Zbornik 24. mednarodne multikonference

INFORMACIJSKA DRUŽBA

Zvezek J

Proceedings of the 24th International Multiconference

INFORMATION SOCIETY

Volume J

IS 2021

Delavnica projekta BATMAN

BATMAN Project Workshop

Urednika • Editors:
Sergio Crovella, Anton Gradišek

4. oktober 2021 Ljubljana, Slovenija • 4 October 2021 Ljubljana, Slovenia • http://is.ijs.si

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PREDGOVOR MULTIKONFERENCI INFORMACIJSKA DRUŽBA 2021

Štiriindvajseta multikonferenca *Informacijska družba* je preživela probleme zaradi korone v 2020. Odziv se povečuje, v 2021 imamo enajst konferenc, a pravo upanje je za 2022, ko naj bi dovolj velika precepljenost končno omogočila normalno delovanje. Tudi v 2021 gre zahvala za skoraj normalno delovanje konference tistim predsednikom konferenc, ki so kljub prvi pandemiji modernega sveta pogumno obdržali visok strokovni nivo.

Stagnacija določenih aktivnosti v 2020 in 2021 pa skoraj v ničemer ni omejila neverjetne rasti IKTja, informacijske družbe, umetne inteligence in znanosti nasploh, ampak nasprotno – rast znanja, računalništva in umetne inteligence se nadaljuje z že kar običajno nesluteno hitrostjo. Po drugi strani se je pospešil razpad družbenih vrednot, zaupanje v znanost in razvoj. Se pa zavedanje večine ljudi, da je potrebno podpreti stroko, čedalje bolj krepi, kar je bistvena sprememba glede na 2020.

Letos smo v multikonferenco povezali enajst odličnih neodvisnih konferenc. Zajema okoli 170 večinoma spletnih predstavitev, povzetkov in referatov v okviru samostojnih konferenc in delavnic ter 400 obiskovalcev. Prireditev so spremljale okrogle mize in razprave ter posebni dogodki, kot je svečana podelitev nagrad – seveda večinoma preko spleta. Izbrani prispevki bodo izšli tudi v posebni številki revije Informatica (http://www.informatica.si/), ki se ponaša s 45-letno tradicijo odlične znanstvene revije.

Multikonferenco Informacijska družba 2021 sestavljajo naslednje samostojne konference:

- Slovenska konferenca o umetni inteligenci
- Odkrivanje znanja in podatkovna skladišča
- Kognitivna znanost
- Ljudje in okolje
- 50-letnica poučevanja računalništva v slovenskih srednjih šolah
- Delavnica projekta Batman
- Delavnica projekta Insieme Interreg
- Delavnica projekta Urbanite
- Študentska konferenca o računalniškem raziskovanju 2021
- Mednarodna konferenca o prenosu tehnologij
- Vzgoja in izobraževanje v informacijski družbi

Soorganizatorji in podporniki multikonference so različne raziskovalne institucije in združenja, med njimi ACM Slovenija, SLAIS, DKZ in druga slovenska nacionalna akademija, Inženirska akademija Slovenije (IAS). V imenu organizatorjev konference se zahvaljujemo združenjem in institucijam, še posebej pa udeležencem za njihove dragocene prispevke in priložnost, da z nami delijo svoje izkušnje o informacijski družbi. Zahvaljujemo se tudi recenzentom za njihovo pomoč pri recenziranju.

S podelitvijo nagrad, še posebej z nagrado Michie-Turing, se avtonomna stroka s področja opredeli do najbolj izstopajočih dosežkov. Nagrado Michie-Turing za izjemen življenjski prispevek k razvoju in promociji informacijske družbe je prejel prof. dr. Jernej Kozak. Priznanje za dosežek leta pripada ekipi Odseka za inteligentne sisteme Instituta "Jožef Stefan" za osvojeno drugo mesto na tekmovanju XPrize Pandemic Response Challenge za iskanje najboljših ukrepov proti koroni. »Informacijsko limono« za najmanj primerno informacijsko potezo je prejela trditev, da je aplikacija za sledenje stikom problematična za zasebnost, »informacijsko jagodo« kot najboljšo potezo pa COVID-19 Sledilnik, tj. sistem za zbiranje podatkov o koroni. Čestitke nagrajencem!

Mojca Ciglarič, predsednik programskega odbora
Matjaž Gams, predsednik organizacijskega odbora

FOREWORD - INFORMATION SOCIETY 2021

The 24th *Information Society Multiconference* survived the COVID-19 problems. In 2021, there are eleven conferences with a growing trend and real hopes that 2022 will be better due to successful vaccination. The multiconference survived due to the conference chairs who bravely decided to continue with their conferences despite the first pandemic in the modern era.

The COVID-19 pandemic did not decrease the growth of ICT, information society, artificial intelligence and science overall, quite on the contrary – the progress of computers, knowledge and artificial intelligence continued with the fascinating growth rate. However, COVID-19 did increase the downfall of societal norms, trust in science and progress. On the other hand, the awareness of the majority, that science and development are the only perspectives for a prosperous future, substantially grows.

The Multiconference is running parallel sessions with 170 presentations of scientific papers at eleven conferences, many round tables, workshops and award ceremonies, and 400 attendees. Selected papers will be published in the Informatica journal with its 45-years tradition of excellent research publishing.

The Information Society 2021 Multiconference consists of the following conferences:

- Slovenian Conference on Artificial Intelligence
- Data Mining and Data Warehouses
- Cognitive Science
- People and Environment
- 50-years of High-school Computer Education in Slovenia
- Batman Project Workshop
- Insieme Interreg Project Workshop
- URBANITE Project Workshop
- Student Computer Science Research Conference 2021
- International Conference of Transfer of Technologies
- Education in Information Society

The multiconference is co-organized and supported by several major research institutions and societies, among them ACM Slovenia, i.e. the Slovenian chapter of the ACM, SLAIS, DKZ and the second national academy, the Slovenian Engineering Academy. In the name of the conference organizers, we thank all the societies and institutions, and particularly all the participants for their valuable contribution and their interest in this event, and the reviewers for their thorough reviews.

The award for lifelong outstanding contributions is presented in memory of Donald Michie and Alan Turing. The Michie-Turing award was given to Prof. Dr. Jernej Kozak for his lifelong outstanding contribution to the development and promotion of the information society in our country. In addition, the yearly recognition for current achievements was awarded to the team from the Department of Intelligent systems, Jožef Stefan Institute for the second place at the XPrize Pandemic Response Challenge for proposing best counter-measures against COVID-19. The information lemon goes to the claim that the mobile application for tracking COVID-19 contacts will harm information privacy. The information strawberry as the best information service last year went to COVID-19 Sledilnik, a program to regularly report all data related to COVID-19 in Slovenia. Congratulations!

Mojca Ciglarič, Programme Committee Chair
Matjaž Gams, Organizing Committee Chair

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PREDGOVOR

Na delavnici sodelujejo partnerji projekta ERA PerMed BATMAN in drugi zainteresirani znanstveniki. BATMAN je akronim za "Biomolecular Analyses for Tailored Medicine in Acne iNversa", biomolekularne analize za personalizirano zdravljenje Acne Inversa. Cilj projekta, ki se je začel leta 2019, je priti do novih spoznanj in boljšega razumevanja mehanizmov kronične bolezni Acne Inversa, imenovane tudi Hidradenitis Suppurativa, in razviti ciljane metode zdravljenja. To bo pripomoglo k boljšemu življenju pacientov. Raznoliki konzorcij projekta sestavljajo partnerji s področij medicine, genetike, modelov tkiv in informacijskih tehnologij.

Delavnica je tudi del letnega sestanka partnerjev konzorcija.

Predsednika delavnice se distancirata od nagrad, ki so bile podeljene med Multikonferenco.

Sergio Crovella in Anton Gradišek, predsednika delavnice

FOREWORD

This Workshop brings together the partners that collaborate on the ERA PerMed project BATMAN, as well as other interested parties. BATMAN stands as the acronym for "Biomolecular Analyses for Tailored Medicine in Acne iNversa". The aim of the project that started in 2019 is to find new knowledge and better understanding of mechanisms of the chronic disease Acne Inversa, also called Hidradenitis Suppurativa, and to provide tailored treatment for the patients, thus improving their quality of life.
The consortium is heterogeneous and brings together partners with experiences in the field of medicine, genetics, tissue models, and information technologies.

This Workshop is also a part of the annual consortium meeting of the partners.

Workshop chairs distance themselves from the awards that were handed out during the Multiconference.

