Ref. |
| 7/6 | 589 (42.7%) | 241 (42.0%) | 1.00 (1.00–1.16) | 28 (34.2%) | 1.02 (0.73–1.43) | 18 (35.3%) | 0.93 (0.61–1.44) |
| 7/7 | 132 (9.6%) | 57 (9.9%) | 1.00 (0.74–1.34) | 12 (14.6%) | 1.05 (0.53–2.06) | 6(11.8%) | 0.87 (0.38–2.07) |

UGT1A1*28 allele is referred to as 7, common genotype as 6.
[a]Adjusted for sex and birth decade.

the opportunity to test the association between UGT1A1 *28 and ALL in childhood in cases compiled over 30 y.

This has led to a reasonably large sample size and a correspondingly high power, reflected in the quite narrow confidence intervals for the primary outcomes.

Case status in the Danish Registry of Childhood Cancer has been meticulously validated and is to the best of our knowledge nationally complete for the study period, making risk of misclassification for both cases and controls negligible.

Of the 903 possible cases, we could not obtain genotypes for 238 (26%). Reasons for cases missing in the biobank were that parents or patients had chosen the dried blood spot not to be available for research purposes, that initial screening analysis or lather research projects not had left enough material for DNA extraction to be done, or that the dried blood spot was in poor condition. This loss of cases is in all likelihood unrelated to both genotype and outcome, and we do not consider it a potential bias in our estimates.

It is known that UGT1A1*28 genotype frequencies vary with ethnicity (19). However, the Danish population is relatively ethnically homogenous, race is considered of little importance to the incidence of ALL in children, and the observed UGT1A1*28 genotype frequencies correspond well to the expected for a North European population (18,31). Consequently, we do not consider population stratification a potential confounder in our study.

Maternal age, birth order, and birth weight have documented association to ALL in childhood, and are not adjusted for in the logistic regression model. However, as these risk factors expectedly are unrelated to genotype, we do not consider this a potential bias in our estimates.

A limitation in the interpretation of our data is the lack of bilirubin levels for cases and controls and the lack of data on association between UGT1A1*28 genotypes and plasma bilirubin for children after the neonatal period. Associations between plasma bilirubin concentration and UGT1A1*28 genotypes are well established in the adult Danish population (18), and as the UGT1A1*28 allele is a functional polymorphism effect upon UGT1A1 activity seems plausible to be similar for children and adults. However, the effect of altered enzymatic activity on plasma bilirubin concentration could differ between age groups. Hepatic UGT1A1 has marked pleiotropy and metabolizes other endogen and exogenous substances besides bilirubin (19). Although we cannot exclude the existence of a geographically specific UGT1A1 metabolized substance with an impact on ALL in children, no evidence of potential candidates has been published to date. We therefore believe that the external validity of our study is good.

The existence of the Nordic Society for Paediatric Haematology and Oncology database additionally allowed us to do further analysis for a number of subgroups within our primary case population. Analysis was performed on age at onset in three groups to test for the effect modification of age and allow for an induction time of genotype. Separate analysis was also done for pre–B-cell ALL and T-cell ALL as they constitute two distinct forms of childhood ALL and for the t(12;21) positive cases as this chromosomal translocation is most convincingly shown to be congenital in origin (1,32,33).

No association between genotype and outcome was found for any of the secondary outcomes. The smaller numbers of cases in these groups means that the statistical strength is more limited as reflected in wider confidence intervals, but the precision of estimates was still good for most subgroup estimates.

The UGT1A1*28 allele is in the adult one of the strongest available genetic instrumental variables for an endogenous anti-oxidant. Further studies into its potential effects could be relevant for other pediatric out-comes. Such studies could resource effectively be executed within the framework of the Danish Neonatal Screening Biobank, the Danish National Patient Register and several other more specialized diagnostic registers. Bilirubin is highly photosensitive, and cannot be estimated from dried blood spots. Separate studies to explore the relationship between plasma bilirubin concentrations and UGT1A1*28 genotypes in the pediatric population would there for be relevant.

