Ⅶ. 学会発表に関する一覧表

研究代表者：松田　文彦

発表者名	演題名	学会名	会場	日時
Matsuda, F.	Genomic analysis of immune-related diseases using GWAS and WES	The Second Kyoto Symposium on Bioinformatics for Next Generation Sequencing with Applications in Human Genetics	Kyoto, Japan	March 14, 2014
Matsuda, F.	Genome-wide association studies in IgG4-RD	Second International Symposium on IgG4 and Related Diseases	Honolulu, USA	February 18, 2014
Matsuda, F.	The Nagahama Study as a model for the comprehensive human bioscience	Kyoto Symposium on Bioinformatics for Next Generation Sequencing with Application in Human Genetics	Kyoto, Japan	January 19, 2013
松田　文彦	地域に根ざした新時代の予防医学の試み	2013 年度ソニー／医科歯科クリニカルサミット	東京医科歯科大学鈴木記念講堂（東京）	2013 年 8 月 20 日
松田　文彦	ヒト生命情報統合研究とゲノムコホート	第 20 回日本遺伝子診療学会大会教育講演	アクトシティ浜松コングレスセンター（浜松）	2013 年 7 月 20 日
松田　文彦	難病・がん等の疾患分野の医療の実用化研究事業の成果を基にした原因遺伝子変異データベースの構築	日本予防医学協会医療と健康のシンポジウム	全国社会保険協会連合会研修センター（東京）	2013 年 3 月 20 日
松田　文彦	ヒト生命情報統合研究とその情報基盤	大阪大学蛋白研究所セミナー「ビッグデータ時代に向けた医療データベース」	大阪大学中之島センター（大阪）	2013 年 3 月 8 日
松田　文彦	分子を通して自分の健康をながめる～ながはま０次コホート研究と次世代の予防医療～	いわて東北メディカル・メガバンク機構　発足記念シンポジウム	岩手医科大学矢巾キャンパス（矢巾）	2013 年 2 月 2 日
松田　文彦	ヒト生命情報統合研究とそのモデルケースとしてのながはまゲノムコホート事業	第 59 回日本臨床検査医学会学術集会シンポジウム「個別化医療と臨床検査」	国立京都国際会館（京都）	2012 年 11 月 30 日

松田　文彦	Human Biology とゲノム情報	日本 DNA 多型学会第 21 回学術集会シンポジウム	京都教育文化センター（京都）	2012 年 11 月 7 日
松田　文彦	分子を通して自分を知る未病社会の健康観～大規模コホート研究とゲノム、タンパク、代謝物～	未病社会の診断技術研究会第 7 回講演会	東京大学武田ホール（東京）	2012 年 10 月 11 日
松田　文彦	ゲノムワイト関連解析を用いた非アルコール性脂肪性肝疾患の関連遺伝子の探索	第 48 回日本肝臓学会	ポルテ金沢（金沢）	2012 年 6 月 7 日

研究分担者：辻　省次

発表者名	演題名	学会名	会場	日時
三井　純、辻　省次	パーソナルゲノム解析が医療を変貌させる	第 85 回日本遺伝学会市民公開講座	慶應義塾大学日吉キャンパス（横浜）	2013 年 9 月 21 日
三井　純、後藤　順、辻　省次	エクソーム解析による遺伝的異質性の高い疾患に対する遺伝子検査	第 20 回日本遺伝子診療学会	アクトシティ浜松（浜松）	2013 年 7 月 19 日