Sergio Crovella and Anton Gradišek, workshop chairs

PROGRAMSKI ODBOR / PROGRAMME COMMITTEE

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Anton Gradišek

Paola Maura Tricarico

Identification of novel genetic variants in Hidradenitis Suppurativa patients through the investigation of familial cases

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ABSTRACT

Hidradenitis Suppurativa (HS) familial cases represent 40% of the total cases observed. Current knowledge on the etio-pathogenesis of these cases is still poor; for this reason, we decided to investigate the genetic variants associated to this disease in 5 HS families. In 3 families we found single nucleotide variation (SNV) in genes never associated with HS: *ZNF318*, *DCD*, *DSC3*. In one family we found a new SNV in *NCSTN* gene, one of the few genes already associated with HS. In another family, due to the low number of individuals analyzed, we did not find with certainty the SNV associated with the disease but we found three SNVs in *PADI3*, *DSP* and *KRTAP10-4* genes. Deepening knowledge on the genetic variants associated with these familial HS cases is a necessary first step to unravel the disease etio-pathogenesis; in fact, to better understand the disease an integrated approach involving different OMICs is the right path to be followed.

KEYWORDS

Hidradenitis suppurativa, familial cases, genetic variants, WES analysis.

Information Society 2021, 4-8 October 2021, Ljubljana, Slovenia

Hidradenitis suppurativa (HS), a chronic autoinflammatory refractory disease with recurrent skin lesions and wounds of difficult resolution, currently represents an area of high-unmet clinical need. HS has multifactorial etiology that involves a strict interplay between genetic factors, immune dysregulation, hormonal influence, bacterial colonization, impaired wound healing and environmental risk factors [1, 2]. Approximately 40% of patients with HS report a family history of the condition, and amongst these only about 10% present mutations in genes involved in the gamma-secretase pathway, namely *NCSTN*, *PSENEN* and *PSEN1* genes [3].

The study of HS familial cases represents a tool identify novel genetic factors, other than the genes of the gamma-secretase pathway, involved in the etio-pathogenesis of this complex disease. Unfortunately, analyzing HS familial cases can be sometimes difficult due to delayed diagnosis, absence of personal and family health history investigation, incomplete penetrance of the disease and also unwillingness to participate in the genetic study of other family members.

Here we investigated 5 HS families aimed at identifying genetic variants associated with the disease, using whole exome sequencing (WES).

Patients with a positive family history of HS were recruited from January 2019 to May 2021 at the Dermatology Unit of the University of Milan (Italy) and at the Dermatology Service of "Hospital das Clinicas", Recife, Brazil. All study participants signed a written informed consent after the approval by the Single Regional Ethical Committee of Friuli Venezia Giulia (CEUR) (CEUR-2018-Sper-127-BURLO and CEUR-2020-Em-380) by the Area B Milan Ethics Committee (protocol no. 487_2020) and by Ethical Committee of the Federal University of Pernambuco (n. 3.048.719; 30/11/2018).

Genomic DNAs have been extracted from saliva by using the Oragene-DNA (Ottawa, Canada) kit following the manufacturer's protocols. WES, with 100X of expected coverage, has been performed in outsourcing by Macrogen

(Seoul, Korea). WES analysis has been performed using the InterOMICs Genome Pro software, as described in our previous study [4]; WES results have been validated by Sanger Sequencing.

In family 1 (11 HS patients and 36 healthy subjects) we found a rare missense single nucleotide variation (SNV) in the exon 4 of *ZNF318* gene in heterozygosis (rs767801219). The SNV was detected in heterozygosis in 17 family members comprising all of the 11 individuals who initially declared to be affected by HS and additional 6 individuals that haven't been mentioned to possess any sign of the disease (**Figure 1**). This identified SNV shows an autosomal dominant inheritance pattern with incomplete penetrance.

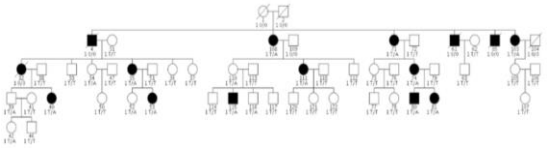

Figure 1: Pedigree of the Family 1. 47 individuals adhered to the study, 11 of which declared to be affected by HS, and the genotype of the selected variant in *ZNF318* gene (rs767801219).

ZNF318 gene encodes the zinc finger 318 (ZNF318) protein involved in the regulation of the androgen receptor by acting both as a co-repressor or co-activator in AR transactivation function. To date the effect of the SNV in the protein structure is hard to predict *in silico* due to the dimension of the protein and the lack of a clearly defined structure, but the role of androgens in HS is well known and has been explored in numerous observational and some interventional studies [5].
In family 2 (2 HS patients and 1 control and 1 child) we found a rare frameshift insertion in exon 4 of *DCD* gene in heterozygosis (rs538180888) in all 2 HS patients; this variant is also present in the daughter, an 11-year-old child who begins to manifest relapsing inguinal furuncles (**Figure 2**).

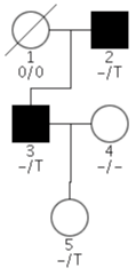

Figure 2: Pedigree of the Family 2. 4 individuals adhered to the study, 2 of which declared to be affected by HS, the genotype of the selected variant in *DCD* gene (rs538180888).

DCD gene encodes Dermcidin, the most abundant antimicrobial peptide (AMP) present in human sweat. The identified frameshift variant disrupts the ORF of *DCD* and results in a 33 amino acid peptide having a completely altered sequence, if compared to the wild- type DCD-1(L) peptide. This affects both the N-terminal and the C-terminal partitions, hence impairing the activity of DCD. This mutant is characterized by a less compact structure and by an increased solvent accessibility, particularly highlighted by the increased flexibility of its C-terminal region.
In HS, a dysbiosis-driven aberrant activation of the innate immune system leading to excessive inflammatory responses, is thought to be partially induced by a marked dysregulation in antimicrobial peptides production, in particular DCD [6, 7]. Indeed, in the skin of HS patients a significant down-regulation of DCD expression has been observed [8, 9].
In family 3 (4 HS patients and 1 control) we found a rare missense SNV at exon 10 of *DSC3* gene in heterozygosis (rs114245564) in all 4 HS patients (**Figure 3**).

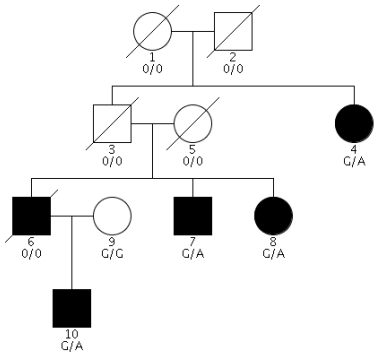

Figure 3: Pedigree of the Family 3. 5 individuals adhered to the study, 4 of which declared to be affected by HS, the genotype of the selected variant in *DSC3* gene (rs114245564)

DSC3 gene encodes Desmocollin-3 a desmosomal cadherin superfamily member, component of the transmembrane core of desmosomes required for maintaining cell adhesion in the epidermis. The critical role of these desmosomal cadherins in epithelial integrity has been illustrated by their disruption in mouse models and human diseases. Alterations in the expression and function of the desmosomal cadherins have been observed in severe autoimmune skin disease pemphigus, epidermolysis bullosa and hypotrichosis and recurrent skin vesicles [10, 11].
In family 4 (4 HS patients, 3 controls and 2 children), enrolled in Brazil, so with individuals showing a different genetic background when compared to the other Italian members of the analyzed families, we found a SNV in *NCSTN* gene exon 2 in heterozygosis (NM_015331:exon2:c.T131A) encoding a premature stop codon [NP_056146 1:p.(L44*)], in all 4 HS patients and also in the 2 children (11- and 16-year-old). To date, these 2 children do not show the disease, probably due to their young age (**Figure 4**).

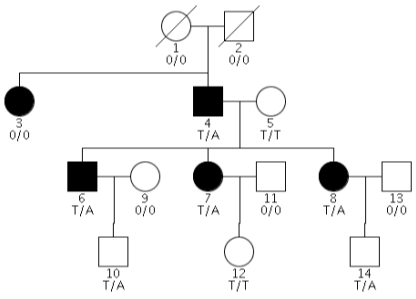

Figure 4: Pedigree of the Family 4. 9 individuals adhered to the study, 4 of which declared to be affected by HS, the genotype of the selected variant in *NCSTN* gene.

