Clinical, immunological, and genetic characterization of Colombian patients with cutaneous recalcitrant warts

Julián Rojas[1,2], Margarita María Velásquez[3,4], Juan Álvaro López [2,5], Emmanuelle Jouanguy [6], José Luis Franco[2], Andrés Augusto Arias[2,5]

SUMMARY

Inborn errors of innate and intrinsic immunity are monogenic diseases that result in a predisposition to a whole spectrum of infectious diseases, including viral infections. Cutaneous warts caused by Human Papillomavirus (HPV) infection have a ~10% incidence in the general population. These lesions are relatively common, and most warts revert spontaneously. However, in otherwise healthy individuals, these warts persist for > 2 years without response to conventional therapy (cryotherapy, salicylic acid, or bleomycin), and they are called recalcitrant warts (RW). Host defense against HPV relies on intact and functioning cellular immunity including T cell, natural killer cell cytotoxicity, and intrinsic immunity. Therefore, in patients in whom warts are recalcitrant, concern for immune defects is raised.

RW has been documented in patients with inborn errors of immunity (IEI), either in combination with broad infectious phenotypes (combined immunodeficiencies) and in HIV+ patients and patients with immunotherapy after transplantation. On the other hand, is well documented that patients with Epidermodysplasia Verruciformis present a specific genetic predisposition to beta-HPV infection, but only very few are known about genetic susceptibility to otherwise healthy patients presenting RW. Therefore, we hypothesized that susceptibility to RW due to HPV viruses in otherwise healthy individuals might be due to underlying genetic defects in intrinsic and innate immunity.

Aim: To describe the clinical and immunologic characteristics and genetic defects responsible for susceptibility to cutaneous recalcitrant warts (RW) of Colombian patients with cutaneous recalcitrant warts.

Methodology: All patients included are HIV negative and present recalcitrant warts. We reviewed medical records, including the history of HPV infection, pharmacological treatments, and genetic defects. We also draw a pedigree, obtain blood samples, perform immunophenotyping and Whole Exome Sequencing (WES) in patients and relatives using *in silico* tools to predict the possible impact of the variants on the patients in terms of conservation, selective pressure in the affected gene, variants allelic frequency, impact in the protein and previously documented association of the candidate gene with HPV infection. According to genetic findings (gene candidates and affected pathways), we perform functional assays to investigate the correspondence between genotype and phenotype. The patient's immunological characterization was performed through peripheral blood count, measurement of subpopulations of T, B, and NK lymphocytes and monocytes, and functional test on peripheral blood mononuclear cells.

Results: We collected 11 patients ages 9 to 34 years old (5 males and 6 females) belonging to 9 families that fulfilled the inclusion criteria. Five patients have a family history of cervix HPV infections and others.

We have drawn pedigrees and performed WES in 7 in which we have found rare variants with high in silico impact in the *PYGO2, CASP9*, *CCNA2*, *CCMB3*, *GLTSCR2*, *PABPC1*, and *CAD* genes which present a high selective pressure process in the gene, are congruent with familial segregation, are related to genes with RW in their phenotype and in which they have been reported to be related to the HPV infection. In addition, phenotyping of peripheral blood leucocytes subpopulations has revealed normal percentages and numbers of T cells, B cells, NK cells, and monocytes in one patient.

[1] Biomedical basic sciences corporation, University of Antioquia, Medellín, Colombia

[2] Group of Primary Immunodeficiencies, University of Antioquia, Medellín, Colombia

[3] Dermatology Section, University of Antioquia, Medellín, Colombia

[4] Dermatologic Research Center (School of Medicine), University of Antioquia

[5] Microbiology school, University of Antioquia, Medellín, Colombia

[6] Human Genetics of Infectious Diseases INSERM / Paris Descartes University (Paris, France).

Contact Email: Julian.rojass@udea.edu.co

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Conclusions

- The clinical characteristics of the patients, as well as their family history of persistent and treatment-resistant warts as well as the presence of general leukocyte subpopulations in the blood, suggest that the immunological defect responsible for this susceptibility is specific to the HPV response.
- The lack of previously described gene variants in which susceptibility to recalcitrant warts accompanied by other clinical phenotypes is reported suggests that these patients have a previously undescribed immunologic defect.
- The presence of variants in genes related by connectivity with previously reported recalcitrant wart susceptibility genes accompanied by other clinical phenotypes, in addition to the family history of recalcitrant warts in our patients, supports the hypothesis that susceptibility to recalcitrant warts is an inborn error of immunity not previously described.

KEY WORDS

Verruga, Verruca, Verrucae, Warts, Resistant, Recalcitrant, WES, HPV.

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