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Research Directions in Genetic Predispositions to Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis

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This paper summarizes the deliberations of a symposium convened by the National Human Genome Research Institute (NHGRI) on March 3–4, 2015 to examine gaps and priorities for future research to eliminate genetically mediated SJS/TEN globally.

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Introduction

Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) is one of the most devastating of adverse drug reactions (ADRs) and was, until recently, essentially unpredictable. With the discovery of several risk alleles for drug-induced SJS/TEN and the demonstration of effectiveness of screening in reducing incidence, the stage is set for implementation of preventive strategies in populations at risk. Yet much remains to be learned about this potentially fatal complication of commonly used drugs.

Keywords

Stevens-Johnson syndrome; toxic epidermal necrolysis; severe cutaneous adverse reactions; medical genomics; implementation; prevention; pharmacogenomics; precision medicine; HLA; MHC; T-cell receptor; peptide; idiosyncratic drug toxicity

Background

Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) is a rare but devastating skin reaction to a number of commonly used drugs. Occurring in roughly one per million of the general population in Europe and the U.S., and 2–4 times that in Asia [1], risk is up to 1,000 times greater in patients with AIDS [2]. The great majority (>80%) of cases is believed to be genetically mediated in response to specific drugs. In 2004, Chung and colleagues identified *HLA-B*15:02* as a potent risk factor, associated with greater than 100-fold increased risk among users of carbamazepine [3]. This variant has a high frequency in Han Chinese and other Southeast Asian ancestry groups but is uncommon outside that region [Figure]. Following the initial discovery of the *HLA-B*15:02* association, several other risk variants have been identified in relation to carbamazepine and other drugs [Supplementary Table 1], and efforts to screen and prevent the condition have been shown to

be effective in regions with high disease incidence, high negative predictive value (approaching 100%), and high risk allele frequencies [1].

The epidemiology and clinical features of SJS/TEN have been described extensively and the reader is referred to recent excellent reviews [2,4]. Much less is understood, however, about the pathogenesis, variability, modulating factors, or penetrance of risk alleles for SJS/TEN. Research efforts are limited and isolated, particularly in the U.S. where the condition is perceived to be extremely rare, though some recent estimates are 1–2 orders of magnitude higher than the one per million quoted above [5].

To explore needs for further research into the epidemiology, pathogenesis, treatment, and prevention of SJS/TEN, the National Human Genome Research Institute (NHGRI) and several other Institutes and Centers of the National Institutes of Health (see Acknowledgments) in collaboration with the U.S. Food and Drug Administration (FDA) convened 30 international experts to examine the role of genomics in the etiology, treatment, and eradication of preventable cases and to identify gaps, unmet needs, and priorities for future research with the ultimate aim of eliminating genetically mediated drug-induced SJS/TEN globally.

Role of Genomics in Etiology and Prevention

Considerable progress has been made in the 13 years since the first causative allele for SJS/TEN was identified [3], including recognition of additional drug-specific risk alleles [1], improved diagnostic criteria [4], and implementation of effective screening programs in high-risk populations [1]. Understanding of the immunopathogenesis is continuing to evolve and has recently been reviewed [1,2,6]. In addition, continued advances in next-generation sequencing and related technologies have greatly expanded the precision and speed with which genetic variants associated with drug response can now be identified [7].

One of the most promising recent advances in the genomics of SJS/TEN, a condition that was previously believed to be entirely idiosyncratic and unpredictable [1,6], has been the translation of genetic associations into effective screening and prevention strategies. Groups in several countries including Singapore, Taiwan, and Thailand have demonstrated the effectiveness of genetic screening for *HLA-B* risk alleles in reducing the incidence of SJS/TEN [1,6], similar to the effective use of *HLA-B*57:01* screening to prevent abacavir hypersensitivity.

Research Gaps and Needs

Advances in understanding of basic pathogenesis, risk variant identification, clinical implementation, and pharmacosurveillance have brought risk prediction and prevention of SJS/TEN into the realm of possibility, at least for some causative drugs, but many barriers remain. Chief among these are the rarity of the condition, the suddenness of onset, and the rapidity of progression. While several national and international consortia have been established [8–9], none is sufficiently large or ancestrally diverse to permit identification of risk alleles of modest effect or minor allele frequencies much below 5%.