This genetic variant was not present in the Genome Aggregation Database (gnomAD) and therefore it was never associated with HS; despite this, the *NCSTN* gene is one of the few genes already associated with HS [3].
In family 5 (2 HS patients and 1 control) we found 25 SNVs in genes expressed in the skin or by the immune system (**Table 1**).

Table 1: List of single nucleotide variations (SNVs) genes expressed in the skin or by the immune system, found in 2 HS patients and not in the control of the family 5

Gene	SNV	Ref	Alt
AQP9	rs1439722664	T	C
PHYKPL	rs559406393	C	G
ACSS2	rs371982555	C	T
ARSK	rs754905227	T	A
CRIP1	rs200883038	C	A
MYH14	rs371244397	C	T
SMYD5	rs61755313	G	A
VEGFA	vi6.43777526	T	G
DHFR2	rs772191447	T	C
TRPS1	rs61745721	T	C
HSPBP1	rs150486738	G	A
MAP3K4	rs1477003192	T	C
PADI3	rs142129409	T	A
PPP1R3D	rs377580619	G	A
SYNE1	rs34028822	G	A
ZNF692	rs201441689	C	T
ADPRHL2	rs139736291	A	G
PTCD1	rs35556439	G	A
COPB2	vi3.139379091	C	T
DSP	rs78652302	A	T
KRTAP10-4	rs782312294	G	T
PRSS1	rs757111793	G	A
SCFD2	rs79025139	C	A
TRIM16	rs143877253	C	A
TTLL12	rs369903948	T	C

Among these genes, the ones considered as possibly related to dermatologic disorders based on their functions are: *PADI3*, *DSP* and *KRTAP10-4* (**Figure 5**).

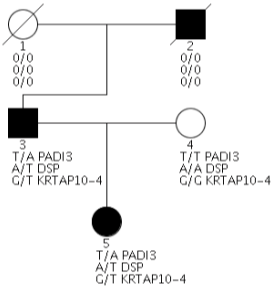

Figure 5: Pedigree of the Family 5. 3 individuals adhered to the study, 2 of which declared to be affected by HS, the genotype of the selected variants in *PADI3, DSP* and *KRTAP10-4* genes.

PADI3 encodes for a member of the peptidyl arginine deiminase family of enzymes, which catalyze the post-translational deimination of proteins by converting arginine residues into citrullines. Deimination is implicated in many physiological processes including keratinocyte biology and skin homeostasis. One example of deiminated protein is the fillagrin, a key protein in the epidermal barrier function, expressed in the hair follicle. In addition to this, *PADI3* gene may also play a role in the cornification-related autophagy process of the epidermis. Uncombable Hair Syndrome 1 and Central Centrifugal Cicatricial Alopecia are diseases associated with *PADI3* gene [12].
DSP encodes for Desmoplakin, an obligate and the most abundant component of functional highly specialized adhesive intercellular junctions known as desmosomes. Desmosomes are abundant in districts that are continuously subjected to mechanical solicitations such as the epidermis and hair follicles, because they confer strong mechanical strength to tissues and contributing to the maintenance of tissue architecture and cohesiveness [13, 14]. Alopecia, palmo-plantar keratoderma, skin fragility woolly-hair syndrome, erythrokeratodermia, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy/dysplasia are disorders also connected to alteration in the expression and function of Desmoplakin [15].
KRTAP10-4 encodes for Keratin Associated Protein 10-4, which are essential for the formation of a rigid and resistant hair shaft through their extensive disulfide bond cross-linking with abundant cysteine residues of hair keratin. This gene plays an important role in the keratinization pathway [16].
Unfortunately, perhaps due to the low number of family individuals analyzed, to date we do not have the ability to identify with certainty the SNV associated with this HS familial case.

Considering the findings obtained by analyzing some HS families, one with different genomic background with respect to the others, we can state that HS familial cases are extremely useful to investigate novel actors involved in this complex disease, so the first need is to augment the number of families to be analyzed; secondly, to more deeply and precisely evaluate the role of the identified genetic factors, at least an integration with transcriptome is needed. To this end it is important to recall that when families are diagnosed and recruited, it should be envisaged, when possible and permitted by the ethical committee, a skin biopsy of lesional, pre-lesional and healthy skin of the patients, to allow RNA extraction and consequent transcriptome analysis.
As conclusive remarks, we should bear in mind that HS is a complex disease and that the genetics by itself is not able to completely unravel the disease etio-pathogenesis; an integrated approach involving different OMICs, such as genomics, transcriptomics and microbiomics etc. is the path to be followed to better understand the disease and consequently design possible tailored treatments.

ACKNOWLEDGMENTS

This work was supported by a Biomolecular Analyses for Tailored Medicine in AcneiNversa (BATMAN) project, funded by ERA PerMed, by a grant from the Institute for Maternal and Child Health IRCCS 'Burlo Garofolo/Italian Ministry of Health' (RC16/ 2018), by a grant Interreg Italia-Slovenia, ISE-EMH 07/2019 and by CNPq (311415/2020-2).

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Generation of animal and human 3D models of Acne Inversa

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ABSTRACT

Acne Inversa (AI; Verneuil's Disease, Hidradenitis Suppurativa) is a chronic inflammatory condition affecting the hair follicles in moist areas of the body (inguinal folds, scrotum, pubic area). As currently understood, AI is triggered by a hair canal obstruction, leading to follicle bursting and entry of cellular debris and bacteria into the dermis, resulting in a powerful and persistent inflammation [1]. Over time, some patients develop severe scarring of the inflamed areas, leading to surgical removal of the affected skin areas. These events might be triggered or exacerbated by bacterial infection or epithelial barrier weakening. Thus far, only mutations in genes encoding the gamma-secretase) have been found to underlie familial forms of AI.

Our laboratory aims at creating ex vivo and in vivo models to better study AI pathogenesis, which are still lacking. To achieve this, we are developing full-thickness skin models built from cells of healthy donors and patients, as well as murine models bearing AI-related defects for autophagy in hair follicles. In addition, we participate in an effort to unravel the potential involvement of B cells, a specific yet poorly studied aspect of AI.

KEYWORDS

Acne inversa, human 3D skin model, mouse, hair follicle, inflammation, immunology, autophagy, B cells

1 Human reconstructed skin model with primary fibroblasts and epidermal cells from either healthy donors or immortalized cell lines (HaCaT)

Previous work from our team allowed the creation of an immunocompetent skin model based on a collagen scaffold [2, 3], monocyte-derived dendritic cells (MoDCs) and primary human skin cells. Our objective is to repurpose this skin model by either using keratinocytes from AI patients producing a defective desmoplakin, or HaCaT genetically modified through CRISPR-Cas9 to carry mutations for the gamma-secretase complex. We expect those mutated epithelial cells to produce an epidermis and influence MoDCs introduced in the scaffold. The final purpose is to induce an inflammatory response close to AI ex vivo.

We tested different scaffold seeding conditions using healthy human fibroblasts, keratinocytes and MoDCs. We also evaluated non-modified HaCaT cells instead of keratinocytes. The resulting models were frozen after up to 6 weeks of culture, sliced and stained with various epithelial and immune markers. Despite promising results, cell seeding and fibroblast proliferation were inconsistent. We assume this to result from the scaffold manufacturing process, which we are currently seeking to optimize.

2 Reproducing auto-inflammatory characteristics of acne inversa in a mouse model.

Dr. Michele Boniotto (Créteil, France) found that AI patient mutations of the gamma secretase complex results in autophagy impairment *in vitro*. This prompted us to breed a mouse model to investigate this matter further *in vivo*, by crossing Sox9creERT2 and $Atg5^{flox/-}$ strains. Since Sox9 is an important transcription factor driving hair follicle stem cells (HFSC) development and function [4, 5], the resulting strain is expected to lack functional autophagy in the infundibulum of the hair follicle. We expect that autophagy loss of function in HFSC to produce a barrier defect and a stronger immune infiltrate, as a result of impaired processing of apoptotic hair follicle cells (efferocytosis) [6].

Two consecutive depilations were performed in the course of two weeks, which may lead to hair occlusions. Skin samples were harvested and studied by flow cytometry and immunochemistry staining. Total skin digestion six hours after the second depilation showed a stronger infiltration of neutrophils and monocytes in the dermis of knock-out mice (Sox9creERT2 $Atg5^{flox/-}$) compared to wild-type ($Atg5^{flox/+}$) and littermates

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(Sox9creERT2 Atg5$^{flox/+}$). Infiltration was resolved after one week in all animals. Further interpretation requires confirmation of these preliminary results by additional experiments. Next, we plan to directly inhibit gamma secretase and autophagy function individually or simultaneously in C57BL/6 mice.

