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INTERNATIONAL ASSOCIATION OF SCIENTIFIC, TECHNICAL & MEDICAL PUBLISHERS

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A Short Introduction

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A carer's problem.....

"*I'm educated to degree level but my degree is in geography. Most research articles that relate to my son's condition are couched in such detailed specialist scientific jargon and presuppose such an immense knowledge of biology, biochemistry, genetics, pharmacology etc that they might as well be written in Esperanto.*"

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"*Even for any articles which are marginally more comprehensible, it is still just about impossible for me to know which, of the many hundreds that appear, represent significant advances in knowledge or significant steps in the quest for a treatment or cure.*"

A recommended solution.....

- *Publishing a lay summary alongside every research article could be the answer to assisting in the wider understanding of health-related information.....*
- *Patients... want easy-to-understand, evidence-based information relating to biomedical and health research....*
- *Dr Liz Lyon, director of UKOLN, University of Bath explains, "The Patients Participate! Project has demonstrated the potential value of lay summaries to make research more accessible to a wider audience. ...."*
- *Medical research charities have an important role in providing patients and the public with information about the research they fund.*

From the Patients Participate! project press release at
http://www.jisc.ac.uk/news/stories/2011/10/participate.aspx

A recommended solution.....

- the Patients Participate! Report recommended publishing a lay summary alongside every research article and had two suggestions as to ways in which this might be achieved:-
  - Each researcher produces such a summary for each paper they publish, with training provided by their institutions and others to help them develop the communication skills necessary to share their findings with a lay audience and so bridge the understanding gap
  - Encourage, support and further leverage the role of medical research charities in providing patients and the public with information about the research they fund.

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ACCESS + INTERPRETATION = UNDERSTANDING + EMPOWERMENT

patientINFORM is a collaborative initiative from STM and the Association of American Publishers' Professional & Scholarly Publishing Division (AAP/PSP) which :-

- Makes it easier for medical research charities, or voluntary health organisations (VHOs), to keep up to date with the latest research in their field by giving them unlimited access to around 1000 subscription based journals from participating publishers

- Provides a mechanism whereby VHO lay summaries of what they judge to be key articles can be linked to the full text of these articles without users encountering paywalls.

- This means that patients and carers can get an intelligible summary of the most significant and important latest research, but can also access and print out the research article on which the summary is based and share it with their physician, as part of their physician-patient dialogue on matters of disease progression

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patientINFORM VHO Partners

American Cancer Society

American Diabetes Association

American Heart Association
Learn and Live

EURORDIS
Rare Diseases Europe

LUPUS
Foundation of America, Inc.

Accelerate CFS Research
Research1ST
SHARPER FOCUS. DEEPER IMPACT. ACCELERATED PROGRESS.

Muscular Dystrophy Campaign

NBCC
National Breast Cancer Coalition

NORD
National Organization for Rare Disorders

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An example of how it works…….

(from the Lupus Foundation of America web site)

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Research

A robust medical research effort is essential to find the causes of lupus, develop more effective treatments, and eventually cure the disease.

Access: Lupus Research

LFA Research Program | Research Summaries

"Access: Lupus Research," produced in collaboration with patientINFORM, presents summaries of late-breaking research published in respected medical journals that report on lupus and related conditions.

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In each category below, you can find summaries that explain the importance of recent research studies about lupus. All summaries provide access to the article abstract; select summaries provide access to the full journal article.

These summaries are intended to help you understand the latest lupus research, and help you and your family have more productive discussions with your doctors and make better-informed decisions about your health care. The information provided is not a substitute for advice from your own doctor or other health care providers. If you have questions about this material, please contact your doctor.

When you see the patientINFORM logo next to a summary, you'll know that the journal article it discusses comes from one of the medical journals participating in patientINFORM. Those summaries will have a link to the full journal article in PDF format.

Select a category to read the latest in lupus research summaries.

- **Animal Models**
- **Antiphospholipid Syndrome**
- **Apoptosis**
- **Blood Components**
- **Cancer**
- **Cardiovascular Disease**
- **Clinical Trials**

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Research

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Access: Lupus Research

LFA Research Program | Research Summaries

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Research Summaries from 2012

Autoantibody Profiling in People with Lupus

Measurement and monitoring of autoantibody levels in people with lupus can be useful in diagnosis and disease monitoring and also have the potential to illustrate the efficacy of drug therapies being taken for lupus over time. There are a number of autoantibodies that are important in lupus, including antibodies to double-stranded DNA (anti-ds-DNA), anti-Smith antibodies, and others, which may have to be tested or measured separately (which can be time-consuming and/or costly). The development of a single test that can simultaneously measure several different autoantibodies important in lupus could be important and useful. The results indicate that a single test can indeed accomplish this and suggest that most lupus patients can be categorized into at least one of two groups that have distinct kinds of autoantibody profiles with unique susceptibilities to specific kinds of lupus manifestations.