High priority research needed to address these challenges can be grouped into overarching and facilitative research as well as basic, clinical, and pharmacovigilance/epidemiologic research (Table 1). Many of the research priorities listed there (in rough priority order) could be facilitated through an expanded international collaboration or global registry of ancestrally diverse and well-phenotyped patients using standardized protocols. Biospecimen collection should include appropriately processed and cryopreserved peripheral blood mononuclear cells (PBMCs) and blister fluid collected early in the course, before massive de-epithelialization has occurred, for analysis of drug-specific CD8+ T cell responses. While blister fluid collection is challenging given that SJS/TEN develops suddenly and its differential diagnosis is difficult in early stages, heightened awareness and increased diagnostic suspicion could enable aspiration of intact bullae to help in characterizing the immunopathogenic cascade [2]. Needed infrastructure would include specialized centers to receive, process, and characterize samples and standard consent forms to facilitate sharing of data and samples across national borders. Public-private funding models sharing responsibility with the pharmaceutical industry, similar to those developed in Japan and Taiwan, are the most sustainable. They are also firmly in industry's interests as SJS/TEN leads not only to disability and death of patients but the "death" or withdrawal of promising new therapeutic agents [6].

Key gaps in basic knowledge that can be translated to early diagnostic and prognostic markers and effective therapeutics include the cellular processes leading to the development of drug neoantigens, the co-factors that drive immunogenicity, and the lack of reliable and effective *in vitro* drug challenge tests. SJS/TEN patients, particularly those being treated for infections such as HIV/AIDS or tuberculosis, are often started on multiple drugs at once making determination of the causative agent much more difficult. At present identification of the culprit drug in such cases is often a hit-or-miss affair, requiring cessation of all drugs and gingerly adding them back in hopes the causative agent will declare itself before too much additional damage is done. An *in vitro/ex vivo* test with high specificity and sensitivity that could quickly determine the specific causative drug would be an enormous advance.

The international network described above could address a variety of needs in clinical research and care, including development of an affordable pharmacogenomic assay, piloting pre-emptive testing to assess impact, and incorporating genotypic information and decision support directly into the medical record and medication prescribing and dispensing systems. The network could also facilitate genome-wide association studies of other implicated drugs, such as oxicam-type non-steroidal anti-inflammatory agents, sulfonamide antimicrobials, and lamotrigine, for which robust genomic risk factors have yet to be characterized.

The epidemiology and burden of SJS/TEN is unknown in many populations, particularly ethnic subgroups in the U.S. and African ancestry and non-European indigenous populations worldwide. Studies in Asian-Americans and Asians immigrating to other environments in other parts of the world would seem particularly important. Studies in implementation and cost-effectiveness should expand beyond one-gene-one-drug risk assessments as the cost of genome-wide assessment declines, in the expectation that multi-gene tests or genome sequencing will soon be more favorable economically.

Despite the development of new pharmacovigilance methods such as NEISS-CADES [<https://www.healthypeople.gov/2020/data-source/national-electronic-injury-surveillance-system-cooperative-adverse-drug-event>] and Sentinel [<https://www.fda.gov/safety/fdassentinelinitiative/ucm2007250.htm>], extraordinary gaps remain in basic epidemiologic data on SJS/TEN in the U.S. Addressing these gaps will require adopting uniform methods for effective identification and assessment of potential cases, particularly through electronic medical records. Existing large databases and integrated medical systems should be queried using standardized data collection processes for reliable case identification and validation. Similar efforts should also be undertaken using databases in other countries. Immediate needs include improved collection of race/ethnic data in databases (including key nation- or region-specific subgroups); adoption of standardized case definitions and e-algorithms; and a minimum set of clinical, diagnostic, and drug exposure criteria for use in retrospective studies. Methods to identify potential retrospective cases against gold standard case definitions should be developed, recognizing the potential for inaccurate classification when clinical data may be incomplete.

Follow-up of SJS/TEN survivors would enable study of outcomes and their predictors. Improved clinician education and awareness of SJS/TEN and engaging patients and their families in specialized research early in their course will help promote early detection, appropriate treatment, and further knowledge and evidence generation.

Whether a common research approach will be generalizable across all implicated drugs is currently unknown, but course and outcome in clinically recognized SJS/TEN are so similar that at present a common framework seems to be the most reasonable. Highest priority drugs for risk identification and prevention would be those in widest use, such as allopurinol, co-trimoxazole, and non-steroidal anti-inflammatory agents, or drugs with risk alleles of known high population frequency.