研究分担者：松原　洋一

発表者名	演題名	学会名	会場	日時
Izumi, R. *et al.*	A mutation in A-band titin is associated with hereditary myopathy with early respiratory failure in a Japanese family	American Society of Human Genetics 63rd Annual Meeting	Boston, USA	October 22-26, 2013
Niihori, T. *et al.*	Exome sequencing identifies mutations in a novel gene in patients with Noonan syndrome	American Society of Human Genetics 63rd Annual Meeting	Boston, USA	October 22-26, 2013
Aoki, Y., Niihori, T., Inoue, S. and Matsubara, Y.	Genetic syndromes associated with the Ras/MAPK pathway and the identification of mutations in a new gene, RIT1, for Noonan syndrome	Third International Meeting on Genetic Syndromes of the Ras/MAPK Pathway: Towards a Therapeutic Approach	Orland, USA	August 2-4, 2013
新堀　哲也ら	エクソームシークエンスによる Noonan 症候群新規原因遺伝子 RIT1 の同定	日本人類遺伝学会第 58 回大会	江陽グランドホテル（仙台）	2013 年 11 月 20～23 日
青木　洋子ら	次世代シークエンサーを用いたヌーナン症候群の遺伝子診断と新規原因遺伝子検索	日本人類遺伝学会第 58 回大会	江陽グランドホテル（仙台）	2013 年 11 月 20～23 日
緒方　勤ら	エクソーム解析により TBX1 変異が同定された家族性の特徴的顔貌・鼻咽頭閉鎖不全・低 Ca 血症を呈する 5 例	日本人類遺伝学会第 58 回大会	江陽グランドホテル（仙台）	2013 年 11 月 20～23 日

井泉　瑠美子ら	Myofibrillar myopathy の大家系における次世代型シークエンサーを用いた原因遺伝子の同定	第 54 回日本神経学会学術大会	東京国際フォーラム（東京）	2013 年 5 月 29 日
青木　洋子ら	次世代シークエンサーを用いたヌーナン症候群の遺伝子診断と新規原因遺伝子検索	第 116 回日本小児科学会学術集会	広島国際会議場（広島）	2013 年 4 月 19～21 日

研究分担者：松本　直通

発表者名	演題名	学会名	会場	日時
Matsumoto, N., *et al.*	De novo mutations in the autophagy gene encoding WDR45 (WIPI4) cause static encephalopathy of childhood with neurodegeneration in adulthood (oral)	European Conference of Human Genetic 2013	Paris, France	June 9, 2013
Matsumoto, N.	Mendelian exome analysis (oral)	The 10th International Workshop on Advanced Genomics	Tokyo, Japan	May 21, 2013
Matsumoto, N.	Medelian exome	The 12th annual meeting of East Asian Union of Human Genetics Societies (invited)	Seoul, Korea	November 29, 2012
Matsumoto, N.	Exome sequencing in mendelian disorders	Translational Genomics Conference 2012 (invited)	Jeju, Korea	October 13, 2012
Matsumoto, N.	Exome analysis in mendelian disorders	2012 Illumina Asica Pcific Scientific Summit (invited)	Gold Coast, Austraria	April 24, 2012
松本　直通	次世代シーケンサー解析と小児医療	平成 25 年度第 2 回バイオビジネス・スタートアップ～ゲノム解析による疾患の原因究明とその基盤技術～	AP 横浜西口（横浜）	2014 年 3 月 5 日
松本　直通	次世代シーケンサーによる難病遺伝子解析（教育講演）	第 8 回ファブリー病シンポジウム	東京コンファレンスセンター有明（東京）	2014 年 3 月 1 日
松本　直通	WDR45 変異が来すヒト疾患	大阪大学蛋白質研究所セミナー・オートファジーと疾患	大阪大学蛋白質研究所（吹田）	2014 年 2 月 21 日

