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The Genetic Landscape of SCID in the US and Canada in the Current Era (2010–2018)

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Dr. Puck reports that J Puck's spouse is employed by and holds stock in Invitae, a genetic diagnosis company.
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Short Summary:

In a 250 patient cohort from the US and Canada in the current era (2010–2018), we show that over 90% of patients with severe combined immunodeficiency (SCID) can be genetically-characterized.

Keywords

severe combined immunodeficiency; SCID; genotype; phenotype

To the Editor:

There has been increased appreciation in recent years that severe combined immunodeficiency (SCID) is not one disease, but rather a collection of genetic disorders that share a common phenotype of very low numbers and insufficient function of lymphocytes, with variable deficiencies in B and NK cells.(1) SCID may be screened for by determining

the numbers of T-cell receptor excision circles (TRECs) on newborn dried blood spots, which will be low to absent.(2, 3) The introduction and now near-complete adoption of population-based newborn screening (NBS) for SCID in the USA has led to earlier diagnosis of both typical SCID and atypical, or leaky, forms of these diseases, the latter caused by hypomorphic gene defects that allow a small amount of gene function with a consequently varied spectrum of immune defects, including Omenn syndrome.(4) Unique clinical features of particular genetic subtypes of SCID, such as increased sensitivity to radiation and alkylating chemotherapy in patients with Artemis/*DCLRE1C* deficiency, impact outcome following allogeneic hematopoietic cell transplantation (HCT) including survival, immune reconstitution, and late effects.(1, 5) The Primary Immune Deficiency Treatment Consortium (PIDTC) 6901 Prospective Study has been enrolling patients with SCID disorders in the USA and Canada since August 2010. PIDTC 6901 is a prospective study approved by the institutional review boards of each center and performed in accordance with the Declaration of Helsinki (NCT01186913). A critical hypothesis of this study is that moving beyond the simple T, B and NK cell phenotypic profile towards a specific genotype-based classification of patients with SCID will improve outcomes by allowing the treatment approach to be tailored to each specific SCID genotype. Genetic analysis of enrolled patients is performed at the discretion of each center using commercially-available sequencing. Additional research-level genetic testing at a central laboratory (J. Puck, UCSF) is also available, as described in full elsewhere.(6)

Unbiased, population-wide NBS for SCID in the USA has facilitated an improved understanding of the true incidence of SCID, which affects 1 in 58,000 (95% CI, 1 in 46,000–80,000) newborns,(3) though this may be much higher in certain populations, such as the Navajo (1 in 2000 newborns).(7) Based on approximately 4.4 million births per year in the USA and Canada (per www.nichd.nih.gov, www.statcan.gc.ca), approximately 76 (range, 55-96) infants will be born with SCID annually. However, estimation of the number of SCID patients born each year with a particular genetic defect requires accurate knowledge of the relative proportion of each of the 20 or more known genetic lesions, plus as-yet unknown defects, that comprise the spectrum of SCID disorders. Indeed, the proportions of SCID-affected infants of each genotype identified by unbiased population-wide screening may differ markedly from historical data reported by transplant centers prior to SCID NBS.(2)

The Table 1 contrasts genetic mutations identified in two distinct cohorts of patients partially overlapping in time of ascertainment: the first 250 eligible patients (regardless of treatment approach) enrolled in the PIDTC Prospective Study 6901 (treated from 2010–2018; NCT01186913) versus the 712 eligible patients enrolled in the PIDTC Retrospective Study 6902 (treated from 1968–2012; NCT01346150).(1, 4, 8) The number of commercially-available genetic tests for SCID has significantly expanded over time.(9) Patients in 6901 were diagnosed by either NBS (60%), family history (20%), or clinical signs (20%). All patients were assigned to strata (typical or atypical) by a review committee after meeting established PIDTC SCID eligibility criteria, including review of available genetic sequencing.(4) Patients with atypical SCID (those with reticular dysgenesis or with leaky, hypomorphic mutations that included Omenn syndrome) were identified more commonly in the more recent, prospective enrollees, representing 27.2% of all cases in Study 6901, as

compared to only 11.4% for the retrospective Study 6902 cohort (p<0.001, chi-square test). This may be due to identification of infants with low, but not absent T cell function due to testing for TRECs through NBS.(3) These patients historically may have been previously labeled as an unknown form of immunodeficiency, they may have had delayed onset of symptoms, or may not have been offered HCT. While we have demonstrated that patients with atypical SCID have similar overall survival to patients with typical SCID, there are important differences in approaches to HCT for atypical SCID as well as differences in post-HCT immune reconstitution.(1, 8)

We observed a shift in the relative incidence of selected SCID genetic subtypes in the prospective, more recent cohort of SCID patients, as compared to those the earlier retrospective cohort. While children with deficiencies in *IL2RG* and *ADA* constituted similar proportions of SCID in both studies (p=0.187 and p=0.914, respectively), defects in *RAG1* and *RAG2*, in contrast, were more commonly identified in the recent, prospective 6901 cohort (19.2% compared to 7.3%; p<0.001). Furthermore, infants with very rare genetic defects (including *RMRP, TTC7A, ORAI1, ZAP70, BCL11B, AK2*, and *MSN*), several only recently discovered, represented over 10% of SCID cases identified in the US and Canada in the 6901 cohort, as compared to only a single case in the 6902 cohort (p<0.001, Fisher's exact test), in large measure due to recent advances in gene discovery. Notably, we observed a marked reduction in the percentage of patients with phenotypic features of SCID, but without an identified genetic mutations, from 38.9% in the retrospective 6902 group to 7.6% in the prospective 6901 group (p<0.001).

