Generalized Pustular Eruptions: Time to Adapt the Disease Taxonomy to the Genetic Architecture?

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TO THE EDITOR

In recent months, *IL36RN* has been investigated in various inflammatory conditions. *IL36RN* variants are common in generalized pustular psoriasis (GPP) (Setta-Kaffetzi *et al.*, 2013) without plaque psoriasis (Sugiura *et al.*, 2013) and acrodermatitis continua of Hallopeau (Setta-Kaffetzi *et al.*, 2013), and somewhat rarer in acute generalized exanthematous pustulosis (Navarini *et al.*, 2013) and palmoplantar pustulosis (Setta-Kaffetzi *et al.*, 2013). They do not predispose to plaque psoriasis (Berki *et al.*, 2013). Sugiura *et al.* (2013) describe the early age of onset, generalized pustular eruptions in *IL36RN* compound heterozygote twins, initially triggered by amoxicillin, which then became recurrent. While infection is reported to trigger pustular eruptions in GPP, given the positive patch test, the drug seems the more likely candidate. Whether such cases should be diagnosed as acute generalized exanthematous pustulosis or drug-elicited GPP remains a matter of expert opinion at present in the absence of a gold standard for separating these two entities, and for RegiSCAR, case ascertainment (Navarini *et al.*, 2013) comprised a scoring system involving clinical and histological criteria and formal board review. However, Sugiura's cases raise the intriguing possibility that *IL36RN* provides the mechanistic link between the two, and supports the notion that the disease taxonomy of pustular eruptions (in general) might be better served when based on pathogenic mechanisms and genetic profiling.

Concerning Sugiura *et al.*'s suggestion of avoiding amoxicillin administration to known patients with clinically manifest DITRA (deficiency of the IL-36 receptor antagonist): we believe that the evidence from the three compound heterozygous/homozygous cases (Navarini *et al.*, 2013; Sugiura *et al.*, 2013) alone is not sufficient to postulate such a general recommendation. However, we suggest that for these patients, collecting data with patch testing for β-lactam antibiotics is worthwhile both on clinical and scientific grounds. Given the rarity of the condition, this could be addressed in dedicated networks such as the newly formed European Rare and Severe Psoriasis Expert Network (ERASPEN).

Sugiura *et al.* (2013) also suggest avoiding administration of amoxicillin or penicillin-related drugs to carriers of variants in *IL36RN*. The value of pretreatment genetic testing is established for only a limited number of drugs, most notably certain HLA risk alleles that predict risk of severe cutaneous adverse drug reactions, for example: HLA-B*57:01 HIV before administration of abacavir (Martin *et al.*, 2012), as 6% are otherwise affected by hypersensitivity. However, *IL36RN* variants are rare, thus the number needed to test would be high, greatly limiting the clinical utility of such a strategy. In addition, although it seems clear that amoxicillin was the trigger of the pustular eruption in the cases reported, it does not automatically follow that all patients with *IL36RN* variants will react similarly, or that the avoidance of amoxicillin would have prevented the subsequent manifestation of GPP. This might have to be demonstrated before adopting such a testing strategy for general use.

Abbreviations: AGEP, acute generalized exanthematous pustulosis; DITRA, deficiency of the IL-36 receptor antagonist; GPP, generalized pustular psoriasis; RegiSCAR, European Registry of Severe Cutaneous Adverse Reactions

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CONFLICT OF INTEREST

J-CR is on the advisory board, or is a consultant or investigator for the following companies: Vertex, Janssen, Boehringer–Ingelheim, OM Pharma, Servier, Menarini, GSK, Novartis, Science and Technology, and has given expert testimony in several court cases on SJS in the United States of America. MM is the coordinator of the international RegiSCAR Project, which is/was funded by grants from the European Commission (QLRT–2002–01738), GIS-Institut des Maladies Rares and INSERM (4CH09G) in France, and by a consortium of pharmaceutical companies (Bayer Vital, Boehringer-Ingelheim, Cephalon, GlaxoSmithKline, MSD Sharp and Dohme, Merck, Novartis, Roche, Sanofi–Aventis, Servier, Tibotec). She has been on the advisory board for Merck, USA, and in the expert panel for Vertex, USA. The other authors state no conflict of interest.

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Author contributions

AAN, NS-K, and CHS had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. AAN, CHS, JNB, and J-CR wrote the manuscript. CHS, MAS, FC, JNB, RCT, DC, MM, NS-K, LV-A, and PS contributed to critical revision of the manuscript for important intellectual

content. CHS, JNB, and MAS were involved in study supervision.

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Skin Is Not the Largest Organ

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TO THE EDITOR

When scanning the newly published literature cited on PubMed/Medline, it is almost a weekly occurrence that I see something go by stating that the skin is the largest organ in the human body. The problem is that there is no factual basis for this ubiquitous dogmatic statement.

As an example, the editor's introduction to the timely and informative Review Series on Dermatology that appeared in the 1 February 2012 issue (volume 122, issue 2) of the *Journal of Clinical Investigation* began with the following sentence ''Though the body's largest organ, the skin may be occasionally forgotten as a site of clinically important disease.'' Similar statements have been made in earlier *Journal of Investigative Dermatology* publications authored by prominent dermatology/skin biology investigators (Setoguchi *et al.*, 1994; Bickers and Athar, 2006; Clark *et al.*, 2007).

On 31 May 2013, a PubMed search using the phrase, ''skin largest organ'' returned 194 citations. A review of the text of the abstracts accompanying the first 20 of those citations revealed that in 16 (80%) it was specifically stated that the skin is the largest human organ. However, published data simply do not support the ''common knowledge'' proposition that the skin is the largest organ in the human body.

An earlier analysis of this question by Goldsmith (1990) eloquently and humorously concluded that the human skin is not the largest organ in the human body. By weight, the skin may be considered to be the largest of the ''medium-sized'' organs such as the liver and brain. However, the skin is no match in weight for the much larger organs of the musculoskeletal system. In such comparisons, clearly the musculoskeletal system must be considered as a human organ system.

Goldsmith's (1990) assumptions and calculations resulted in a determination that the human skin (epidermis plus dermis) weighs 3.86 kg, or 5.5% of the total body weight of the proverbial 70 kg man.

It has been reported that the skeleton accounts for ~14% of the human body's weight (Reynolds, 1977). In addition, it has been reported that an average adult male is made up of 42% of skeletal muscle and an average adult female is made up of 36% (as a percentage of body mass; Marieb and Hoehn, 2007).

If one included the subcutaneous fat, the skin by mass would be a stronger contender for being the largest organ in the human body. However, as its name implies ''subcutaneous'' fat is not an official part of the skin. Wikipedia also states that human skin is the largest organ. However, Wikipedia, that fount of conventional wisdom, also states that the skin is composed of the epidermis and dermis. It specifies that the hypodermis (subcutaneous tissue) underlies the skin but is not part of the skin (http://en.wikipedia.org/wiki/Skin#Hypodermis/, accessed 31 May 2013).

Nor can the skin be considered to be the largest human organ with respect to functional surface area. The human skin surface area is identical to body surface area. The body surface area of the proverbial 70 kg man is 1.7 m^2 (Goldsmith, 1990). By comparison, the gas exchanging surface of the lung's

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