松本　直通	希少疾患･難病の全エクソーム解析 –現状と課題–	日経バイオテク「希少疾患・難病の治療薬開発におけるゲノム活用」	秋葉原コンベンションホール（東京）	2013年 12月3日
松本　直通	ヒト疾患エクソーム解析の現状と課題（シンポジスト）	第58回日本人類遺伝学会大会	江陽グランドホテル（仙台）	2013年 11月23日
松本　直通	次世代シーケンサーを用いた疾患ゲノム解析：現状と限界（特別講演）	第22回発達腎研究会	高槻市生涯学習センター（高槻）	2013年 9月27日
松本　直通	NGSがもたらしたヒト疾患ゲノム解析のパラダイムシフト（基調講演）	現場の会第三回研究会	神戸国際会議場（神戸）	2013年 9月4日
松本　直通	疾患ゲノム解析における次世代シーケンサーの有用性（シンポジスト）	第20回日本遺伝子診療学会大会	アクトシティー浜松コングレスセンター（浜松）	2013年 7月19日
松本　直通	次世代シーケンサーを用いてわかってきたこと（特別講演）	第17回小児分子内分泌研究会	札幌北広島クラッセホテル（札幌）	2013年 7月7日
松本　直通	遺伝性疾患のエクソーム解析	Advans研究会2012（招聘講演）	ホテルグランドパレス東京（東京）	2012年 12月15日
松本　直通	発達障害におけるゲノム解析：次世代技術を用いて	第35回日本分子生物学会年会(ワークショップ)	福岡国際会議場（福岡）	2012年 12月13日
松本　直通	エクソーム解析	第152回染色体研究会（招聘講演）	東京医科大学病院（東京）	2012年 12月1日
Matsumoto, N.	Isolation of genes causative for genetic diseases by next generation sequencer	The 57th annual meeting, Japanese Society of Human Genetics (invited)	京王プラザホテル（東京）	2012年 10月25日
松本　直通	次世代シーケンスを用いた疾患ゲノム解析	ゲノム解析懇話会（招聘講演）	京王プラザホテル（東京）	2012年 10月25日
松本　直通	遺伝性疾患のエクソーム解析	生命医薬情報学連合大会2012（招聘講演）	タワーホール船堀（東京）	2012年 10月17日
松本　直通	自閉症スペクトラムとてんかんに着目したゲノム解析	第34回日本生物学的精神医学会（招聘講演）	神戸国際会議場（神戸）	2012年 9月28日
松本　直通	小児神経疾患における遺伝子研究の新潮流	第5回みやこ小児神経臨床懇話会（招聘講演）	メルパルク京都（京都）	2012年 6月9日

研究分担者：山田　亮

発表者名	演題名	学会名	会場	日時
Narahara, M., Matsuda, F., Yamada, R., et al.	Establishing an eQTL map of the Japanese population.	American Society of Human Genetics 63rd Annual Meeting	Boston, USA	October 25, 2013
Narahara, M., Matsuda, F., Yamada, R., et al	日本人における eQTL マップの構築	日本人類遺伝学会第 58 回大会	江陽グランドホテル（仙台）	2013 年 11 月 22 日

研究分担者：日笠　幸一郎

発表者名	演題名	学会名	会場	日時
日笠　幸一郎	日本人の遺伝子リファレンスライブラリーデータベース	日本人類遺伝学会第 58 回大会	江陽グランドホテル（仙台）	2013 年 11 月 21 日
日笠　幸一郎	大規模ゲノムコホート研究に基づく日本人遺伝子多型データベース	医学研究のためのバイオデータベース講習会	東海大学医学部伊勢原キャンパス講堂 B（伊勢原）	2013 年 12 月 25 日
日笠　幸一郎	ヒト生命情報統合研究に向けた大規模ゲノムコホート事業の推進	NGS 現場の会	神戸国際会議場（神戸）	2013 年 9 月 4 日

研究分担者：寺尾　知可史

発表者名	演題名	学会名	会場	日時
Yoshifuji, H., Terao, C., Murakami, K., Kawabata, D., Ohmura, K., Fujii, T., Kawaguchi, Y., Yamanaka, H., Mimori, T.	Association between HLA-B's amino acid variation and disease-susceptibility to Takayasu arteritis.	American College of Rheumatology 2013	San Diego, USA	October 27, 2013
寺尾　知可史、吉藤元、木村　彰方、松村貴由、大村　浩一郎、成瀬　妙子、佐藤　愛子、前島　康浩、和田庸子、成田　一衛、川口　鎮司、山中　寿、前川　平、小川　誠司、小室　一成、永井　良三、田原　康玄、磯部光章、三森　経世、松田　文彦	IL12B は高安動脈炎の新規疾患感受性遺伝子であり HLA-B*52:01 と相互作用を示す	第 41 回日本臨床免疫学会	海峡メッセ（下関）	2013 年 11 月 28 日
寺尾　知可史、吉藤元、村上　孝作、川端大介、大村　浩一郎、秋月　正史、川口　鎮司、山中　寿、三森　経世	高安動脈炎感受性と相関する 3 つの新規 HLA-B アミノ酸多型	第 57 回日本リウマチ学会総会・学術集会	国立京都国際会館（京都）	2013 年 4 月 20 日