CONCLUSION

The identification of major risk alleles for SJS/TEN and the implementation of effective screening and prevention strategies, particularly in Southeast Asia, have provided a compelling example of the power of personalized medical care to improve drug safety. The relatively localized nature of these successes to date, however, impels us to find and apply effective approaches in other population groups, for which we must identify additional risk predictors and develop needed infrastructure for implementation. Extension of such approaches to other genetically mediated severe adverse reactions such as drug-induced liver and kidney injury should be explored.

Such efforts are within our grasp, particularly as genomic technology and medical informatics improve in economy and efficiency, making feasible widespread screening and effective interdiction of culprit drugs in susceptible individuals, even prior to drug approval and release. As these are in essence iatrogenic events, however unintentional, we as physicians and health care providers must take responsibility for them. It is our obligation, and now our great good fortune, to seize the opportunities for clinical translation and prevention presented by the new discoveries and future prospects described briefly here.

Such efforts could serve as a paradigm for broader ADR prevention strategies. By expanding these investigations to other population groups and causative drugs, and extending our knowledge of pathogenic mechanisms and population trends, we should aim for a real reduction in the incidence of genetically-mediated drug-induced SJS/TEN, and indeed, someday, for its global eradication.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure.

Global frequency of drug-specific HLA alleles. Allele frequencies in percents are shown in red for *HLA-B*57:01*, in blue for *HLA-B*58:01*, and in black for *HLA-B*15:02*.

Table 1**High Priority Research Areas**Overarching and Facilitative Research

- **** 1. Develop a large international network to collect and pool large numbers of cases diverse in ethnicity and implicated drugs, including:
- a.** Standardized case definitions and data collection tools for both prospective and retrospective studies
 - b.** Biospecimens from early in the disease course collected by standardized protocol for identification of diagnostic and prognostic biomarkers
 - c.** Patient registries with associated biobanked samples in partnership with advocacy groups
 - d.** Long-term outcomes, including morbidity and mortality and downstream sequelae
2. Engage burn units in SJS/TEN case-finding and research in regions like the U.S. where patients are commonly transferred to their care

Basic Research

- *** 1. Identify novel biomarkers in acute phases of the disease to improve diagnosis, prognosis and treatment
- *** 2. Identify new predictive markers in addition to HLA and cytochrome P450 variants including other genetic and metabolic factors and new immunopathogenic mechanisms
3. Develop *in vivo*, *ex vivo*, *in vitro*, and animal models to inform studies of causative drugs and preclinical testing of new drugs
4. Improve cheminformatics of drug culprits and develop small molecule assays

Clinical Research

- *** 1. Develop low-cost pharmacogenomic assay(s) for implementation in state/national health programs
- *** 2. Pilot pre-emptive testing for feasibility prior to studying its effectiveness in reducing Incidence
- *** 3. Incorporate genotypic information and decision support directly into the medical record and medication prescribing and dispensing systems
4. Implement testing in high-risk populations and study impact on both safety and efficacy
5. Examine the efficacy, safety, costs, and possible side effects of prescribing alternative medications
6. Develop robust electronic phenotyping algorithms for case identification
7. Expand beyond one gene-one drug models in research to multi-gene panels or genomic sequencing
8. Study ethnic-specific HLA associations or associations/differences between admixed groups and their parent populations, such as Asian Americans compared to Asians in Southeast Asia
9. Engage multiple medical subspecialties that prescribe causative drugs, such as neurologists and rheumatologists, in educational and case-finding efforts
10. Consider universal HLA typing or wider genomic screening and linking to EMR for association with multiple health outcomes
11. Identify factors that discriminate risk allele carriers who have a reaction from those who do not

Pharmacovigilance and Epidemiologic Research

- *** 1. Conduct additional epidemiologic studies for basic measures of morbidity, mortality, outcomes, including:
- a.** Factors associated with disease progression and long-term outcomes, including “non-standard” outcomes such as extracutaneous and neuropsychiatric sequelae and future drug use
 - b.** Burden and risk studies of racial-ethnic groups within the U.S. and other global regions
 - c.** Foundational data needed for cost-effectiveness and other health economic research
- *** 2. Collect race/ethnicity information and study key population subgroups with high case burdens in the U.S. and globally
3. Conduct additional cost-effectiveness analyses, informed by ongoing research, to support decision-making on implementation of routine genotyping by hospitals and/or medical care systems
4. Develop pilot projects to ascertain patient preferences on benefits and trade-offs of pharmacogenomic testing
5. Address challenges of current screening recommendations such as low frequency and positive predictive value of risk alleles

(highest priority indicated with **, high priority with *)