3 B cell populations in blood samples from families affected by acne inversa

Dr. Sergio Crovella (Trieste, Italy) has identified a familial mutation of the transcription factor Znf318 in AI patients of an Italian family (unpublished data). It was previously published that Znf318 is necessary for IgD expression by B cells in mouse models [7, 8]. Interestingly, AI is among the few dermatological conditions that show prominent B cell infiltrates in lesions [9, 10].

This prompted us to investigate the role of B cells in AI pathogenesis. As a preliminary work, we intend to identify variations in B cell subsets among PBMCs from patients with familial or sporadic forms of AI. Our cytometry panel allows us to study the naive, memory and plasmablast B cell populations in patient blood.

Covid-19 crisis prevented blood sampling from Italian patients, who may show B-cell related defects related to their Znf318 mutation. Yet, we analyzed healthy and diseased individuals of affected families from Innsbruck, Austria, for which whole-exon sequencing is not yet available. So far, blood B cells of 7 patients from 3 different families have been studied. Currently aggregated data identified patients that deviate from usual population percentages, although we require additional unaffected people from the same families to confirm our analyses. Raw PBMCs have also been frozen, which will be assayed for T cell responses and used to produce MoDC for our 3D skin models.

DISCUSSION

Despite significant delays related to COVID-19 for animal breeding and interruption of cell cultures for more than 3 months, we have improved our 3D scaffold production method and achieved successful seeding with human-derived cells, including MoDCs. We managed to establish protocols and produce preliminary results on the *in vivo* studies in the mice, and have plans to go more in depth in the future by studying systemic gamma-secretase inhibition. Finally, our analyses of AI patients in Austria will be interpreted in the light of their upcoming whole exome sequencing data, and extended by samples from Italian patients with Znf318 mutation.

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Development of new cellular models to identify molecular mechanisms in Hidradenitis Suppurativa

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ABSTRACT

No satisfactory in-vivo and in-vitro models to recapitulate Hidradenitis Suppurativa (HS) hallmarks have been developed so far. The first transgenic Ncstn KO mice model, engineered after the finding that g-secretase mutations were associated with HS in several families, lacked important HS features such as skin inflammation, abscess formation, fistulas, and scarring. In -vitro, the use of skin explants has helped in the identification of the IL-1 contribution to HS skin inflammation in HS, but this technique depends on skin biopsies availability.

For these reasons we have developed different models to obtain skin cells and skin organoids from Induced Pluripotent Stem cell lines carrying HS-associated mutations

KEYWORDS

CRISPR/Cas9, Induced Pluripotent Stem Cells, Outer root sheath epithelial cells, Skin Organoids, keratinocytes, sebocytes

1 INTRODUCTION AND RESULTS

Hidradenitis suppurativa (OMIM#142690; HS) is a chronic inflammatory disease involving hair follicles that presents with painful nodules, abscesses, fistulae, and hypertrophic scars, typically occurring in apocrine gland bearing skin [1]. Adequate models reflecting hallmarks of HS pathogenesis are a prerequisite to not only better characterize the molecular activity of genetic mutations in HS, but also to allow the discovery and of therapeutic targets in personalized approaches to cure the disease.

About 10% of HS patients present mutations in three of the four components of the gamma-secretase complex, namely NCSTN, PSEN1 and PSENEN with most of the mutations found in NCSTN [2]. These findings led to the analysis of the NCSTNflox/flox;K5-Cre mice that showed some HS hallmarks such as follicular hyperkeratosis and inflammation [3]. Unfortunately, mica and humans differ not only in hair distribution and hair follicle anatomy, but important genes such as *DCD* identified in a HS family by our consortium doesn't have a homologous in the mouse.

Ex vivo models using patients lesional skins have also been developed [4]. In fact, Vossen et al. [5] cultured punch biopsies from HS patients showing a major contribution of IL-1 in skin inflammation in HS. Moreover, these Authors were able to test different drugs to tame skin inflammation showing the effectiveness of the anti-TNF-a therapy.

Even if this ex-vivo model can be used to test a candidate treatment, specific limitations make this model useless for precision medicine. In fact, different genetic variants seem to cause the disease, so a skin model for each patient (or family) should be developed.

Our Team is developing new cellular models to identify the main biological pathways affected in HS and 3D models to be used to test novel candidate drugs. We are making use of hair follicle epithelial cells isolated from selected patients to build 3D reconstituted immunocompetent skins in collaboration with Dr. Flacher: these models will allow the study of the cross-talk among skin cells and immune cells

At the same time, we have developed skin organoids bearing hair follicles from Induced Pluripotent Stem cells obtained from patients with specific candidate mutations (Figure 1). By using the CRISPR/Cas9 methodology we have been able to correct the candidate mutation and obtain isogenic cell lines differing only for the selected mutation. IPSCs have been differentiated in CD200+/ITGA6+ hair follicle stem cells that could be further differentiated in TP63+/CK14+ keratinocytes or CK7+/MUC1+/PPARG+ sebocytes.

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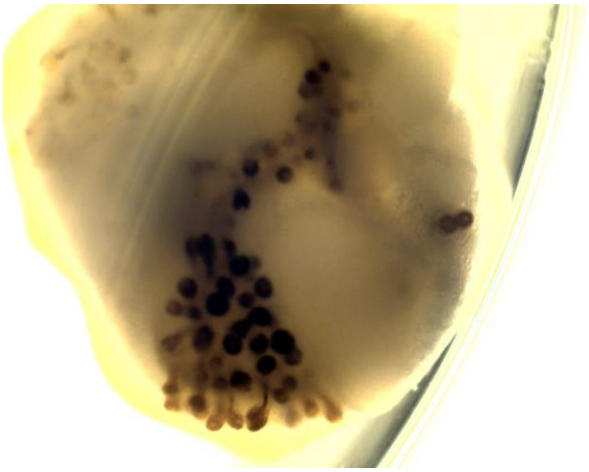

Figure 1: Skin organoids bearing hair follicles from IPSCs

IPSCs obtained from an HS patient with a novel mutation in NCSTN and presenting with HS and DDD were cultivated as described by Lee et al. [6] for 140 days and skin organoids bearing hair follicles obtained from a mutated and corrected clone.

From the skin organoids, thanks to a collaboration with StemCell Technologies, we have been able to isolate and cultivate TP63+/CK14+ keratinocytes (Figure 2)

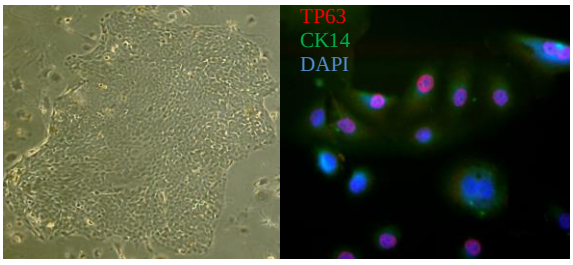

Figure 2: TP63+/CK14+ Keratinocytes isolated from skin organoids

Keratinocytes were obtained after dispase I digestion of skin organoids and cultivated in StemCell Technologies Keratinocyte Medium.

As we have already shown a defect in lysosomes in NCSTN deficient HaCaT cells, we are studying the lysosome structures in TP63+/CK14+ keratinocytes derived from mutated and corrected using lysosomal markers (Figure 3).

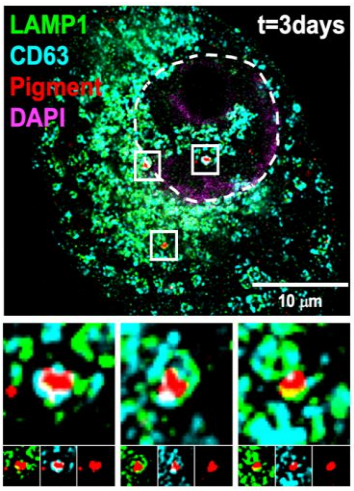

Figure 3: Lysosome distribution in KC obtained from skin organoids

Study of lysosome distribution in mutated and corrected keratinocytes using lysosomal markers CD63, LAMP1 and melanosomes degradation (Pigment)

2 OUTLOOK

Skin organoids will be analyzed by immunofluorescence and immunohistochemistry.

