**CISH** promoter polymorphism effects on T cell cytokine receptor signaling and type 1 diabetes susceptibility

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**Abstract**

**Background:** Impaired regulatory T cell immunity plays a central role in the development of type 1 diabetes (T1D). Interleukin-2 receptor (IL-2R) signaling is essential for regulatory T cells (T\textsubscript{REG}), and cytokine-inducible SH2-containing protein (CIS) regulates IL-2R signaling as a feedback inhibitor. Previous studies identified association of CISH promoter region single nucleotide polymorphisms (SNPs) with susceptibility to infectious diseases.

**Methods:** Here we analyzed allele frequencies of three CISH SNPs (i.e., rs809451, rs414171, rs2239751) in a study of T1D patients (n = 260, onset age < 5 years, duration > 10 years). Minor allele frequencies were compared to a control cohort of the 1000 Genomes Project. Assigned haplotypes were determined for effects on T1D manifestation and severity. Finally, the CISH haplotype influence on cytokine signaling and function was explored in T cells from healthy donors.

**Results:** We detected similar minor allele frequencies between T1D patients and the control cohort. T1D onset age, residual serum C-peptide level, and insulin requirement were comparable between different haplotypes. Only minor differences between the haplotypes were found for in vitro cytokine (i.e., IL-2, IL-7)-induced CIS mRNA expression. STATS phosphorylation was induced by IL-2 or IL-7, but no differences were found between the haplotypes. T\textsubscript{REG} purified from healthy donors with the two most common haplotypes showed similar capacity to inhibit heterologous effector T cells.

**Conclusions:** This study provides no evidence for an association of CISH promoter SNPs with susceptibility to T1D or severity of disease. In contrast to previous studies, no influence of different haplotypes on CIS mRNA expression or T cell-mediated functions was found.

**Keywords:** CIS, CISH, Single nucleotide polymorphisms, IL-2, Regulatory T cells, Effector T cells

**Background**

Type 1 diabetes (T1D) is a chronic autoimmune disease characterized by the destruction of pancreatic β cells. Autoreactive effector T cells are involved in T1D pathogenesis, and impaired regulatory T cell (T\textsubscript{REG}) functions promote self-reactive effector T cells [1, 2]. T\textsubscript{REG} crucially depend on IL-2, and IL-2 receptor (IL-2R) variants are associated with increased susceptibility to T1D [3]. T1D-associated IL-2R variants affect T\textsubscript{REG} phenotype and function [4]. Therefore, decreased IL-2R signaling is assumed to be central for impaired T\textsubscript{REG} function in T1D pathogenesis [5]. IL-2R expression and signaling of T cells are tightly regulated, and cytokine-inducible SH2-containing protein (CIS), a member of the suppressor of cytokine signaling (SOCS) family, contributes as a feedback inhibitor [6]. The CIS protein (encoded by the CISH gene) plays a role in T cell activation and cytokine-induced proliferation [7]. Several cytokines (including IL-2 and IL-7) induce CIS expression during receptor binding mediated by the Jak/STAT pathway [8]. CIS expression is induced within few hours and inhibits...
IL-2R signaling by binding of the IL-2Rβ chain and blocking of STAT5 phosphorylation [9, 10].

Previous studies demonstrated important roles of CIS on T cell function during allergic, malignant, and infectious diseases [11–13]. These studies showed that CIS regulated T cell activation and polarization of CD4+ and CD8+ T cells [12, 13]. Furthermore, genetic CISH variants were found to be associated with susceptibility to infectious diseases including tuberculosis [11, 14, 15]. Tuberculosis-associated single nucleotide polymorphisms (SNPs) (i.e., rs809451, rs414171, rs2239751) are located in CISH promoter regions and were accompanied with differential CIS expression [11, 16]. Tuberculosis risk allele (i.e., rs414171T/rs809451C) carriers had decreased CIS mRNA expression after IL-2 in vitro stimulation and increased IL-10 serum levels [16]. This suggested increased T REG function of tuberculosis risk allele carriers due to decreased CIS expression [16].

