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Polygenic risk score from steroid-sensitive nephrotic syndrome GWAS indicates overlapping genetic basis with steroid-resistant cases

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Pediatric idiopathic nephrotic syndrome (INS) includes steroid-sensitive (SSNS) and steroid-resistant (SRNS) forms, which differ in treatment response and prognosis. We constructed a polygenic risk score (PRS) using summary statistics from the largest pediatric SSNS GWAS meta-analysis (2,440 cases and 36,023 controls) and evaluated it in an independent Chinese cohort of 2,507 controls, 123 SRNS patients, and 493 SSNS patients. ANOVA showed significant between-group differences ($F(2, 3120) = 59.42$, $P < 2 \times 10^{-16}$). Post-hoc tests revealed higher PRS in SSNS than controls ($P < 0.001$), with SRNS intermediate but still elevated compared to controls ($P = 0.021$) and lower than SSNS ($P = 0.001$). The elevation of SSNS-derived PRS in SRNS suggests shared polygenic susceptibility between these clinically distinct forms of INS, indicating that overlapping common variants may converge on similar biological pathways and supporting the potential utility of PRS in genetic risk stratification and guiding precision management.

Idiopathic nephrotic syndrome (INS) is the most prevalent glomerular disorder among pediatric patients, representing a significant burden on pediatric nephrology. Clinically, children with INS can be classified into steroid-sensitive nephrotic syndrome (SSNS) and steroid-resistant nephrotic syndrome (SRNS) according to their response to standard corticosteroid therapy at disease onset. However, both conditions are associated with long-term complications, and varying degrees of genetic heterogeneity[1–3]. This clinical dichotomy suggests distinct underlying mechanisms, yet their fundamental genetic relationship remains poorly defined.

Recent advances in genome-wide association studies (GWAS) have identified numerous genetic loci associated with these conditions, highlighting the role of polygenic inheritance in their pathogenesis[4]. SRNS has been the focus of extensive genetic research, with approximately 30% of cases attributed to monogenic mutations, primarily involving genes related to podocyte function, such as *NPHS1*, *NPHS2*, *WT1*, and *PLCE1*[2,4–6]. These findings have led to the development of targeted therapies for specific genetic subtypes of SRNS. Notably, no comparable large-scale GWAS exists for SRNS, leaving its potential polygenic components completely uncharacterized. In contrast, large-scale genetic studies of SSNS have been limited, and its genetic architecture was largely unexplored until recently. The largest GWAS of pSSNS to date, a multi-population meta-analysis of 2,440 cases and 36,023 controls, identified eight significant risk loci, providing the first robust evidence for a polygenic contribution to this condition[7]. This emerging picture presents a compelling genetic contrast: SRNS is often characterized by highly penetrant, deleterious monogenic variants, whereas SSNS appears to be influenced by the cumulative effect of numerous common genetic variants of small effect.

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A critical gap remains in understanding the polygenic basis of SRNS, for which no large-scale GWAS exists. This is particularly relevant as most (~ 70%) of SRNS cases lack a monogenic explanation, implicating other genetic factors. The shared clinical and pathological features between SSNS and SRNS suggest they may represent a spectrum of disease. This raises a key hypothesis: SSNS and SRNS share a common polygenic susceptibility background, upon which additional genetic (e.g., rare monogenic variants) or non-genetic factors determine steroid response. The polygenic risk scores (PRS), which aggregates the weighted effects of multiple risk-associated single nucleotide polymorphisms (SNPs) into a single quantifiable metric, offers a promising approach to test this hypothesis. This method has demonstrated utility in dissecting the polygenic architecture of complex diseases[8–10], while explored in other kidney diseases[11], its potential to clarify the genetic relationship between INS subtypes remains untapped. Specifically, a PRS derived from SSNS GWAS can be used as an exploratory tool to assess whether SSNS and SRNS share aspects of their polygenic background. Under this framework, enrichment of the SSNS-derived PRS in SRNS patients relative to healthy controls would be consistent with some degree of shared polygenic susceptibility, whereas differences in PRS distributions between SSNS and SRNS may suggest heterogeneity in their underlying genetic contributions. This cross-phenotype PRS analysis provides an indirect approach to examining shared genetic architecture in the absence of large-scale SRNS GWAS data.