In addition, we plan to understand the activity of *NCSTN* mutation in skin organoids maturation by performing single cell RNA sequencing (Sc-RNAseq). Our hypothesis is that a g-secretase impaired activity skews the differentiation of hair follicle stem cells towards the epithelial keratinocytes. We do expect to see smaller or absent sebaceous glands in our skin organoids and an enlarged population of outer root and inner root sheath keratinocytes.

We plan to carry on the same experiments with IPCSs cell from a patient with a novel *ZNF318* mutation. ZNF318 is involved in Androgen Receptor (AR) signaling [7, 8], that has a major role in sebocytes differentiation [9]. We do expect that a perturbed AR signaling will skew the differentiation of hair follicle stem cells towards the keratinocyte population, still affecting sebaceous gland development.

IPSCs will be differentiated in 2D in CD200+/ITGA6+ hair follicle stem cells and treated to become CK7+/MUC1+/PPARG+ sebocytes (Figure 4) to understand what the activity of the novel ZNF318 mutation is.

IPSCs-derived keratinocytes and sebocytes will be provided to Dr. Flacher's team to build 3D immunocompetent skins.

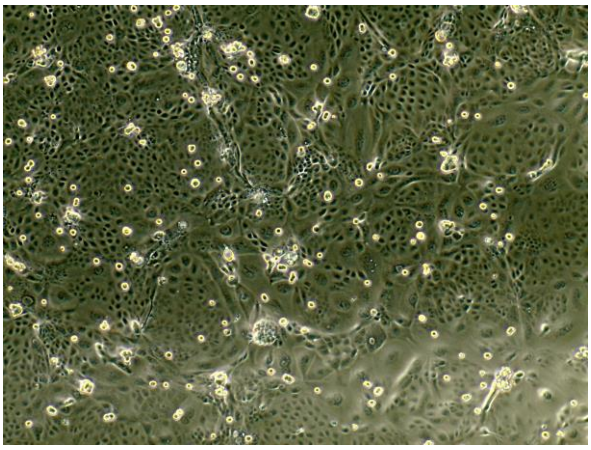

Figure 4: CK7+/MUC1+/PPARG+ sebocytes differentiated from IPSCs. Sebocytes were obtained from IPSCs after 22 days in Sebocyte Culture Medium.

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Hidradenitis suppurativa: from clinic to bench and back

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ABSTRACT

Hidradenitis suppurativa (HS) is a chronic inflammatory disease presenting with nodules, abscesses, and fistulas on the apocrine gland-bearing skin. HS may be classified as sporadic, familial or syndromic (PASH, PAPASH, PASH/SAPHO overlapping), the latter one being rare and characterized by a constellation of conditions regarded as autoinflammatory in their origin.

BAT2021 aims to bring together medical, genetic, experimental and lifestyle data to create holistic health records (HHR), which will allow us to build a tailored approach of each patient.

The inclusion criteria for patient enrollment are the compliance to the diagnostic criteria for HS; patient's demographics, clinical signs, anatomic phenotype classification, lifestyle habits, severity classification and treatment (former and current) are documented.

DNA/RNA obtained from biological samples (predominantly saliva and skin biopsies) of HS patients will be analysed by whole exome sequencing, whole genome genotyping SNPs arrays and transcriptomics. Clinical and molecular data will be stored into a special platform developed for the purpose of the project and will be analysed using advanced algorithms of artificial intelligence to propose a novel stratification method that clinicians can use in daily clinical practice.

KEYWORDS

Hidradenitis suppurativa, clinical practice, research workflow, whole-exome sequencing, whole genome genotyping SNPs arrays, transcriptomic, stratification, genotype-phenotype correlation, therapeutic outcomes

1 Clinical background

Hidradenitis suppurativa (HS), also known as acne inversa, is a chronic, inflammatory, recurrent, debilitating skin disease (of the terminal hair follicle), clinically characterized by inflammatory nodules that progress into abscesses and draining tunnels with foul smelling. Three main clinical HS phenotypes have been proposed, namely the classic or axillary- mammary, follicular and gluteal ones [1]. More recently, Van der Zee et al. proposed six different phenotypes, including the regular, frictional furuncle, scarring folliculitis, conglobata, syndromic and ectopic types [2]. Additional clinical phenotypes and cluster classifications have also been reported [3-5], but a definitive consensus has not been reached and any of these classifications addresses a prediction of therapeutic outcome. IHS4 (International Hidradenitis Suppurativa Severity Score System) is a validated tool for the severity assessment of HS and is arrived at by the number of nodules

(multiplied by 1) plus the number of abscesses (multiplied by 2) plus the number of draining tunnels (multiplied by 4). A total score of 3 or less signifies mild, 4-10 means moderate and 11 or higher correspond to severe disease [6].
HS has a profound impact on patients and their family life, leading to a high extent of emotional and physical distress, with social embarrassment, isolation, and depression [7]. With a prevalence in Europe varying between 0.3% and 1% [8], and a diagnosis often underestimated and usually delayed for 7.2 ± 8.7 years [9], HS is not a rare disease.
HS is associated with several other disorders: i) autoimmune or inflammatory comorbidities, particularly inflammatory bowel diseases, ii) rheumatologic diseases, such as seronegative spondyloarthropathies and Adamantiades– Behçet disease spondylarthritis and iii) malignancies, where the most severe complication is the development of squamous cell carcinoma in areas of chronically diseased HS skin. Other comorbidities associated with HS include obesity, dyslipidemia, diabetes mellitus, metabolic syndrome, hypertension, cardiovascular disease, secondary amyloidosis, lymphedema, polycystic ovary syndrome and sexual dysfunction. Finally, HS is also associated with mental comorbidity and psychosocial impairments [10]. HS is usually a sporadic disease but may more rarely occur as a familial disorder [11]. In a minority of patients, HS can present in combination with other diseases as a complex clinical syndrome. The main autoinflammatory syndromes characterized by the presence of HS are pyoderma gangrenosum (PG), acne and suppurative hidradenitis (PASH), pyogenic arthritis, PG, acne and suppurative hidradenitis (PAPASH), psoriatic arthritis, PG, acne and suppurative hidradenitis (PsAPASH), pustular psoriasis, arthritis, PG, synovitis, acne and suppurative hidradenitis (PsAPSASH) and PG, acne, suppurative hidradenitis, and ankylosing spondylitis (PASS) [12]. However, HS can also occur in the context of complex syndromes such as Familial Mediterranean Fever (FMF), synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO), follicular occlusion syndrome, Down syndrome, Keratitis-ichthyosis-deafness (KID) syndrome, Dowling-Degos disease and Bazex-Dupré- Christol syndrome [13].
Risk factors such as smoking, obesity and other lifestyle triggers have been linked to HS onset, while genetic factors are considered to play a crucial role in HS etiopathogenesis [14].

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30% of HS patients report a family history of HS; mutations in γ-secretase genes (NCSTN, PSENEN and PSEN1) have been identified as the most common genetic changes involved in HS familial cases and these variants lead to an impairment of Notch signaling. Notch signaling pathway dysregulation results in an alteration in the proliferation and differentiation of keratinocytes leading to disruption of the normal hair follicle cycle and the formation of follicular cysts, typical for HS [15]. Our group recently hypothesized HS as a member of neutrophilic dermatoses based on the elevated concentration of the cytokines IL-1β and IL-17 in skin lesions [16]. Moreover, some of our collaborators deeply involved in this project have also identified patients with HS occurring in the context of autoinflammatory syndromes, showing that PASH and PAPASH patients bear genetic variants in genes coding for proteins of the inflammasomes such as PSTPIP1, MEFV, NOD2 and NLRP3 [17]. Moreover, the up regulation of pro- inflammatory cytokines/chemokines in both lesional skin and serum are involved in the multifactorial HS pathogenesis [18]. With several new gene mutations coming into play, such as those involved in the keratinization pathways [19], on the background of a dysregulated innate immune response to commensal microbes and alterations in the skin microbiome as well, HS can be regarded as a multifactorial, polygenic autoinflammatory disease [18].

Medical treatments in HS are aimed at reducing incidence and flares thus improving HS patients' quality of life. Mild cases are usually treated by topical antibiotics having anti- inflammatory properties. Widespread disease is treated by systemic antibiotics and most severe cases by biologics such as adalimumab (anti-TNFα), currently the only biologic approved by the United States Food and Drug Administration [20] and by European Medicines Agency for treatment of HS [20,21].

Surgical resection of irreversibly damaged skin is often required, but often leads to functional impairments [20]. Different clinical trials for biologics targeting IL-17, IL-1 (alpha and beta), IL-36 and Janus kinase (JAK) 1 signaling response are currently ongoing, but simple outcome measures or novel biological models are demands to measure the efficacy of treatments [22].