Read more >>

Lupus Anticoagulant Affects Pregnancy Outcomes

Having antibodies typical of anti-phospholipid syndrome (APS) can increase the risk of pregnancy complications. However, whether or not specific women with APS, such as women who also have lupus, may be at even greater risk of pregnancy complications has not been fully established or agreed upon. Identification of specific women with APS or specific characteristics, such as the presence of specific APS antibodies, which can predict increased risk of adverse pregnancy outcomes, could be very useful. The results of this study highlight the important role of lupus anticoagulant, as well as that of a previous blood clot, in adverse pregnancy outcomes.

Read more>>

Men Require More Lupus Genes to Develop Lupus

Lupus is thought to develop due to a combination of both genetic and environmental factors and is more common in women. Numerous studies have identified genes that increase the likelihood of developing lupus. The disparate incidence of lupus in women over men may be related to sex-specific genetic or hormonal factors. However, the degree to which these sex-specific factors favor the development of lupus in women over men has not been well established. The results of this study indicate that men require more lupus genes than women in order to develop lupus. The implications of these results are discussed in the context of possible sex- and hormone-related differences between men and women with lupus.

Read more>>

Vitamin D Indicates Lupus Disease Activity But Not Organ Damage

Vitamin D promotes calcium absorption from the gut and also helps to maintain appropriate levels of calcium in the blood. It is essential for maintaining bone health, but also regulates immune functions. Vitamin D is normally produced in the body upon exposure to sunlight. However, since many people with lupus avoid sun exposure, they may be at risk for

Men Require More Lupus Genes to Develop Lupus

- **Analysis of autosomal genes reveals gene-sex interactions and higher total genetic risk in men with systemic lupus erythematosus.**
  Hughes T, Adler A, Merrill JT, Kelly JA, Kaufman KM, Williams A, Langefeld CD, Gilkeson GS, Sanchez E, Martin J, Boackle SA, Stevens AM, Alarcón GS, Niewold TB, Brown EE, Kimberly RP, Edberg JC, Ramsey-Goldman R, Petri M, Reveille JD, Criswell LA, Vilá LM, Jacob CO, Gaffney PM, Moser KL, Vyse TJ, Alarcón-Riquelme ME; BIOLUPUS Network, James JA, Tsao BP, Scofield RH, Harley JB, Richardson BC, and Sawalha AH. *Annals of the Rheumatic Diseases*. 2011 Nov 21. [epub ahead of print]

What is the topic?

Lupus is thought to develop due to an interaction between genetic susceptibility and environmental triggers. Previous studies have identified a number of genes referred to as "lupus susceptibility genes," the presence of which are thought to increase the likelihood of developing lupus.

Importantly, lupus is about nine times more common in women than in men. This increased susceptibility may be made possible, at least in part, due to differences related to hormones and sex chromosomes. However, to what extent these sex differences contribute to the development of lupus is largely unknown.

What did the researchers hope to learn?

The researchers hoped to learn about the degree to which sex-specific genetic differences contribute to the susceptibility to developing lupus. They also investigated possible sex-related differences in levels of anti-double-stranded DNA antibodies (anti-dsDNA) between men and women with lupus.

Who was studied?

3936 people with lupus (3592 females and 344 males), as well as 3491 healthy people (2340 females and 1151 males), of European descent were studied.

How was the study conducted?

- What is the topic?
- What did the researchers hope to learn?
- Who was studied?
- How was the study conducted?
- What did the researchers find?
- What were the limitations of the study?
- What do the results means for you?

is identical except for this one base, so male samples would generate a heterozygous genotype and female samples would generate a homozygous genotype. Samples with increased heterozygosity (>5SD around the mean) were then removed. Finally, genetic outliers were identified and excluded as determined by principal components analysis and admixture proportions calculated using ADMIXMAP, as previously described.[16] Samples included in the analysis consisted of 344 male patients a total of 287 men and 2982 women with SLE.