Ⅷ．研究成果による特許等の知的財産権の出願・登録状況

研究分担者：松本　直通

1. 特願 2012-180356・松本直通／三宅紀子・ミトコンドリア複合体 III 欠乏症の確定診断法・2012 年 8 月 16 日

2. PCT/JP2012/77903 才津浩智／松本直通・孔脳症又は脳出血のリスクを予測する方法・2012 年 10 月 29 日

3. PCT/JP2012/83113 松本直通／鶴崎美徳／三宅紀子・コフィンーシリス症候群の検出方法・2012 年 12 月 20 日

4. 特願 2013-123660　才津浩智／松本直通　小児期のてんかんおよび不随意運動をきたす疾患の検出方法　2013 年 6 月 12 日

5. 特願 2013-157339　松本直通／三宅紀子　ケトン血症を伴うリー脳症患者または保因者の検出法　2013 年 7 月 31 日

6. 特願 2013-252720　鶴崎美徳／松本直通　Coffin-Siris 症候群の新規遺伝子診断法　2013 年 12 月 6 日

7. PCT/JP2013/71620　松本直通／三宅紀子　ミトコンドリア複合体 III 欠乏症患者又は保因者の検出方法　2013 年 8 月 9 日・2014 年 2 月 7 日

Ⅸ. 研究成果の刊行物・別刷

論文リスト

1. Okada, Y., Wu, D., Trynka, G., Raj, T., Terao, C., Ikari, K., Kochi, Y., Ohmura, K., Suzuki, A., Yoshida, S., Graham, R. R., Manoharan, A., Ortmann, W., Bhangale, T., Denny, J. C., Carroll, R. J., Eyler, A. E., Greenberg, J. D., Kremer, J. M., Pappas, D. A., Jiang, L., Yin, J., Ye, L., Su, D. F., Yang, J., Xie, G., Keystone, E., Westra, H. J., Esko, T., Metspalu, A., Zhou, X., Gupta, N., Mirel, D., Stahl, E. A., Diogo, D., Cui, J., Liao, K., Guo, M. H., Myouzen, K., Kawaguchi, T., Coenen, M. J. H., van Riel, P. L. C. M., van de Laar, M. A. F. J., Guchelaar, H. J., Huizinga, T. W. J., Dieude, P., Mariette, X., Bridges Jr, S. L., Zhernakova, A., Toes, R. E. M., Tak, P. P., Miceli-Richard, C., Bang, S. Y., Lee, H. S., Martin, J., Gonzalez-Gay, M. A., Rodriguez-RodriguezL., Rantapaa-Dahlqvist, S., Arlestig, L., Choi, H. K., Kamatani, Y., Galan, P., Lathrop, M., the RACI consortium, the GARNET consortium, Eyre, S., Bowes, J., Barton, A., de Vries, N., Moreland, L. W., Criswell, L. A., Karlson, E. W., Taniguchi, A., Yamada, R., Kubo, M., Liu, J. S., Bae, S. C., Worthington, J., Padyukov, L., Klareskog, L., Gregersen, P. K., Raychaudhuri, S., Stranger, B. E., De Jager, P. L., Franke, L., Visscher, P. M., Brown, M. A., Yamanaka, H., Mimori, T., Takahashi, A., Xu, H., Behrens, T. W., Siminovitch, K. A., Momohara, S., Matsuda, F., Yamamoto, K. and Plenge, R. M. (2014) Genetics of rheumatoid arthritis contributes to biology and drug discovery. *Nature* **506**, 376-381.

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72. 三井　純、石浦　浩之、辻　省次（2013）東大病院ゲノム医学センターにおける取り組み　パーキンソン病のパーソナルゲノム解析を中心に　*Brain and Nerve* **65**, 247-255.