In this study, we leverage the largest available SSNS GWAS summary statistics to construct a PRS and evaluated it in an independent Chinese cohort (2,507 controls, 123 SRNS, 493 SSNS). It is critical to emphasize that this SSNS-derived PRS is not intended to predict SRNS risk, but serves as a tool to explore shared genetic susceptibility. Our objectives are twofold: (1) to assess the shared polygenic architecture by testing whether SSNS-derived PRS is elevated in SRNS patients compared to controls; (2) to evaluate distinct polygenic contributions by comparing PRS distributions between SSNS and SRNS patients.

Methods

Participants

The study population comprised 628 pediatric idiopathic nephrotic syndrome patients from Shandong Provincial Hospital Affiliated to Shandong First Medical University, comprising 127 steroid-resistant (SRNS) and 501 steroid-sensitive (SSNS) cases, with all diagnoses rigorously confirmed according to KDIGO 2025 Clinical Practice Guideline for the Management of Nephrotic Syndrome in Children. SSNS are defined as complete remission within 4 weeks of prednisone or prednisolone at standard dose. SRNS are defined as lack of complete remission within 4 weeks of daily prednisone or prednisolone at standard dose. Control subjects ($n = 2,506$) were selected from the Chinese Academy of Sciences (CAS) prospective multi-omics cohort, which includes 3,197 employees from various research institutions in Beijing, with exclusion of individuals reporting any history of idiopathic nephrotic syndrome or other kidney diseases through comprehensive questionnaire screening. Written informed consent was obtained from all participants or their legal guardians. The study protocol was approved by the Institutional Review Boards of Shandong Provincial Hospital Affiliated to Shandong First Medical University and Beijing Institute of Genomics, Chinese Academy of Sciences. All research procedures were conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.

Genotyping, quality control (QC) and imputation

Genotyping was performed using the Infinium Asian Screening Array platform following standard protocols. Stringent quality control measures were implemented, excluding samples demonstrating genotype call rates below 95%, gender mismatch, evidence of contamination, or genetic outliers from the Chinese Han population. Variant-level filtering removed SNPs located on non-autosomal chromosomes, those with missing call rates ≥ 5%, minor allele frequencies ≤ 1%, or showing significant deviations from Hardy-Weinberg equilibrium ($P \leq 1 \times 10^{-5}$). Population stratification was assessed through principal component analysis using the EIGENSTRAT method, Genotype imputation was conducted using Minimac3 with the 1000 Genomes Project Phase 3 version 5 reference panel to enhance genomic coverage.

PRS construction

The GWAS summary statistics used for polygenic risk score construction in this study were obtained from a multi-population GWAS meta-analysis comprising 2,440 cases and 36,023 controls from populations of Admixed American, African, East Asian, European, Maghrebian, and South Asian ancestries. To estimate posterior SNP effect sizes for PRS construction, we applied the advanced Bayesian polygenic prediction method PRS-CS[12].

PRS-CS is implemented as a Python-based command-line tool that infers posterior SNP effect sizes using GWAS summary statistics and an external LD reference panel. The method employs a Bayesian high-dimensional regression framework with continuous shrinkage (CS) priors, which allow for marker-specific adaptive shrinkage, meaning the amount of shrinkage applied to each genetic marker is adaptive to the strength of its association signal in GWAS. PRS-CS generates posterior SNP effect size estimates separately for each chromosome. Individual-level polygenic risk scores were then calculated by concatenating these per-chromosome files and applying PLINK's scoring function. It should be noted that the publicly available GWAS summary statistics are the combined trans-ancestry results; the ancestry-stratified statistics required for methods such as PRS-CSx[13] are not accessible. Therefore, we applied PRS-CS with an East Asian LD reference panel, which represents a widely adopted and practicable approach under the current data constraint. We employed the standard PRS-CS with default hyperparameters (a = 1, b = 0.5) and set the global shrinkage parameter phi (φ) to 1×10^{-2}, a value commonly used and well-justified for GWAS of comparable scale. It is important to note that, given the exploratory, group-level comparative nature of our study (as opposed to optimizing individual-level prediction), we did not perform parameter tuning (e.g., for φ) on an independent training dataset. The primary