RESULTS

We first performed case–control association tests in men and women separately. The majority of associations previously reported in women-only or combined populations were recapitulated in our male patients (table 1). Moreover, three of these

Table 1 Genetic associations in men and women with systemic lupus erythematosus compared with normal healthy male and female controls of European descent

		Male				Female			
		Risk allele frequency				Risk allele frequency			
SNP	Gene locus	Case	Control	OR (95% CI)	p Value	Case	Control	OR (95% CI)	p Value
rs2476601	*PTPN22*	0.102	0.081	1.28 (0.96 to 1.71)	0.089	0.110	0.0802	1.41(1.24 to 1.61)	1.5×10^{-7}
rs1801274	*FCGR2A*	0.528	0.499	1.13 (0.94 to 1.34)	0.18	0.542	0.513	1.13 (1.05 to 1.21)	0.0017
rs2205960	*TNFSF4*	0.276	0.209	1.44 (1.19 to 1.75)	2.3×10^{-4}	0.269	0.2167	1.33 (1.22 to 1.45)	1.6×10^{-10}
rs7574865	*STAT4*	0.285	0.213	1.47 (1.21 to 1.79)	1.2×10^{-4}	0.309	0.2302	1.49 (1.37 to 1.63)	4.0×10^{-20}
rs231775	*CTLA4*	0.352	0.346	1.03 (0.86 to 1.23)	0.79	0.362	0.3475	1.07 (0.87 to 1.01)	0.11
rs11568821	*PDCD1*	0.878	0.875	1.03 (0.79 to 1.34)	0.83	0.889	0.8851	1.04 (0.93 to 1.18)	0.47
rs6445975	*PXK*	0.311	0.280	1.16 (0.96 to 1.40)	0.12	0.291	0.2564	1.19 (1.10 to 1.30)	3.6×10^{-5}
rs10516487	*BANK1*	0.746	0.675	1.42 (1.17 to 1.72)	4.3×10^{-4}	0.737	0.701	1.19 (1.10 to 1.30)	2.8×10^{-5}
rs907715	*IL21*	0.680	0.655	1.12 (0.93 to 1.34)	0.23	0.687	0.656	1.15 (1.06 to 1.24)	5.2×10^{-4}
rs3131379	*HLA Region 1*	0.222	0.099	2.61 (2.08 to 3.27)	1.3×10^{-17}	0.172	0.0923	2.05 (1.82 to 2.30)	1.7×10^{-34}
rs1270942	*HLA Region 2*	0.225	0.097	2.71 (2.16 to 3.40)	5.9×10^{-19}	0.172	0.0921	2.05 (1.82 to 2.30)	2.1×10^{-34}
rs729302	*IRF5*	0.737	0.684	1.23 (1.02 to 1.49)	0.032	0.745	0.675	1.41 (1.30 to 1.53)	1.3×10^{-16}
rs2070197	*IRF5*	0.204	0.106	2.15 (1.71 to 2.69)	2.6×10^{-11}	0.172	0.1028	1.82 (1.62 to 2.03)	9.3×10^{-26}
rs10954213	*IRF5*	0.699	0.639	1.31 (1.09 to 1.58)	0.0038	0.678	0.618	1.30 (1.21 to 1.41)	1.9×10^{-11}
rs13277113	*C8orf13-BLK*	0.321	0.229	1.60 (1.32 to 1.93)	1.3×10^{-6}	0.288	0.2421	1.27 (1.16 to 1.38)	6.5×10^{-8}
rs1800450	*MBL*	0.143	0.140	1.03 (0.80 to 1.31)	0.83	0.146	0.1392	1.05 (0.85 to 1.06)	0.34
rs4963128	*KIAA1542*	0.664	0.673	0.96 (0.80 to 1.15)	0.68	0.712	0.664	1.25 (1.15 to 1.35)	4.7×10^{-8}
rs1143679	*ITGAM*	0.201	0.138	1.57 (1.26 to 1.96)	5.4×10^{-5}	0.193	0.1202	1.75 (1.58 to 1.95)	1.3×10^{-25}

SNP, single nucleotide polymorphism.

associations attained genome-wide significance ($p<5.0\times10^{-8}$) in men. We then compared risk allele frequencies between men and women with SLE (table 2).