LETTER

doi:10.1038/nature12873

Genetics of rheumatoid arthritis contributes to biology and drug discovery

A list of authors and their affiliations appears at the end of the paper

A major challenge in human genetics is to devise a systematic strategy to integrate disease-associated variants with diverse genomic and biological data sets to provide insight into disease pathogenesis and guide drug discovery for complex traits such as rheumatoid arthritis (RA)[1]. Here we performed a genome-wide association study meta-analysis in a total of >100,000 subjects of European and Asian ancestries (29,880 RA cases and 73,758 controls), by evaluating ~10 million single-nucleotide polymorphisms. We discovered 42 novel RA risk loci at a genome-wide level of significance, bringing the total to 101 (refs 2–4). We devised an *in silico* pipeline using established bioinformatics methods based on functional annotation[5], *cis*-acting expression quantitative trait loci[6] and pathway analyses[7–9]—as well as novel methods based on genetic overlap with human primary immunodeficiency, haematological cancer somatic mutations and knockout mouse phenotypes—to identify 98 biological candidate genes at these 101 risk loci. We demonstrate that these genes are the targets of approved therapies for RA, and further suggest that drugs approved for other indications may be repurposed for the treatment of RA. Together, this comprehensive genetic study sheds light on fundamental genes, pathways and cell types that contribute to RA pathogenesis, and provides empirical evidence that the genetics of RA can provide important information for drug discovery.

We conducted a three-stage trans-ethnic meta-analysis (Extended Data Fig. 1). On the basis of the polygenic architecture of RA[10] and shared genetic risk among different ancestry[3,4], we proposed that combining a genome-wide association study (GWAS) of European and Asian ancestry would increase power to detect novel risk loci. In stage 1, we combined 22 GWAS for 19,234 cases and 61,565 controls of European and Asian ancestry[2–4]. We performed trans-ethnic, European-specific and Asian-specific GWAS meta-analysis by evaluating ~10 million single-nucleotide polymorphisms (SNPs)[11]. Characteristics of the cohorts, genotyping platforms and quality control criteria are described in Extended Data Table 1 (overall genomic control inflation factor $\lambda_{GC} < 1.075$).

Stage 1 meta-analysis identified 57 loci that satisfied a genome-wide significance threshold of $P < 5.0 \times 10^{-8}$, including 17 novel loci (Extended Data Fig. 2). We then conducted a two-step replication study (stage 2 for *in silico* and stage 3 for *de novo*) in 10,646 RA cases and 12,193 controls for the loci with $P < 5.0 \times 10^{-6}$ in stage 1. In a combined analysis of stages 1–3, we identified 42 novel loci with $P < 5.0 \times 10^{-8}$ in any of the trans-ethnic, European or Asian meta-analyses. This increases the total number of RA risk loci to 101 (Table 1 and Supplementary Table 1).

Comparison of 101 RA risk loci revealed significant correlations of risk allele frequencies (RAFs) and odds ratios (ORs) between Europeans and Asians (Extended Data Fig. 3a–c; Spearman's $\rho = 0.67$ for RAF and 0.76 for OR; $P < 1.0 \times 10^{-13}$), although five loci demonstrated population-specific associations ($P < 5.0 \times 10^{-8}$ in one population but $P > 0.05$ in the other population without overlap of the 95% confidence intervals (95% CIs) of the ORs). In the population-specific genetic risk model, the 100 RA risk loci outside of the major histocompatibility complex (MHC) region[12] explained 5.5% and 4.7% of heritability in Europeans and Asians, respectively, with 1.6% of the heritability explained by the novel loci. The trans-ethnic genetic risk model, based on the RAF from one population but the OR from the other population, could explain the majority (>80%) of the known heritability in each population (4.7% for Europeans and 3.8% for Asians). These observations support our hypothesis that the genetic risk of RA is shared, in general, among Asians and Europeans.

We assessed enrichment of 100 non-MHC RA risk loci in epigenetic chromatin marks[13] (Extended Data Fig. 3d). Of 34 cell types investigated, we observed significant enrichment of RA risk alleles with trimethylation of histone H3 at lysine 4 (H3K4me3) peaks in primary $CD4^+$ regulatory T cells (T_{reg} cells; $P < 1.0 \times 10^{-5}$). For the RA risk loci enriched with T_{reg} H3K4me3 peaks, we incorporated the epigenetic annotations along with trans-ethnic differences in patterns of linkage disequilibrium to fine-map putative causal risk alleles (Extended Data Fig. 3e, f).