2 Patient's enrollment and biological samples collection

Acting as one of the clinical partners of the project, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico of Milan has a large outpatient clinic with specialization in HS. The inclusion criteria for patient enrollment are the compliance to the diagnostic criteria for HS [23]. Patient's demographics, clinical signs, anatomic phenotype classification, lifestyle habits, severity classification and treatments (former and current) are documented. For the data documentation, the REDCap platform is used.

The study population include approximately 300 patients with moderate-to-severe HS, of which most are sporadic. 6% of patients have a HS positive family history and 14 patients present a HS syndromic form (4 PASH patients, 3 PAPASH, 5 PASH/SAPHO overlapping, 1 SAPHO and 1 patient with PASS).

Before biological samples collection, all patients and their relatives provide written informed consent for genomic analysis (protocol no. 487_2020) and receive pre-test genetic counselling in accordance with guidelines; indeed, the occurrence of the same condition among family members is a key factor to consider. Pedigree analysis of the families with more than one member affected is very useful for determining the patterns of disease inheritance.

All biological samples are collected, stored, and used in agreement with the ethical and research guidelines set. Currently, we have collected saliva from 200 HS patients through Oragene DNA collection Kit (for human DNA) that allows for a high-quality human DNA to assess biomarkers and genetic variants associated to HS, its severity and response to biologic therapy. In collaboration with IRCCS Burlo Garofolo of Trieste, we have analyzed through Whole Exome Sequencing, 12 syndromic patients (PASH, PAPASH, PASH/SAPHO

overlapping) and in the first report, we have demonstrated genetic variants involving genes regulating the keratinization process and vitamin D metabolism, suggesting that a dysregulation of these two pathways may contribute to the HS pathogenesis. Vitamin D has been predicted as able to regulate skin homeostasis by controlling proliferation and differentiation of hair follicle and the low levels of vitamin D observed in all studied patients support the idea that vitamin D insufficiency could be involved in PASH and PAPASH pathogenesis.

We have also recruited 9 familial cases of HS, two of which in collaboration with IRCCS Burlo Garofolo of Trieste and the Italian Association of HS patients, respectively. Genetic analyses of HS familial cases and their family members are ongoing.

Our group has collected HS skin biopsies from lesional, perilesional and unaffected tissue (approximately 2 cm from the lesional skin) from the same anatomical region. Important is i) to take biopsies from different kind of HS lesions, including abscesses, plaques and fistulae (in the same patient, if it is possible); ii) smaller lesions (up to 1 cm in diameter) such as cysts and inflammatory and non-inflammatory nodules, should be completely excised while a deep biopsy (extending to subcutaneous tissue) should be made from abscesses and fistulae and iii) typical sites, such as axillary or inguinal folds as well as anogenital area should be chosen for taking biopsy but having samples also from atypical sites, i.e. dorsum or cervical region as well as foruncles on different areas of the body, could be of interest.

Skin samples has been subdivided into two parts, one of which for conventional histology (formalin-fixed, paraffin- embedded) and the other one frozen for additional studies (immunohistochemistry, protein array, real - time PCR). An additional skin samples is taken and stored in Rna ladder for transcriptomic analyses.

For functional and validation studies, we have performed hair follicle pick up according to the following procedure: a firm pull motion with forceps must be performed at the base of the hair. Only plucked hair in the anagen phase (minimum of five from each subject) contain enough keratinocytes for a successful culture initiation. The hair has been plucked from the occipital and temporal scalp regions but facial hair types like beard, eyebrow, or hair from the nose can be used. The hair shaft has been cutted slightly behind the follicle with sterile scissors resulting in an approximate 5 mm long piece consisting mainly of the follicle. The plucked hairs were stored in a tube filled with 5 mL Defined keratinocytes-SFM medium (DKSFM; Gibco – Thermo Fisher Scientific, Switzerland) at room temperature [24].

3 Conclusions

The comparison of the results obtained from DNA/RNA sequencing between patients and controls will highlight possible causative genes and signalling pathways. Thepossible detection of genotype-phenotype correlations willallow a more

exhaustive and precise clinical patient stratification which, in addition to the existing pharmacogenetic data banks, will help the development of new effective drugs and a future individualized treatment of HS patients.

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Disease burden of hidradenitis suppurativa and assessment of a non-invasive treatment option

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ABSTRACT

Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease of intertriginous body areas. Due to an often delayed diagnosis and various symptoms, disease burden is often under estimated. In the present work, we summarize our results obtained from several studies aiming at a better description of disease activity and an improved assessment of patient-related symptoms.

Treatment options for HS are limited; treatment ranges from medical to surgical options. However, despite numerous treatment options for HS, efficacious and noninvasive treatment options resulting in long-term remission and management of symptoms of the disease are still needed. We present a meta-analysis of topical treatment options and discuss the need of real world data for estimation of treatment efficacy.

KEYWORDS

Acne inversa, Hidradenitis suppurativa, human, disease burden, DLQI, treatment options, topical treatment, medical device, IHS4

INTRODUCTION

Hidradenitis suppurativa (HS) as a chronic inflammatory disease of the skin characteristically manifests in inguinal, axillary and submammary body areas. HS patient suffer severely from the disease due to pain, stigmatization and often delayed diagnosis, since the disease is often misinterpreted as repeated abscesses for a long time. Consultation of a dermatologist early after disease onset is important.

Treatment of HS is often frustrating, since the options are limited. Medical treatments including antibiotics, hormones, and anti-TNFα [1]) can successfully control symptoms, but discontinuation is often associated with relapses. Surgical interventions can induce long-term symptom control, but may not be useful for all patients due to long remission times and scarring tissue.

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ASSESSMENT OF HS DISEASE BURDEN

To contribute to the development of a validated tool for the (objective, physician-based) assessment of disease severity/activity, we participated in a consensus towards the development of an International HS Severity Score System (IHS4) initiated by members of the European Hidradenitis Suppurativa Foundation (EHSF) [2]. Within the IHS4, a variety of clinical signs were rated by 11 centers including and assessing 236 patients. The resulting IHS4 score is arrived at by the number of nodules (multiplied by 1) plus the number of abscesses (multiplied by 2) plus the number of draining tunnels (multiplied by 4). A total score of 3 or less signifies mild, 4-10 signifies moderate and 11 or higher signifies severe disease. The IHS4 was developed and published in 2017 and since then, a variety of studies have utilized the score to assess disease severity both in real-life, as well as within clinical trials [3]. As such, the baseline IHS4 score has proven to be a meaningful predictor for recurrences during adalimumab therapy of HS [3].

Using a German data base with information on ~1800 HS patients, the patients' quality of life (QoL) was assessed [4]. The aim of this study was to present more robust data on patients' QoL using the Dermatology Life Quality Index (DLQI). Overall, within this large cohort, the mean DLQI was 13.2±8.1 again stressing the strong burden of HS on affected patients and a severely impaired quality of life. QoL correlated with pain, disease severity as assessed by the IHS4 sore, as well as Hurley score.

Pain is one of the important aspects affecting QoL in HS patients. Pain was assessed by a numerical rating scale (0= no pain to 10= severe pain) by affected HS patients (1,795 individuals) [5]. Pain was reported by 84% of patients with the majority reporting mild pain (78%). Interestingly, females and smokers experienced more intense pain. Pain levels correlated with the number of affected areas and disease severity, as expected.

To gain further insights into the frequency of familial cases within 1795 German patients, we performed a patient survey in 4 independent, patient network-run social media platforms within Germany. Within 7 days, a cumulative number of 642 responses was acquired. Out of these responses, 249 (38%) of the patients confirmed that at least one first-degree relative (parents, children, siblings) are also affected by the disease. This complements already existing data from the literature stating hereditary HS in 5-40% of cases [6]. Earlier reports described hereditary HS to be more severe; studies analyzing the

pathomechanism in these families involving gamma-secretase and inflammasome activation are underway [6,7].