Interestingly, the frequency of the risk alleles in the HLA locus was significantly higher in men than in women with SLE (rs3131379: $OR_{male\text{-}female}$ 1.37 (95% CI 1.14 to 1.66), p=0.0010; rs1270942: $OR_{male\text{-}female}$ 1.40 (95% CI 1.16 to 1.69), p=0.00046). This was also the case for an SNP in *IRF5* (rs2070197: $OR_{male\text{-}female}$ 1.23 (95% CI 1.01 to 1.49), p=0.039). It is important to note that there was no difference in the risk allele frequencies in the control group between men and women (p=0.39, 0.52 and 0.64, for rs3131379, rs1270942 and rs2070197, respectively). Therefore, it was not surprising to see a trend for a higher association OR in men than in women in sex-specific case–control analysis in these loci (figure 1). This trend was further examined by calculating the heterogeneity I^2 index (range 0–100) and *Q* statistic p values to assess heterogeneity between male and female case–control ORs (rs3131379: OR_{male} 2.61 (95% CI 2.08 to 3.27), OR_{female} 2.05 (95% CI 1.82 to 2.30), I^2 index=71.69 and *Q* statistic p=0.060; rs1270942: OR_{male} 2.71 (95% CI 2.16 to 3.40), OR_{female} 2.05 (95% CI 1.82 to 2.30), I^2 index=78.68, *Q* statistic p=0.030; rs2070197: OR_{male} 2.15 (95% CI 1.71 to 2.69), OR_{female} 1.82 (95% CI 1.62 to 2.03), I^2 index=39.73, *Q* statistic p=0.20). A post hoc analysis showed that our study had 100% power to detect genetic associations in the HLA region and *IRF5* in men (α= 0.05), suggesting that a smaller sample size of men than women in our study did not result in inflation of the ORs in our male set.[20 21]

Significant allelic differences between men and women with SLE were also observed for rs4963128, a polymorphism located in *KIAA1542* ($OR_{male\text{-}female}$ 1.25 (95% CI 1.06 to 1.48), p=0.0095) (table 2). rs4963128 was associated with SLE in women but not in men in our study (OR_{male} 0.96 (95% CI 0.80 to 1.15), p=0.68; OR_{female} 1.25 (95% CI 1.15 to 1.35), $p=4.7\times10^{-8}$; I^2 index=84.79, *Q* statistic p=0.010).

We next used a case-only pairwise epistasis analysis implemented in PLINK and confirmed the sex–gene interactions found (table 3). We further validated our results using a non-parametric methodology for non-linear epistasis by applying the MDR test (table 3).

Genetic differences associated with anti-dsDNA antibody positivity among patients with SLE were recently reported by Chung *et al*.[22] We investigated sex differences in the prevalence of anti-dsDNA antibodies among our test population to account for possible confounding. No significant difference in the presence of anti-dsDNA antibodies between men and women with SLE was observed (p=0.15). As men with SLE have previously been reported to experience more severe disease than women, it is important to examine if the difference in the frequencies of the HLA region risk alleles and the risk alleles in *IRF5* and *KIAA1542* that we observed between men and women is not influenced by differences in disease severity. We determined the frequencies of severe SLE manifestations in men and women included in the study (renal involvement, neurological involvement, serositis and thrombocytopenia) and found no differences in the frequencies of neurological involvement or serositis between men and women. However, consistent with previous reports, men with SLE in our study were almost twice as likely to have renal involvement as women (OR 1.70 (95% CI 1.34 to 2.17), $p=1.2\times10^{-5}$). Likewise, men with SLE were more likely to have thrombocytopenia (OR 2.26 (95% CI 1.62 to 3.15),

Table 2 Sex–gene disparities between men and women with systemic lupus erythematosus

		Risk allele frequency					
SNP	Gene	Male	Female	OR	95% CI LL	95% CI UL	p Value
rs2476601	*PTPN22*	0.102	0.110	1.08	0.84	1.40	0.55
rs1801274	*FCGR2A*	0.528	0.542	1.06	0.90	1.24	0.48
rs2205960	*TNFSF4*	0.276	0.269	1.04	0.87	1.24	0.67
rs7574865	*STAT4*	0.285	0.309	1.12	0.94	1.34	0.21
rs231775	*CTLA4*	0.352	0.362	1.05	0.89	1.23	0.60
rs11568821	*PDCD1*	0.878	0.889	1.11	0.87	1.42	0.38
rs6445975	*PXK*	0.311	0.291	1.10	0.93	1.30	0.27