GWAS summary statistics and our target cohort are entirely independent, ensuring a clean discovery-evaluation separation for testing our hypothesis of shared polygenic susceptibility.

Statistical analysis

All statistical analyses were performed using R version 4.3.3. The polygenic risk scores were first adjusted for potential confounding effects through general linear modeling incorporating the top five principal components and sex as covariates. The distributions of adjusted PRS values were then compared across diagnostic groups (healthy controls, SRNS patients, and SSNS patients) using one-way analysis of variance, with post-hoc pairwise evaluations conducted via Wilcoxon rank-sum tests to characterize specific between-group differences.

Results

Sample quality control and ancestry assessment

Following stringent sample-level quality control procedures, we excluded 12 individuals due to either low genotype call rates (< 95%, $n = 9$) or discrepancies between reported and genetically inferred sex ($n = 3$). After these exclusions, principal component analysis (PCA) was performed using reference data from the 1000 Genomes Project to assess ancestry composition and potential population outliers. The PCA plot (Fig. 1) demonstrated that all retained samples clustered tightly within the East Asian reference range, indicating a high degree of genetic homogeneity. No evidence of significant population stratification was detected, suggesting that downstream PRS analyses would not be confounded by major ancestry differences. The final analytical cohort comprised 2,506 controls, 123 SRNS patients, and 493 SSNS patients. The clinical characteristics of the study cohort are summarized in Table 1.