TOPICAL AND DEVICE-BASED THERAPY FOR MILD HS

Treatment options for HS are often unsatisfactory. We recently studied the effect of a combination therapy of intense pulsed light (IPL) and radiofrequency (RF). To this aim, the first study with 47 patients was performed as a prospective, monocentric, randomized, three-arm parallel-group design trial with a prior 12 weeks observation period (NICE study) [8,9]. Treatment arms were IPL and RF monotherapies or IPL + RF combination therapy. After 12 weeks, all patients received IPL + RF for additional 12 weeks (cross-over). After 12 weeks, active lesion counts of the IPL + RF group decreased by 50% in 50% of patients, in 33% even by 75% (Hurley I/II patients, less effective in Hurley III) correlating with an even better improvement in DLQI. A controlled follow up trial (RELIEVE study) compared topical clindamycin with topical clindamycin plus IPL + RF in 88 patients [10]. After 16 weeks of treatment, the IHS4 score was improved by 60% in the combination therapy group compared to 18% improvement in clindamycin-treated patients. Secondary endpoints (e.g. DLQI) showed similar results.

The aim of a follow-up study was to perform a meta-analysis on the effectiveness of local and instrument-based therapies under the prism of their efficacy and safety profile [11]. We thus performed a literature search and analyzed clinical evidence for the various therapeutic options. Effective treatments for out-patient care of HS patients exist including topical clindamycin, resorcinol, and intralesional corticosteroids. New devices such as LAight therapy (combining IPL with radiofrequency) are available, which can be used as monotherapy or adjunct therapy in combination with systemic treatment and/or surgery for the management of HS patients. All topical treatment options are best suited for mild to moderate HS and aid to control disease activity.

REQUIREMENT FOR REAL WORLD DATA ON TREATMENT EFFICACY

Publication of real world data on the results of treatment with (approved) drugs and/or medical devices is important to allow for a reasonable judgement about the efficacy of a medication, especially since due to the nature of controlled clinical studies certain patient groups, who in daily clinical routine would best benefit from such new treatments, are excluded from study inclusions. Real world data on the treatment of HS was summarized [12]. Adalimumab, the only approved biological treatment so far, represents a cost-efficient and effective therapy.

Additional publications about real world data with high(er) numbers of patients, including those with different risk factors, are required. Real world data will help to really assess the developing therapeutic spectrum of HS in our daily routine.

DISCUSSION

HS is a chronic inflammatory disease of the skin, which requires raising better awareness, good scoring tools and more (outpatient) treatment alternatives. Although the disease was previously treated using surgery, new treatment modalities allowing for an effective treatment of mild and moderate cases in an ambulatory setting are currently developed.

HS appears to present as a disease with a variety of different mutations and pathways involved in its pathogenesis. Assessing these familial cases of HS will aid in a better understanding of the disease and open avenues for therapeutic modification.

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An Overview of the BATMAN Platform

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ABSTRACT

This paper presents an overview of the platform used in the project BATMAN. We look at the architecture and at the interactions between the components, namely the website, the smartphone app, and the server, and how these components are used by the medical doctors, patients and data scientists.

KEYWORDS

BATMAN platform, web platform, smartphone application, questionnaires

1 INTRODUCTION

In recent years, the use of smartphone applications related to health has expanded substantially. Smartphones and other wearable sensors have become being daily companions for a majority of the population in developed countries. Probably the most commonly-known health-related applications focus on aspects such as exercise (i.e., fitness trackers) or nutrition and are typically independent of involvement of a medical doctor. On the other hand, there is ongoing research dealing with the use of data from the wearables to assist the clinicians in improving treatment of patients. An example of such research is the ERA PerMed project BATMAN [1] that aims at improving the understanding of the chronic dermatological condition Hidradenitis Suppurativa (HS), also called Acne Inversa. HS is a chronic inflammatory disease involving hair follicles that presents with painful nodules that release pus. Within the framework of the BATMAN project, we aim in bringing together medical, genetic, experimental, and lifestyle data to build a truly personalized model of each patient in order to tailor specific treatments.

This paper presents the overview of the platform developed within the BATMAN project. This platform collects data from patients, such as answers to questionnaires, and enable doctors to follow the patient's state and assign additional questionnaires when appropriate. The gathered data are anonymized and further processed by data scientists by building models for HS patients and seeking for new knowledge.

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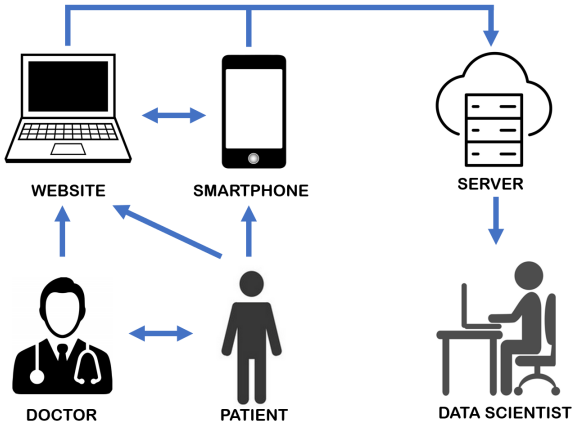

Figure 1: The basic schema showing the interactions of the platform users with the technical components.

The rest of the paper is organized as follows. Section 2 presents the BATMAN platform. The smartphone application is described in Section 3. Finally, Section 4 concludes the paper with summary and future plans.

2 THE BATMAN PLATFORM AND ITS USERS

In this section, we present an overview of the BATMAN platform, namely how its components work and how they are used by the participants in the project, i.e., medical doctors, patients, and data scientists. The basic schema of the interactions is shown in Figure 1. The patient and the doctor input the patient data through a website. Patients also use a smartphone app for activity tracking. The information collected via the website and the smartphone app are stored on a server where it is then available to data scientists.

The BATMAN platform website has a double functionality: it serves as the main information point about the BATMAN project and it is also the entry point to the platform. Users can log in with their usernames and passwords. Depending on their role, they can see different types of content. To ensure the security and to prevent any unauthorized access, the user accounts are created by the platform administrators and assigned to users.

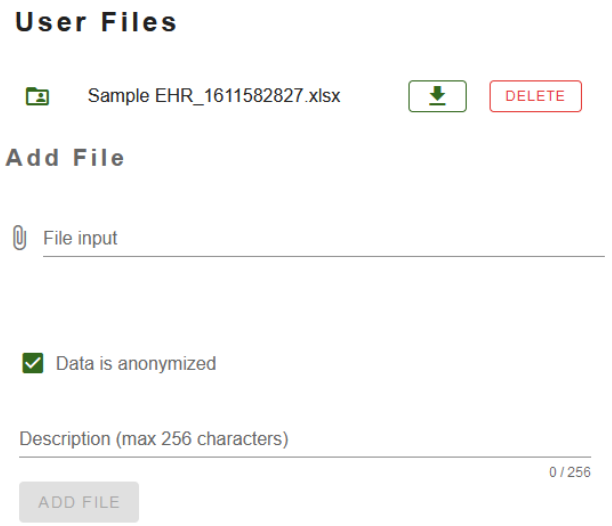

Figure 2: Online form for doctors to upload the patient's EHRs.

2.1 Doctors

Medical doctors can view and manage the patients' files. They are also able to manually upload the patients' medical records (see Figure 2). If convenient, patients can be assigned to different groups. The doctors have the possibility to create new questionnaires (see Figure 3) and to assign questionnaires to their patients (see Figure 4). There are three types of general questionnaires:

- Major Depression Inventory
- Dermatology Quality of Life
- Food preferences

The food preferences questionnaire has been split to several forms with a small number of questions since the list of food preferences includes around 200 items, which makes it tiresome for the patient to fill in one sitting.

Depending on the preferences, each questionnaire can be assigned to a patient more than once, which is relevant especially for the Depression and Quality of life questionnaires. On the other hand, the food preferences typically do not change frequently thus this questionnaire can be assigned only once.

The doctor gets the list of available user accounts for patients from the administrator. Then the doctor then assigns accounts to patients. This procedure enables us to keep the identity of the patients anonymous for all other participants.

2.2 Patients

Each patient obtains the user account information from his/her medical doctor. Patients interact with the platform either through the website or via the smartphone application. On the website, they can view their data (see, for example, Figure 5) and they can also use it as the interface with which they can fill in the questionnaires. In addition, they can also fill in the questionnaires through the smartphone application, which we describe in Section 3.

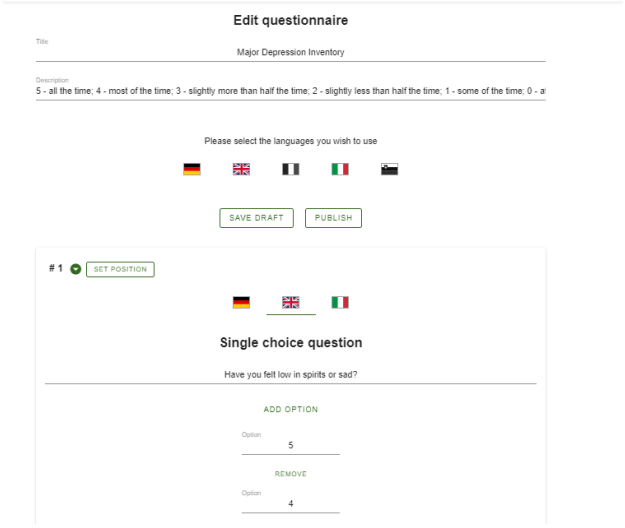

Figure 3: User interface for editing a questionnaire.