A limitation of these data is that the PIDTC does not capture all SCID infants diagnosed in the US and Canada. Since August 2010, the 6901 protocol has enrolled a median of 37 eligible patients per year (range, 14–60 patients/year). We therefore estimate that we captured approximately 49% (range, 39–67%) of SCID cases imputed from incidence data and birth rates. Knowing gene distributions in the US and Canada will be useful for scientists studying SCID, especially those planning trials of new gene-specific treatments, for example, correction of genes such as *ADA, IL2RG*, or *DCLRE1C* in autologous cells. Moreover, SCID infants identified as neonates by screening are more likely than in previous times to be infection-free at diagnosis, offering the opportunity to observe genotype/phenotype correlations without confounding effects of infectious complications. Furthermore, these data underscore that, even in the era of advanced genetic sequencing, the molecular basis of SCID remains undefined in over 7% of patients. Finding the genetic basis of SCID in these remaining patients may provide additional mechanistic insights into developmental pathways of the adaptive immune system, the implications of which may extend well beyond primary immunodeficiency.

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Abbreviations:

(SCID)	Severe Combined Immunodeficiency
(PIDTC)	Primary Immune Deficiency Treatment Consortium
(TRECs)	T-cell receptor excision circles
(HCT)	Hematopoietic Cell Transplantation

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Table 1.

Changes in Relative Frequency of SCID Genotypes over Time

Genotype	6902(1968–2012)				6901 to Date (2010–2018)				Predicted # of Patients per Year*
	Typical SCID	Atypical SCID	Total		Typical SCID	Atypical SCID	Total		Total
	631 (88.6%)	**81 (11.4%)**	**N=712**		**182 (72.8%)**	**68 (27.2%)**	**N=250**		**N=76**
IL2RG	178 (28.2%)	9 (11.1%)	**187 (26.3%)**		72 (39.6%)	5 (7.4%)	**77 (30.8%)**		**23**
JAK3	24 (3.8%)	-	**24 (3.4%)**		10 (5.5%)	3 (4.4%)	**13 (5.2%)**		**4**
ADA	89 (14.1%)	5 (6.2%)	**94 (13.2%)**		29 (15.9%)	3 (4.4%)	**32 (12.8%)**		**10**
PNP	1 (0.2%)	-	**1 (0.1%)**		-	2 (2.9%)	**2 (0.8%)**		**<1**
IL7R	40 (6.3%)	-	**40 (5.6%)**		18 (9.9%)	1 (1.5%)	**19 (7.6%)**		**6**
CD3 subunit	6 (1%)	1 (1.2%)	**7 (1%)**		3 (2.6%)	-	**3 (1.2%)**		**1**
CD45	1 (0.2%)	-	**1 (0.1%)**		-	-	**-**		**<1**
RAG1/2	28 (4.4%)	24 (29.6%)	**52 (7.3%)**		20 (11%)	28 (41.2%)	**48 (19.2%)**		**15**
DCLRE1C	27 (4.3%)	1 (1.2%)	**28 (3.9%)**		6 (3.3%)	2 (2.9%)	**8 (3.2%)**		**2**
LIG4	-	-	**-**		1 (0.5%)	1 (1.5%)	**2 (0.8%)**		**<1**
NHEJ1	-	-	**-**		1 (0.5%)	1 (1.5%)	**2 (0.8%)**		**<1**
RMRP	-	-	**-**		4 (2.2%)	5 (7.4%)	**9 (3.6%)**		**3**
ZAP70	-	-	**-**		-	4 (5.9%)	**4 (1.6%)**		**1**
AK2	-	1 (1.2%)	**1 (0.1%)**		-	4 (5.9%)	**4 (1.6%)**		**1**
Other Rare^	-	-	**-**		7 (3.8%)	2 (2.9%)	**9 (3.6%)**		**3**
Unknown°	237 (37.6%)	40 (49.4%)	**277 (38.9%)**		11 (6%)	7 (10.3%)	**18 (7.2%)**		**5**

*In USA and Canada (assuming an incidence of 1 in 58,000 and 4.4 million live births per year, all numbers approximate)

^Other Rare in 6901: Typical SCID: *TTC7A* (n=1), *ORAI1* (n=1), *MSN* (n=1), *BCL11B* (n=1), Novel (n=3); Atypical SCID: *MSN* (n=1), Novel (n=1)

°Unknown by Whole Exome Sequencing vs. Conventional Testing in 6901: Typical SCID: 3 & 9; Atypical SCID: 1 & 6