In the present study, we addressed the question if CISH SNPs are associated with susceptibility to develop T1D and/or with age at onset and disease severity. We determined minor allele frequencies (MAFs) of three CISH SNPs in patients with early-onset and long-term T1D and compared results with controls from the 1000 Genomes database (www.internationalgenome.org) [17]. In addition, we characterized the effects of CISH SNPs on cytokine-induced T cell functions.

**Methods**

**Patients and healthy controls**

Two hundred sixty patients with T1D (mean age 16.4 years, range 10.7–20.9 years; onset age < 5 years, > 10 years diabetes duration) were recruited for the pediatric diabetes biobank within the German Center for Diabetes Research (DZD). Further information on selection and characteristics of the study cohort has been given previously [18]. Healthy adult donors were recruited from the staff working at the University Hospital Duesseldorf (n = 14).

**Genotyping of CISH SNPs**

DNA was isolated from peripheral blood using QIAamp DNA Mini Kit (Qiagen). TaqMan assays (Applied Biosystems) were used for genotyping of three CISH SNPs (i.e., rs809451, rs414171, rs2239751). CISH SNP inheritance was analyzed, and linkage disequilibrium was estimated using a publically available tool (https://anaylistools.nci.nih.gov/LDlink). The structure of the CISH gene region and SNP localization within the promoter region (chromosome 3). Dependency in inheritance of SNPs is indicated as linkage disequilibrium coefficients (R², estimated according to https://anaylistools.nci.nih.gov/LDlink). Three respective haplotypes were assigned (H1/H2/H3).

**Parameters of T1D severity**

Residual random serum C-peptide levels and daily insulin requirement were used as proxies for disease severity. C-peptide was measured with a high-sensitivity assay [18]; data on insulin requirement were retrospectively obtained from the German/Austrian nationwide DPV registry [18].

**In vitro T cell assays**

For quantification of cytokine-induced CIS mRNA expression and STAT5 phosphorylation, peripheral blood mononuclear cells (PBMCs) from healthy donors genotyped for CISH SNPs rs809451, rs414171, and rs2239751 were isolated and stored in liquid nitrogen. Samples were then concomitantly thawed for in vitro assays. For measurement of CIS mRNA expression, PBMCs were stimulated with IL-2 (100 IU/ml, Sigma-Aldrich) or IL-7 (10 ng/ml, Sigma-Aldrich) for 1 or 2 h. mRNA was then isolated and reverse transcribed. CIS
mRNA was quantified by real-time quantitative (q)PCR as described previously [20]. A non-stimulated PBMC sample was used to determine ex vivo CIS expression in PBMC. GAPDH was used as a qPCR house-keeping control [20].

For STAT5 phosphorylation, PBMCs were stimulated with IL-2 (10 IU/ml) or IL-7 (1 ng/ml) for 15 min and simultaneously stained with a monoclonal antibody against CD4-PacificBlue (OKT4, BioLegend). PBMCs were immediately fixed thereafter using fixation/permeabilization buffer (True-Nuclear-kit, BioLegend) according to manufacturer’s instructions. Samples were then stained with a monoclonal antibody against pSTAT5-PE (SRBCZX, eBioScience) and measured by flow cytometry (LSRFortessa, BD). Analyses were done using FlowJo software (Miltenyi Biotech). Representative depictions of flow cytometry data are provided as part of Fig. 3b.