As umbilical cord concentrations of plasma bilirubin, rather than UGT1A1*28 genotypes, may provide a useful measure of bilirubin exposure in the first days of life this measure should be considered in research aiming to estimate perinatal exposures associations to later outcomes.

In conclusion, we found no association between the UGT1A1*28 genotypes and ALL in children.

## METHODS

### Setting

The study was done in Denmark, which has a public health care system that grants universal access to both primary and specialized care.

### Materials

Our study combined clinical information from The Danish Registry of Childhood Cancer and the registry of the Nordic Society for Paediatric Haematology and Oncology, with genotypes assessed using

dried blood spot samples stored in the Danish Newborn Screening Biobank.

The Danish Registry of Childhood Cancer, which contains a complete and validated register of all children with ALL in Denmark (34), was used to identify incident cases of ALL cases amongst children 1982–2010. The registry of the Nordic Society for Paediatric Haematology and Oncology encompasses clinical variables on Scandinavian ALL cases since 1982 (35,36). From this registry data on ALL subtypes (pre–B cell or T cell), t(12;21) status and age at onset were obtained for cases.

As part of the Danish national neonatal screening for metabolic diseases, a dried blood spot sample is collected from all newborn infants shortly after birth. Since 1982, the excess dried blood spots have been stored in the Danish Neonatal Screening Biobank, which today covers about 99% of all children born after 1982 (37).

All Danish citizens are at birth assigned a unique 10-digit civil registration number (CPR), which gives information on date of birth and sex and allows unambiguous individual-level identification and data linkage across nationwide public health registers (38).

Our study utilized the CPR number to identify cases in the Danish Newborn Screening Biobank. The controls were selected by taking blood spot samples stored in front of and behind a case in the biobank. As the dried blood spot samples in the biobank are stored chronologically in the original packages from local sample sites, this ensured a frequency match between the case and control populations with regard to time and, to some extent, geography.

From each of the dried blood spot samples two 3.2 mm disks were punched, DNA extracted, and subsequently whole-genome amplified (wgaDNA) in triplicates, as previously described (39). Genotyping of wgaDNA made from dried blood spot samples has been shown to be feasible and valid (40). Genotyping was performed at LGC Genomics (Teddington, UK) using a custom made Kompetitive Allele Specific PCR genotyping assay. The genotyping laboratory had no knowledge of the identity of either individual samples or the type of project the samples came from.

### Statistical Methods

The STATA statistical software package version 12.1 (StataCorp, College Station, TX) was used for statistical analyses. Hardy-Weinberg equilibrium for genotype frequencies was explored for controls with the *hwsnp* command. Associations between genotype and outcome were expressed as ORs using logistic regression with participants with the common genotype as the reference group. Due to the dose–response relationship between UGT1A1*28 genotypes and plasma bilirubin, the genotypes were in primary analysis treated as a continuous variable (0, 1, and 2) and secondarily tested as categorical. Confidence intervals are reported with 95% limits.

*A priori*, we decided to control for sex and birth decade as categorical covariates in the logistic models. Testing for a potential effect modulation by covariates was done by fitting interaction terms and inspecting the *P* values of these for statistical evidence against no interaction, and further by stratifying the analysis on covariates and inspecting results.

Subgroup analysis was done for age at onset in three groups (1–4 y, 5–9 y, and 10–14 y), and for the ALL subtypes: precursor B cell, T cell and t(12;21) translocation positive status.

### Ethics

The study was approved by the regional Ethics Committees on Human Studies (Jr.nr. M-20110288), the Danish Data Protection Agency (Sagsnr. 1-16-02-238-11), and the Danish Neonatal Biobank Steering Committee and conducted according to the principles of the Declaration of Helsinki. According to Danish law, the regional Ethics Committee can grant exemption from obtaining informed consent for research projects based on biobank material under certain circumstances. For this study, such an exemption was granted.

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