We found that approximately two-thirds of RA risk loci demonstrated pleiotropy with other human phenotypes (Extended Data Fig. 4), including immune-related diseases (for example, vitiligo, primary biliary cirrhosis), inflammation-related or haematological biomarkers (for example, fibrinogen, neutrophil counts) and other complex traits (for example, cardiovascular diseases).

Each of 100 non-MHC RA risk loci contains on average ~4 genes in the region of linkage disequilibrium (in total 377 genes). To prioritize systematically the most likely biological candidate gene, we devised an *in silico* bioinformatics pipeline. In addition to the published methods that integrate data across associated loci[7,8], we evaluated several biological data sets to test for enrichment of RA risk genes, which helps to pinpoint a specific gene in each loci (Extended Data Figs 5, 6 and Supplementary Tables 2–4).

We first conducted functional annotation of RA risk SNPs. Sixteen per cent of SNPs were in linkage disequilibrium with missense SNPs ($r^2 > 0.80$; Extended Data Fig. 5a, b). The proportion of missense RA risk SNPs was higher compared with a set of genome-wide common SNPs (8.0%), and relatively much higher in the explained heritability (~26.8%). Using *cis*-acting expression quantitative trait loci (*cis*-eQTL) data obtained from peripheral blood mononuclear cells (5,311 individuals)[6] and from $CD4^+$ T cells and $CD14^+CD16^-$ monocytes (212 individuals), we found that RA risk SNPs in 44 loci showed *cis*-eQTL effects (false discovery rate (FDR) q or permutation $P < 0.05$; Extended Data Table 2).

Second, we evaluated whether genes from RA risk loci overlapped with human primary immunodeficiency (PID) genes[14], and observed significant overlap (14/194 = 7.2%, $P = 1.2 \times 10^{-4}$; Fig. 1a and Extended Data Fig. 5c). Classification categories of PID genes showed different patterns of overlap: the highest proportion of overlap was in 'immune dysregulation' (4/21 = 19.0%, $P = 0.0033$) but there was no overlap in 'innate immunity'.

Third, we evaluated overlap with cancer somatic mutation genes[15], under the hypothesis that genes with cell growth advantages may contribute to RA development. Among 444 genes with registered cancer somatic mutations[15], we observed significant overlap with genes implicated in haematological cancers (17/251 = 6.8%, $P = 1.2 \times 10^{-4}$; Fig. 1b and Extended Data Fig. 5d), but not with genes implicated in non-haematological cancers (6/221 = 2.7%, $P = 0.56$).

Table 1 | Novel rheumatoid arthritis risk loci identified by trans-ethnic GWAS meta-analysis in >100,000 subjects