For the regulatory T cell assay, freshly isolated PBMC from healthy donors genotyped for CISH SNPs were enriched for TREG using the CD4+CD25+CD127dim/− Regulatory T Cell Isolation Kit II and by magnetic cell sorting (MACS) (both BD Biosciences) according to the manufacturer’s instructions. The purity of enriched TREG cells was determined by flow cytometry using the following antibodies: CD4-PacificBlue (OKT4, BioLegend), CD127-A647 (HIL-7R-M21, BD Biosciences), CD25-PeCy7 (2A3, BD Biosciences). Only samples containing more than 95% enriched TREG cells were included. Heterozygous CD3+ T cells (termed “effector T cells” (TEFF) throughout) were enriched using the non-contact T Lymphocyte Enrichment Kit and MACS technology (both BD Biosciences). A purity of more than 95% was confirmed by flow cytometry using monoclonal antibodies for CD3-APC (UCHT1, BD Biosciences). TEFF were labeled with carboxyfluorescein succinimidyl ester (CFSE) proliferation dye (eFluor™ 450, Thermo Fisher) following the manufacturer’s instructions. TEFF (1 × 10^5) alone or in co-culture with different concentrations of TREG (i.e., 2.5 × 10^4, 5 × 10^4, 1 × 10^5) were then stimulated with CD3/CD28 beads (1 μl, Gibco) for 4 days in RPMI medium containing 10% human AB serum and 1% penicillin/streptomycin. CFSE dilution indicating cellular division of effector T cells was measured by flow cytometry (LSRFortessa, BD). Analyses were performed using FlowJo software (Miltenyi Biotech). Representative flow cytometry histograms are provided in Fig. 4a.

Statistical analysis
MAFs for CISH SNPs were calculated according to standard methods and compared to the European (EUR) cohort from the 1000 Genomes Project [17] using Fisher’s exact test; 95% confidence intervals (CI) were calculated with the Newcombe method. The Mann-Whitney U test was applied to compare disease characteristics (i.e., onset age, C-peptide level, insulin dose) between haplotypes. Further, the Friedman test was used to evaluate the effect of IL-2 and IL-7 stimulation on CIS mRNA expression and pSTAT5 induction between haplotypes as well as for the effect of different TREG/TEFF ratios on TEFF proliferation. Two-tailed p values below 0.05 were considered statistically significant. All analyses and figure preparations were performed with GraphPad Prism (Version 7.0a. GraphPad Software) and SAS for Windows version 9.4 (SAS Institute, Cary, North Carolina, USA).

Results
In a cohort of 260 T1D patients from the pediatric diabetes biobank (German Center for Diabetes Research, DZD), three CISH promoter SNPs (i.e., rs809451, rs414171, rs2239751) were analyzed. We found comparable MAFs for rs809451 (11.3%) and rs414171 (12.1%) (Table 1). This similarity was due to a strong linkage disequilibrium between these SNPs (R^2 = 0.92), whereas inheritance of the rs2239751 SNP was largely independent from rs414171 (R^2 = 0.06) and rs809451 (R^2 = 0.002) (Fig. 1a). The rs2239751 MAF was low (0.8%) and homozygous carriers were not found (Table 1). Next, we

### Table 1 CISH SNP genotype frequencies of T1D patients and controls

| SNP ID     | Genotype | Frequencies | MAF T1D | MAF control group* | Observed difference (95% CI) | p value |
|------------|----------|-------------|---------|--------------------|-----------------------------|---------|
| rs414171   | T/T      | 2 (0.8%)    | 12.1%   | 11.6%              | 0.49% (−2.82; 4.08)          | 0.81    |
|            | T/A      | 59 (22.7%)  |         |                    |                             |         |
|            | A/A      | 199 (76.5%) |         |                    |                             |         |
| rs809451   | C/C      | 2 (0.8%)    | 11.3%   | 11.0%              | 0.31% (−2.90; 3.82)          | 0.86    |
|            | C/G      | 55 (21.2%)  |         |                    |                             |         |
|            | G/G      | 203 (78.1%) |         |                    |                             |         |
| rs2239751  | C/C      | 0 (0.0%)    | 0.8%    | 0.6%               | 0.17% (−0.67; 1.41)          | 0.74    |
|            | C/A      | 4 (1.5%)    |         |                    |                             |         |
|            | A/A      | 256 (98.5%) |         |                    |                             |         |

*According to 1000 Genomes database (EUR cohort), n = 503; 260 T1D patients were included.
compared MAFs of T1D patients with data from a European cohort genotyped as part of the 1000 Genomes Project \((n = 503)\) (Table 1). We detected similar MAFs and no significant differences between both cohorts (Table 1).

