

Personalised Medicine for Psoriasis: A Real Possibility Ahead

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In the last decade, our understanding of psoriasis has increased by leaps and bounds, resulting in many new targeted therapies being introduced for those with recalcitrant psoriasis. However, despite the plethora of new treatment options and biologics to treat the most difficult cases of psoriasis, dermatologists are still confronted with the heterogeneity of treatment effects for psoriasis in the area of treatment response as well as adverse drug effects. While many factors (age, obesity, drug-drug interactions, hepatic and renal function etc.) affect drug responses and adverse effects, genetic factors have been recognised to play a big role in drug response and toxicity. With the unravelling of the human genetic code and discovery of single nucleotide polymorphisms, researchers can now study DNA polymorphisms in our patients and this, coupled with recent improvement in genomic technologies, allow us to reveal disease processes at molecular levels that were not available in the past. This new powerful knowledge and technologies now provide clinicians with the real possibility of personalising medicine for our patients, predicting who will respond to which treatment options and the likelihood of toxicity associated with the proposed treatment.

This promise of “personalised medicine”, an exciting area of development that is especially relevant to a chronic disease like psoriasis, is certainly not science fiction and could be a reality in the near future. This idea of “personalised medicine” can be applied to 3 main areas in the future management of psoriasis, namely a) Identifying new molecular targets for new treatment options, b) Prediction of course of disease, and c) Prediction of toxicity of treatment.

Identification of New Targets for Treatment

Great leaps have been made in the areas of understanding the molecular basis of psoriasis, and with this new knowledge, better treatment options were devised. A good example is the discovery of the role of TH-17 cells in the pathogenesis of psoriasis resulting in the development of Ustekinumab for the treatment of psoriasis vulgaris. What is missing now is the linking of psoriasis susceptibility genes to molecular pathogenetic pathways. As our understanding of the psoriasis susceptibility gene increases (Table 1), the identification and characterisation of these susceptibility alleles would definitely enable one to look for new molecular targets for pharmacological intervention.

In addition, the current practice of dermatology is very much morphologically driven and psoriasis is no different. We currently subclassify psoriasis into psoriasis vulgaris, guttate psoriasis, pustular psoriasis and erythrodermic psoriasis. It is inconceivable that a condition with so many different subtypes have the same molecular basis in their pathogenesis. As such, delineating the different genes responsible for the different phenotypic subtypes would enable one to start classifying psoriasis at the molecular level, eventually allowing clinicians to better select the optimal treatment option for the various subgroups of patients.

Prediction of Course of Disease

Currently, some knowledge is emerging with regards to genetic polymorphism affecting the course of psoriasis. An example is the association of HLA-Cw0602 with early onset psoriasis,⁷ more extensive disease and higher incidences of koebner’s phenomena and more frequent exacerbations.⁸ Another example is the published study by Young et al who

Table 1. Known Psoriasis Susceptibility Genes and Their Functions

Locus Name	Chromosome Location	Candidate Gene	Gene Function	Reference
PSOR1	6p21.3	HLA-C	Human Leucocyte antigen	1
PSOR2	17q25	RAPTOR	Regulatory associated protein of mTOR	2
PSOR3	4q25	IRF-2	IFN regulatory factor 2	3
PSOR4	1q21	Pglyrp3 & 4	Peptidoglycan recognition protein	4
PSOR5	3q21	SLC12A8	Solute carrier family 12 member A 8	5
PSOR7	1p	IL23R	Interleukin 23 receptor	6

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found that patients with single nucleotide polymorphisms in VEGF had earlier onset and more severe psoriasis⁹ with Psoriasis Area and Severity index (PASI) score >12. While these and other studies are interesting and illuminating, the drawbacks of these studies are the small sample size and gene-environmental interaction is not taken into account. In addition, we are looking at genes very primitively, from an on-or-off, yes-or-no perspective but in reality, the expression of the gene products and its interactions with the environment, are continuous variables which make clinical phenotype difficult to predict. Notwithstanding that, it is certainly conceivable that we will be able to predict the course of disease, especially with respect to specific complications like psoriatic arthropathy. Interesting developments in this area include the identification of an immune response gene on chromosome 6 and its association with psoriatic arthropathy. In particular, a triple repeat polymorphism in this gene is found in about 60% of patients with psoriatic arthropathy.¹⁰⁻¹³ Identifying subgroups of patients like these can be extremely useful as clinicians can now be more proactive and aggressive in managing this group of patients to prevent joint damage, functional impairment and reduced quality of life.

Prediction of Response and Toxicity of Treatment

Treatment response has always been variable for patients with psoriasis on the same drug and even for the same patient but at different time points. Pharmacogenetic analysis might provide clues to such variability in response. A good example of this is the identification of the A-1012G polymorphism of the vitamin D receptor associated with improved responses to topical calcipotriol.¹⁴ Similar studies for the use of biologics has already been done in Crohn's disease^{15,16} and Rheumatoid Arthritis^{17,18} but not for psoriasis as yet. Such studies should be quickly carried out so as to determine who will benefit from which biologics and more importantly, at what dosages to reduce complications rates.

Finally, pharmacogenetics to prevent drug toxicity is not a new science. The earliest application of such a field dates back to 510BC, when Pythagoras recognised the dangers of fava beans in certain individuals, which was subsequently discovered by Carson et al in 1956¹⁹ to be due to Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency. Fast forward to the current day and screening for methylenetetrahydrofolate reductase polymorphism has been shown to be a useful tool to predict methotrexate toxicity for psoriasis patients treated with methotrexate, negating the need for the age old practice of liver biopsy. Going forward, it would not be inconceivable that one would be able to apply the science of pharmacogenetics to identify subgroups of patients who will develop toxicities to drugs, especially for the newer, more expensive immunosuppressives like the biologics.

Conclusion

The field of pharmacogenetics is still nascent but hold much promise for chronic debilitating diseases like psoriasis. It opens up the possibility of individualised medicine, allowing clinicians to predict who will get the disease, whether it will be a short benign or long debilitating course and who will get complications from the disease. More importantly, it will allow clinicians to better tailor treatment options for patients, avoiding drug toxicities and achieving long-term remission for patients.

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