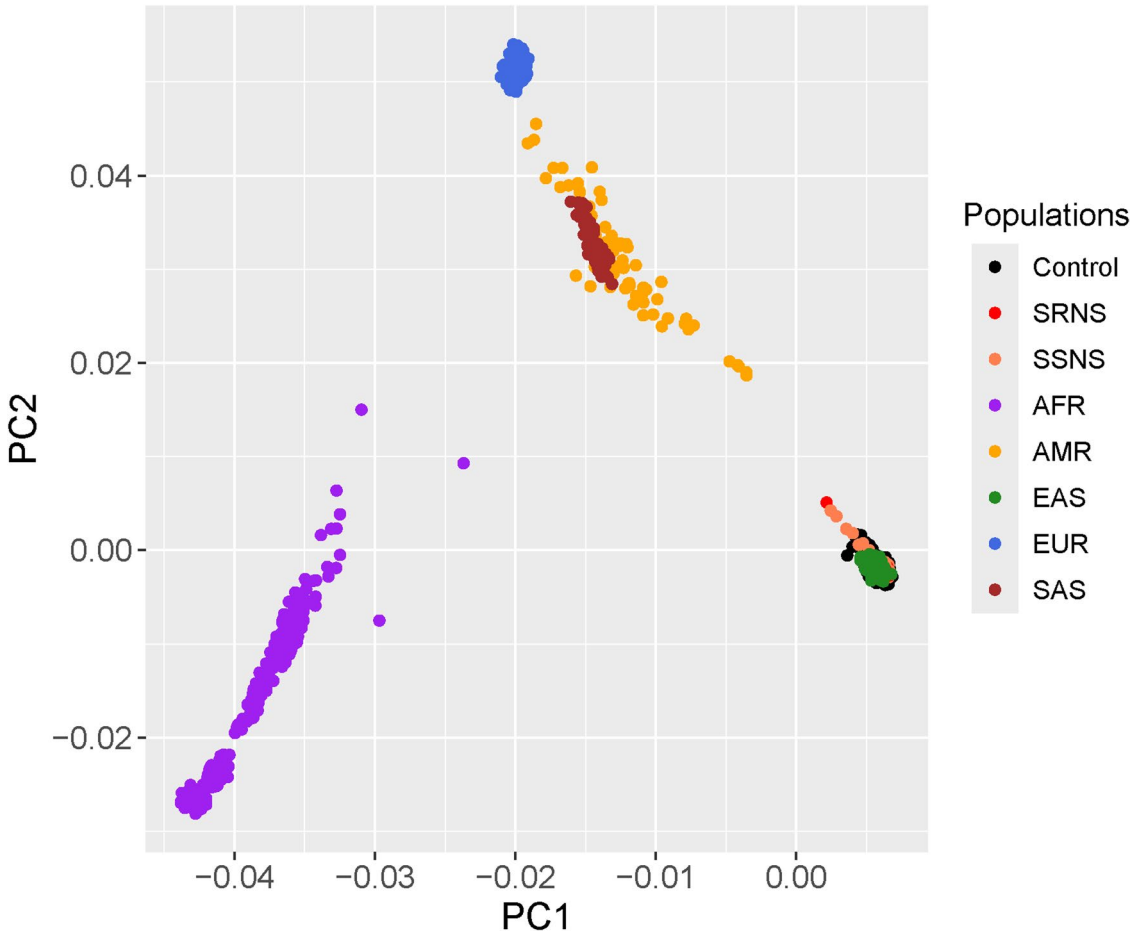

Fig. 1. Principal component analysis (PCA) for ancestry quality control in the Chinese cohorts. The plot displays genetic clustering patterns of SRNS cases (red), SSNS cases (pink) and controls (black) against HapMap3 reference populations: African (AFR, purple), Admixed American (AMR, orange), East Asian (EAS, green), European (EUR, blue), and South Asian (SAS, brown). PCA was performed using EIGENSTRAT, with PC1 and PC2 representing the first two principal components. All study samples (cases and controls) cluster within the East Asian (EAS) reference group (green), confirming the exclusively East Asian ancestry of the analyzed cohorts.

Sample size	Controls 2506	SSNS 501	SRNS 127
Sex			
Male	1226	373	77
Female	1280	128	50
Age	58.16 ± 6.01	4.98 ± 3.15	6.01 ± 3.74

Table 1. Clinical characteristics.