Characterization of SNPs rs809451, rs414171, and rs2239751 led to the assignment of three haplotypes \((H1, H2, H3, \text{Fig. 1b})\). The vast majority of T1D patients had the homozygous genotype \(H1/H1\) \((n = 199)\) whereas a lower proportion was heterozygous for \(H1\) and \(H2\) \((H1/H2, n = 55)\). Hardly any T1D patients with homozygous \(H2\) \((H2/H2, n = 2)\) or \(H3\) (heterozygous \(H1/H3; n = 4)\) genotypes were identified (Fig. 2). To investigate a possible influence of haplotypes on T1D disease manifestation and severity, we compared T1D onset age, serum C-peptide levels, and insulin requirement between T1D patients with different haplotypes (Fig. 2). No differences in age at manifestation (Fig. 2a), C-peptide levels (Fig. 2b), or daily insulin requirement (Fig. 2c) were found. These results did not suggest an association of \(CISH\) promoter SNPs with manifestation age or severity of T1D.

Previous studies described impaired IL-2 induced CIS expression of T cells with \(H2\) \([11, 16]\). We applied IL-2 and IL-7 in vitro T cell stimulation for comparison of samples from healthy individuals assigned to the three genotypes (i.e., homozygous \(H1/H1\), \(H2\) carrier \((H1/H2\) and \(H2/H2)\), and \(H3\) carrier \((H1/H3); \text{Fig. 3})\). Because of the low frequency of homozygous \(H2\) carriers, only one homozygous \(H2\) donor was included. In vitro stimulation with IL-2 or IL-7 for 1 and 2 h induced an increase of CIS mRNA expression (both \(p < 0.001\), Fig. 3a). We detected no differences between the three genotypes 1 or 2 h after stimulation.

To determine functional effects of \(CISH\) haplotypes on cytokine receptor signaling, we measured IL-2 and IL-7 induced STAT5 phosphorylation for the same study groups (Fig. 3b). Both IL-2 and IL-7 increased pSTAT5 \((all \, p < 0.001)\) without perceptible differences between the three genotypes (Fig. 3b).

Finally, we compared \(T_{\text{REG}}\) from the two dominant genotypes \(H1/H1\) and \(H1/H2\) for their in vitro ability to limit \(T_{\text{EFF}}\) proliferation. Different proportions of \(T_{\text{REG}}\) were co-cultured with allogenic effector T cells, and effector cell proliferation was measured after 5 days (Fig. 4a). A significant reduction of \(T_{\text{EFF}}\) proliferation was detected when \(T_{\text{REG}}\) were added and the effects increased with higher \(T_{\text{REG}}\) proportions \((p = 0.005\), Fig. 4b). However, comparable \(T_{\text{REG}}\) effects were found for samples from \(H1/H1\) and \(H1/H2\) carriers. We concluded that no association of \(CISH\) SNPs with susceptibility to T1D was detectable and that haplotypes had no influence on IL-2/IL-7 signaling or \(T_{\text{REG}}\) functions.
Discussion

This study showed that CISH promoter SNP rs809451, rs414171, and rs2239751 frequencies were comparable between patients with early onset of T1D and controls from the publicly available 1000 Genomes database. Therefore, no evidence for an association of CISH promoter variants and susceptibility to develop T1D was detected. Available cohort sizes restricted the sensitivity of this study and moderate effects of CISH SNPs cannot be excluded. In addition, the 1000 Genomes Project cohort comprised individuals from different European regions and, therefore, effects due to ethnic differences between study groups are possible [17].

We detected no differences in T1D manifestation age between different haplotypes. However, all T1D patients included in the present study had an early onset of T1D below 5 years of age and this preselection limited differences in onset age between haplotypes. Differences in disease course are indicated by residual β-cell activity—measured by residual C-peptide levels—and daily insulin requirements of T1D patients. We detected no differences between the haplotypes for these parameters. Thus, these results do not suggest haplotype-dependent effects on autoimmune mechanisms and disease course in T1D patients.