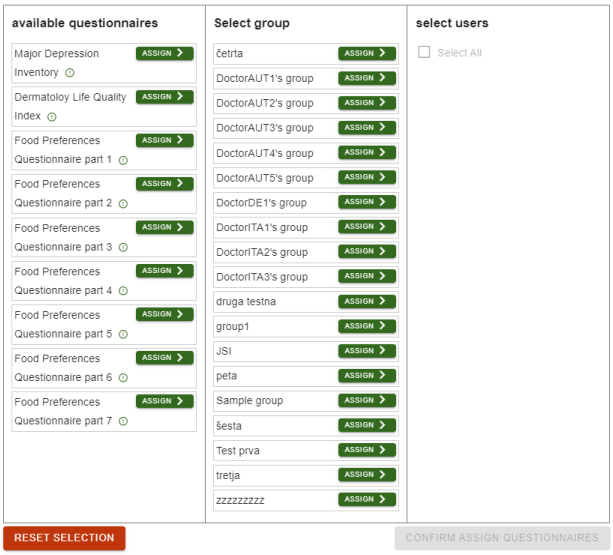

Figure 4: User interface for assigning questionnaires.

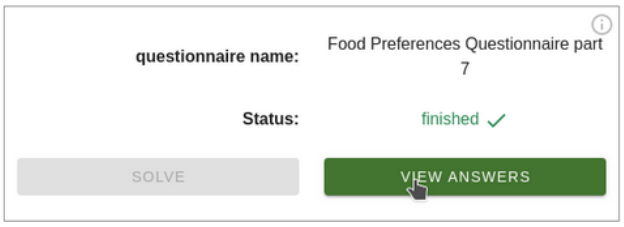

Figure 5: Patient's view of the platform to see the completed part of the food preferences questionnaire.

2.3 Data Scientists

Data scientist can access all the data that the medical doctors and the patients enter into the platform. The data available to the data scientists is anonymized.

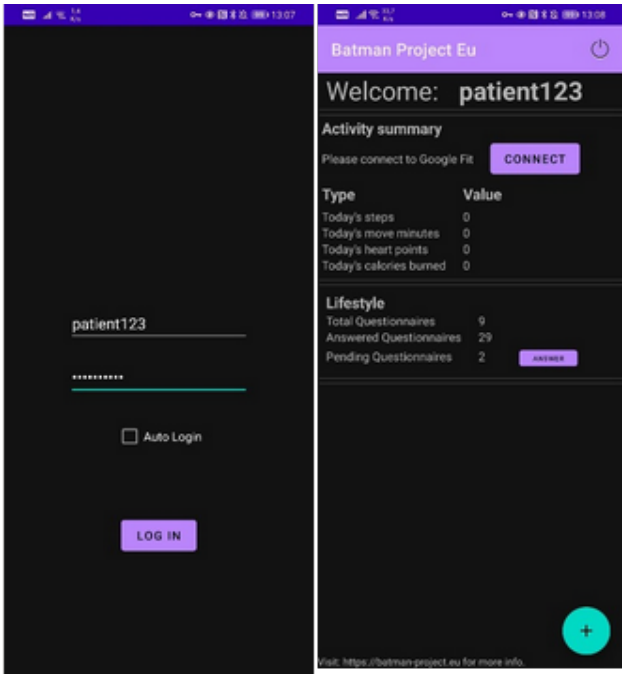

Figure 6: Login dialog and home screen of the smartphone application. The home screen shows the summary of daily activities and the pending questionnaires.

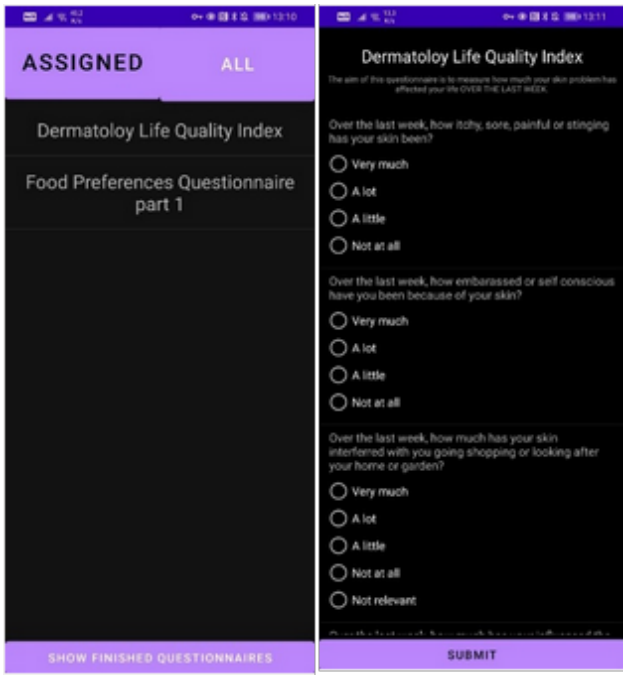

Figure 7: Questionnaire menu and an example of a questionnaire, in this case the Dermatology Quality of Life.

The data is currently being collected in the pilot study and will be then used to build models for HS patients and to seek for new knowledge.

2.4 Administrators

The highest level of access belongs to the administrator. Regarding the platform functionality, the administrator can access pages for managing users, groups, and for making changes on questionnaires.

3 SMARTPHONE APPLICATION

The smartphone application is available for Android-based phones only. It can be accessed through Play Store [2], or found with search for "Biomolecular Analyses for Tailored Medicine".

Patients log in the smartphone application using the same account as to the platform. The login and home screen for a sample patient are shown in Figure 6.

There are two main functionalities of the smartphone application: to monitor the daily activity of the patient, and to help them to fill in the questionnaire, which is likely easier on the smartphone than requiring to log in to a separate website just for that purpose.

The application uses the Google Fit [3] plug-in to trace the patient's steps and calories burned. The activity summary updates in real time based on the patient's activity. The collected daily activity serves as a reasonable proxy for the patient's wellbeing, e.g., if the HS condition is bad at a given time, the patient is likely to move less because of the pain, while if the patient starts moving more after a treatment, this likely implies that the treatment has been successful.

As for the questionnaires, the application allows the patient to easily fill in the forms using the screen. An example of the questionnaire is shown in Figure 7.

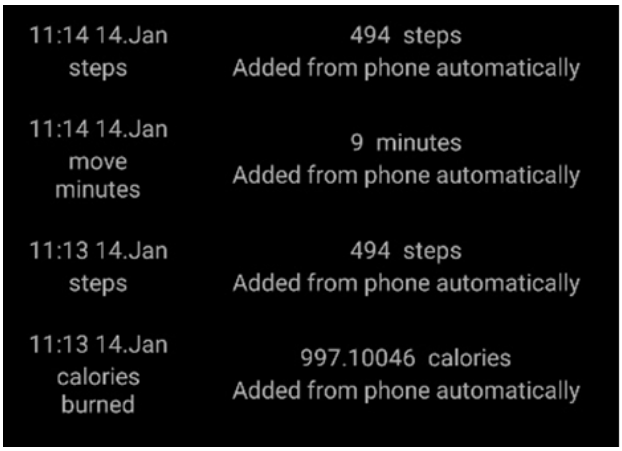

Figure 8: Example of the data that the smartphone application sends to the server.

In order to keep the application transparent to the users, the patients can access the data log showing all information that the application has communicated to the server (see Figure 8). Additional functionality of the application is a pedometer, which allows the user to track steps when activated (as opposed to the integrated step counter that tracks the steps during the entire day).

4 CONCLUSION

In this paper, we presented an overview of the components of the BATMAN platform. The platform is currently used to collect the heterogeneous patient data, including medical, genetic, activity, and self-reported data.

In the last stage of the project, the collected data will allow us to find novel knowledge about the patients suffering from HS and

will allow the doctors to create personalized treatments that could turn out to be more effective. This will be specially supported by the data scientists who will develop AI-based approaches for automatic knowledge extraction.

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