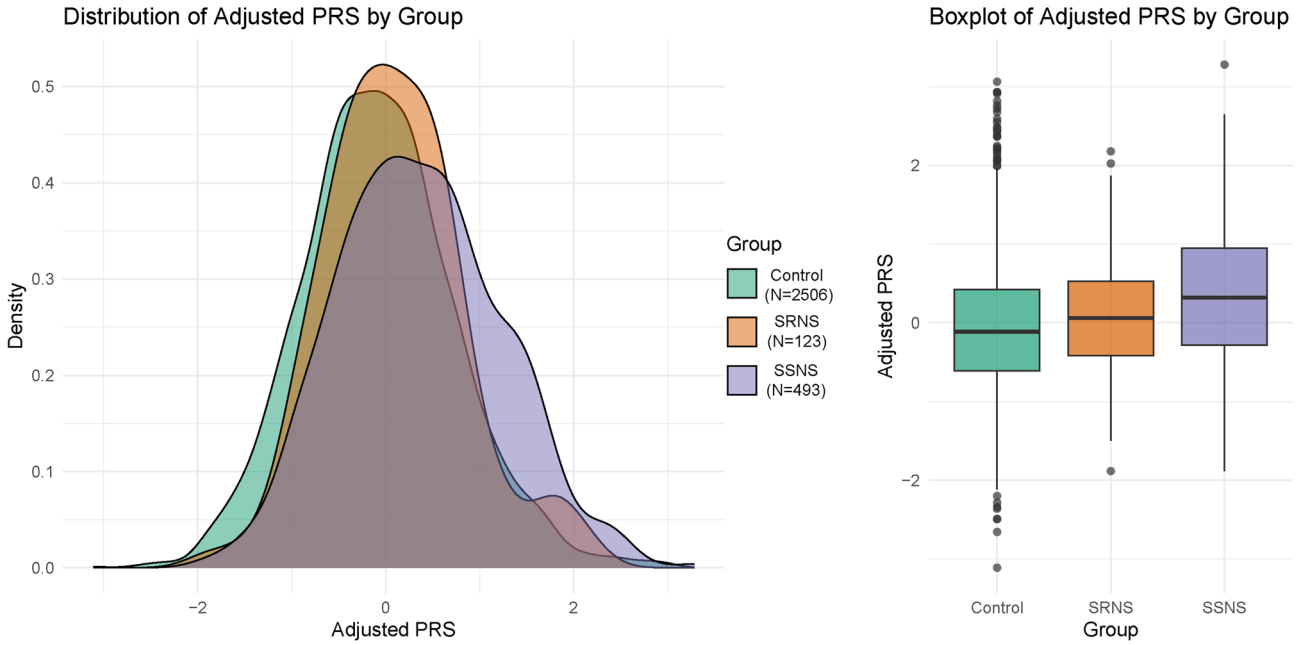

Fig. 2. Distribution of adjusted polygenic risk scores (PRS) across clinical groups. The left panel shows kernel density estimates with control exhibiting the leftmost peak, SRNS displaying an intermediate distribution, and SSNS showing the rightmost shift. The right panel's boxplots confirm this graded pattern: control group demonstrates the lowest median PRS, SRNS shows intermediate values, and SSNS presents the highest scores.

Polygenic risk score analysis across diagnostic groups

We next evaluated the distribution of SSNS-derived polygenic risk scores (PRS) in the independent Chinese cohort. Density plots (Fig. 2) revealed a clear and progressive rightward shift in PRS distributions across diagnostic groups, with SSNS patients showing the highest values (mean 0.36 ± 0.86), followed by SRNS patients (0.09 ± 0.74) and controls (−0.08 ± 0.81). One-way ANOVA indicated significant between-group differences ($F(2, 3120) = 59.42$, $P < 2 \times 10^{-16}$). Post-hoc comparisons using the Wilcoxon test with Bonferroni correction confirmed pronounced differentiation between SSNS patients and controls ($P < 0.001$). Interestingly, SRNS patients also differed significantly from both controls ($P = 0.021$) and SSNS patients ($P = 0.001$), occupying an intermediate position in the PRS distribution. This intermediate placement suggests that, although SRNS patients carry a lower polygenic burden than SSNS patients, their scores remain elevated relative to controls, indicating potential shared genetic susceptibility between these clinically distinct forms of INS. The consistency between the visual distribution pattern and statistical results underscores the robustness of this gradient and supports the hypothesis that common polygenic variation contributes to both disease susceptibility and heterogeneity in steroid treatment response.

Discussion

In this study, we employed a cross-phenotype, exploratory approach to evaluate the polygenic architecture of SRNS using a PRS derived from SSNS GWAS data. Our key findings reveal a dual pattern: the SSNS-derived PRS was significantly elevated in SRNS patients compared to controls, indicating a shared polygenic susceptibility; concurrently, it exhibited an intermediate, graded distribution between SSNS and controls, reflecting distinct polygenic contributions. These results provide genetic evidence supporting the concept of INS as a disease spectrum, where common variants contribute to both shared risk and clinical heterogeneity.

The SSNS-derived PRS demonstrated the ability to distinguish SSNS patients from controls in our Chinese cohort. While previous multi-ethnic GWAS identified eight significant loci for SSNS[7], the predictive performance of PRS derived from these findings had not been assessed in independent populations. Our results provide

supporting evidence that the polygenic architecture of SSNS may be consistent across ethnicities, although this conclusion is tempered by current limitations in sample size and the limited ethnic diversity of available GWAS data. This observation is noteworthy given the variability in PRS performance across populations[8].