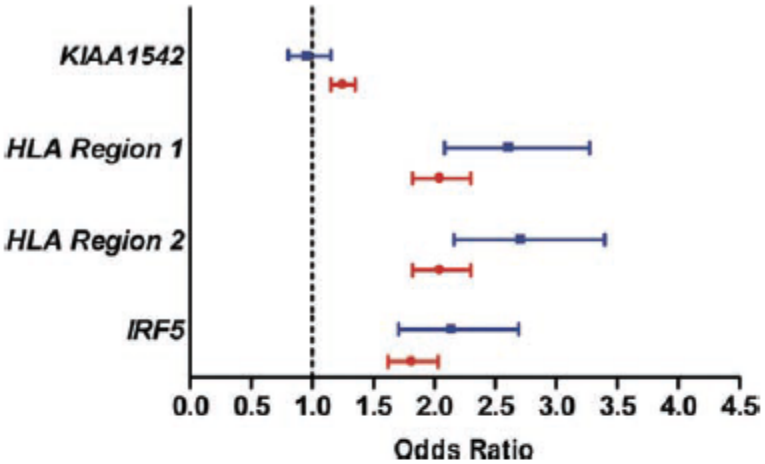

Figure 1 Sex-specific differences in genetic associations in systemic lupus erythematosus (men in blue and women in red).

and p=1.00, respectively). These data indicate that the difference in allele frequency between men women with SLE in the HLA region, *IRF5* and *KIAA1542* is not explained by a higher frequency of renal involvement or thrombocytopenia in men than in women.

We further investigated sex-specific differences in overall SLE genetic risk between men and women by calculating a cumulative genetic risk score for SLE in each individual included in the study. Scores were calculated based on the ORs obtained in the sex-specific case–control association analyses using the equation shown in figure 2A. Using a Student t test we observe that, on average, male patients have a significantly higher genetic risk than female patients ($p=4.52\times10^{-8}$; figure 2B). Interestingly, but not unexpectedly, the gap between men and women widens upon removal of rs4963128 (*KIAA1542*), the effect specific to women, while the disparity narrows as one HLA SNP is removed and the difference disappears entirely when both HLA SNPs are taken away (p=0.30).

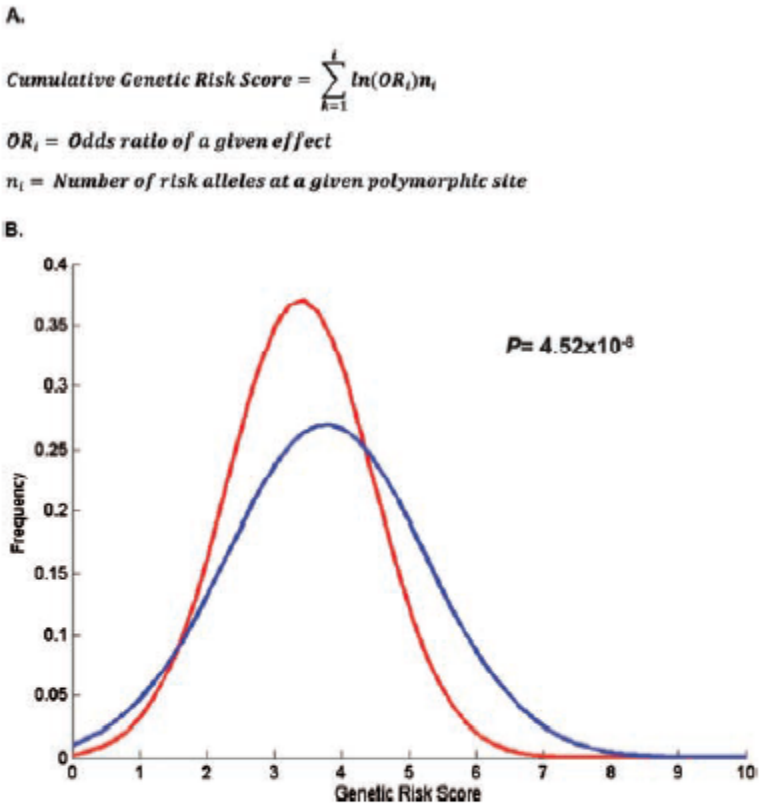

Figure 2 (A) The equation by which cumulative genetic risk scores were calculated. Scores were obtained for each patient by multiplying the natural logarithm of the OR for each of the associated loci by the number of risk alleles present at each locus. Cumulative risk was then calculated in each patient by summing the risk scores for 15 out of 18 risk loci included in this study. Three loci were not included when calculating the cumulative genetic risk scores because they were not associated with systemic lupus erythematosus in our study (*CTLA4*, *PDCD1* and *MBL*). (B) Distribution curves for cumulative genetic risk scores for systemic lupus erythematosus in men (blue) and women (red) showing a higher genetic risk in men than in women ($p=4.5\times10^{-8}$). Sex-specific ORs (table 1) were used to calculate the cumulative genetic risk score in male and female patients.

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