Previous studies suggested a role of CISH promoter SNPs on CIS mRNA expression [11, 16]. Whereas Khor
et al. detected CIS mRNA expression differences only for the homozygous minor allele carriers (H2/H2 according to the nomenclature used here) [11], Sun et al. also detected decreased CIS mRNA for heterozygous (H1/H2) patients carrying the rs809451 minor allele [16]. Only one H2/H2 carrier was found among healthy individuals recruited and, therefore, we were not able to reproduce the results for the homozygous H2 genotype. In contrast to Sun et al. [16], we detected no differences in CIS mRNA for H1/H2 carriers as compared to H1/H1 carriers. In addition, we did not detect H1/H2 effects on IL-2 induced STAT5 phosphorylation. Differences between rs809451 and rs414171 minor allele carriers described [16] could not be reproduced in the present study because of the strong linkage disequilibrium between these SNPs.

In addition, the study by Sun et al. found differences in IL-10 serum levels of rs414171 minor allele carriers [16]. These findings suggested functional effects of CISH haplotypes on T_REG, the main producers of IL-10 [22], described differences in IL-10 serum levels may be explained by non-T_REG-mediated mechanisms.

Our results do not suggest a role of CISH SNPs in the susceptibility to T1D, whereas other reports showed an association with susceptibility to infectious diseases [11]. CIS is involved in the regulation of several cytokines including IL-7, which is crucial for naïve and memory T cell homeostasis and may promote autoreactive T cell responses in T1D [23]. Therefore, a possible role of CIS in T1D may be more complex and not based on impaired cytokine-induced CIS expression of different haplotypes. In accordance, multiple roles of CIS in different immune cell populations have been described [12, 13, 24]. Further analyses are needed to address this question.

**Conclusions**

This study provides no evidence for an association of CISH promoter SNPs with susceptibility to T1D or severity of the disease. In contrast to previous studies that demonstrated marked effects of CISH SNPs on T cells, no influence of different haplotypes on CIS mRNA expression or T cell-mediated functions was found. Further studies are needed to address the question, how CISH...
variants mechanistically carry out their role during allergic, malignant, and infectious diseases.

Additional file

Additional file 1: Figure S1. Post-hoc power calculations and confidence intervals for MAF differences. (PPTX 99 kb)

Abbreviations
CIS: Cytokine-inducible SH2-containing protein; IL-2R: Interleukin-2 receptor; MAFs: Minor allele frequencies; PBMCs: Peripheral blood mononuclear cells; SNP: Single nucleotide polymorphism; T1D: Type 1 diabetes; Treg: Effector T cells; TREG: Regulatory T cells

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Availability of data and materials
The datasets generated and analyzed during the current study are available from the corresponding author on request.

Authors’ contributions
JS contributed to conceptualization of the study, performed experiments, analyzed and interpreted data, and wrote the manuscript. HA performed experiments, analyzed data, and reviewed/edited the manuscript. MJ designed the study, analyzed, and interpreted data, and wrote the manuscript. TM, JR, CB, RWH, and MR discussed results and reviewed/edited manuscript. MJ designed the study, analyzed, and interpreted data, and wrote the manuscript. TM, JR, CB coordinated the Pediatric Diabetes Biobank activities for patients with early-onset and long-term T1D within the German Center for Diabetes and the pediatric biobank. EM, TM, JR, CB, RWH, and MR discussed results and reviewed/edited manuscript. MJ designed the study, analyzed, and interpreted data and wrote the manuscript. All of the contributing authors approved the final version of the manuscript.

Ethics approval and consent to participate
The study was approved by the Ethical Committee of the Medical Faculty of the Heinrich Heine University Duesseldorf, Germany (reference number 4431 and 4444). Sample analyses were approved by the biobank consortium. Written informed consent was received from all donors (older than 14 years) and the children’s legal guardians.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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