The observation that a PRS derived from SSNS GWAS remains significantly elevated in SRNS patients compared with controls—albeit with attenuated effect sizes—indicates a shared polygenic susceptibility between these clinically distinct forms of INS. This supports the concept that SRNS and SSNS lie along a spectrum of podocyte injury[2]. The intermediate PRS distribution in SRNS further suggests that common polygenic factors contribute to disease pathogenesis beyond the established role of monogenic mutations[4]. This is particularly relevant given that ~ 70% of SRNS cases lack an identified monogenic cause[6], underscoring the importance of exploring polygenic contributions to treatment response heterogeneity.

The significant difference in PRS distributions between SSNS and SRNS patients indicates distinct polygenic contributions to these conditions. This observation may reflect fundamental differences in disease mechanisms, consistent with their divergent responses to corticosteroid therapy. The stronger polygenic signal in SSNS could suggest a greater role for immune-mediated pathways, while the attenuated signal in SRNS might indicate more heterogeneous mechanisms involving both monogenic and polygenic factors[11].

The study has some limitations that should be acknowledged. First, pertaining to PRS construction, the discovery GWAS summary statistics are derived from a multi-ancestry meta-analysis, with only the combined trans-ancestry results publicly available. This precluded the use of more refined cross-ancestry methods (e.g., PRS-CSx) that require ancestry-stratified statistics. We therefore applied PRS-CS with an East Asian LD reference panel, a practical approach under these constraints. However, as the SNP effects reflect an average across populations, this may limit the capture of genetic influences that are particularly prominent in East Asians, such as *NPHS1* loci that have been associated with an increased disease risk in this population, potentially affecting the score's precision and representativeness in our cohort. Second, in applying PRS-CS, we used a fixed global shrinkage parameter ($\varphi = 1\times10^{-2}$) without independent tuning on a separate dataset. While this is a common practice for exploratory group-level comparisons, and sensitivity analyses supported the robustness of our primary conclusions, the absence of formal optimization remains a methodological consideration. Third, the SRNS cohort size ($n = 123$), while comparable to previous genetic studies of this rare condition, may limit power to detect smaller polygenic effects. In addition, due to healthcare system constraints in our clinical setting, comprehensive genetic screening for monogenic forms of SRNS was not routinely available for the entire cohort. As a result, our SRNS group may include some patients with underlying monogenic mutations. Since such cases are not expected to share the polygenic architecture of SSNS, the inclusion could potentially attenuate the observed PRS signal, leading to more conservative estimates of shared polygenic susceptibility. Future studies incorporating systematic genetic screening will be essential to stratify SRNS patients by monogenic status and more accurately delineate the polygenic contribution in genetically unexplained cases. Finally, our analysis was restricted to common variants identified through GWAS, and future studies incorporating rare variants through whole-genome sequencing may provide more comprehensive insights.

In conclusion, our study provides compelling evidence for polygenic contributions to both SSNS and SRNS susceptibility, while highlighting important differences in their genetic architectures. These findings advance our understanding of INS pathogenesis and lay the foundation for more precise genetic risk assessment in pediatric nephrology. Future research should focus on expanding GWAS efforts and integrating polygenic and monogenic risk factors to improve clinical management of these conditions.

Data availability

Upon reasonable request, the corresponding author will provide the dataset.

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Author contributions

Cong Wang and Guotao Yin: Writing—original draft, Data curation, Conceptualization. Yidi Zhou and Yingchao Song: Formal analysis, Data curation. Minle Tian, Xiaoyuan Wang, Jing Wang, Qian Li and Ruixian Zang: Resources, Methdology. Zhenle Yang, Lichun Yu, Suwen Liu, Li Wang, Xiujun Yao and Aihua Zhou: Methodology, Visualization, Software. Shuzhen Sun and Xiao Chang: Conceptualization, Writing—review & editing, Funding acquisition.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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