SNP	Chr	Genes	A1/A2 (+)	Trans-ethnic OR (95% CI)	Trans-ethnic P	European OR (95% CI)	European P	Asian OR (95% CI)	Asian P
rs227163	1	*TNFRSF9*	C/T	1.04 (1.02–1.06)	3.9×10^{-4}	1.00 (0.97–1.03)	9.3×10^{-1}	1.11 (1.08–1.16)*	3.1×10^{-9}*
rs28411352	1	*MTF1-INPP5B*	T/C	1.11 (1.08–1.14)*	2.8×10^{-12}*	1.10 (1.07–1.14)*	5.9×10^{-9}*	1.12 (1.06–1.19)	7.8×10^{-5}
rs2105325	1	*LOC100506023*	C/A	1.12 (1.08–1.15)*	6.9×10^{-13}*	1.12 (1.08–1.15)*	3.3×10^{-11}*	1.13 (1.04–1.23)	5.2×10^{-3}
rs10175798	2	*LBH*	A/G	1.08 (1.06–1.11)*	1.1×10^{-9}*	1.09 (1.06–1.12)*	4.2×10^{-8}*	1.07 (1.02–1.13)	6.4×10^{-3}
rs6732565	2	*ACOXL*	A/G	1.07 (1.05–1.10)*	2.7×10^{-8}*	1.10 (1.07–1.14)*	9.4×10^{-9}*	1.04 (1.00–1.08)	4.0×10^{-2}
rs6715284	2	*CFLAR-CASP8*	G/C	1.15 (1.10–1.20)*	1.8×10^{-9}*	1.15 (1.10–1.20)*	2.5×10^{-9}*	-	-
rs4452313	3	*PLCL2*	T/A	1.09 (1.06–1.12)*	1.6×10^{-10}*	1.11 (1.08–1.15)*	5.2×10^{-11}*	1.04 (0.99–1.09)	9.2×10^{-2}
rs3806624	3	*EOMES*	G/A	1.08 (1.05–1.11)*	8.6×10^{-9}*	1.08 (1.05–1.12)*	2.8×10^{-8}*	1.06 (0.99–1.14)	1.0×10^{-1}
rs9826828	3	*IL20RB*	A/G	1.44 (1.28–1.61)*	8.6×10^{-10}*	1.44 (1.28–1.61)*	8.7×10^{-10}*	-	-
rs13142500	4	*CLNK*	C/T	1.10 (1.07–1.13)*	3.0×10^{-9}*	1.10 (1.06–1.15)	2.4×10^{-6}	1.10 (1.04–1.15)	2.8×10^{-4}
rs2664035	4	*TEC*	A/G	1.07 (1.04–1.10)	9.5×10^{-8}	1.08 (1.05–1.11)*	3.3×10^{-8}*	1.03 (0.97–1.08)	3.3×10^{-1}
rs9378815	6	*IRF4*	C/G	1.09 (1.06–1.12)*	1.7×10^{-10}*	1.09 (1.05–1.12)	1.4×10^{-7}	1.10 (1.04–1.15)	2.3×10^{-4}
rs2234067	6	*ETV7*	C/A	1.15 (1.10–1.20)*	1.6×10^{-9}*	1.14 (1.09–1.19)*	4.1×10^{-8}*	1.22 (1.06–1.41)	7.0×10^{-3}
rs9373594	6	*PPIL4*	T/C	1.09 (1.06–1.12)*	3.0×10^{-9}*	1.07 (1.02–1.12)	6.5×10^{-3}	1.11 (1.07–1.15)*	4.8×10^{-8}*
rs67250450	7	*JAZF1*	T/C	1.10 (1.07–1.14)*	3.7×10^{-9}*	1.11 (1.07–1.14)*	2.6×10^{-9}*	1.02 (0.84–1.23)	8.5×10^{-1}
rs4272	7	*CDK6*	G/A	1.10 (1.06–1.13)*	5.0×10^{-9}*	1.10 (1.07–1.14)*	1.2×10^{-8}*	1.06 (0.98–1.15)	1.3×10^{-1}
rs998731	8	*TPD52*	T/C	1.08 (1.05–1.11)*	1.9×10^{-8}*	1.09 (1.06–1.12)*	6.6×10^{-9}*	1.02 (0.96–1.10)	4.9×10^{-1}
rs678347	8	*GRHL2*	G/A	1.08 (1.05–1.11)*	1.6×10^{-8}*	1.10 (1.06–1.13)*	7.3×10^{-9}*	1.03 (0.98–1.10)	2.6×10^{-1}
rs1516971	8	*PVT1*	T/C	1.15 (1.10–1.20)*	1.3×10^{-10}*	1.16 (1.11–1.21)*	3.2×10^{-11}*	-	-
rs12413578	10	10p14	C/T	1.20 (1.13–1.29)*	4.8×10^{-8}*	1.20 (1.12–1.29)	7.5×10^{-8}	-	-
rs793108	10	*ZNF438*	T/C	1.08 (1.05–1.10)*	1.3×10^{-9}*	1.07 (1.04–1.10)	6.1×10^{-7}	1.09 (1.04–1.14)	4.4×10^{-4}
rs2671692	10	*WDFY4*	A/G	1.07 (1.05–1.10)*	2.8×10^{-9}*	1.06 (1.03–1.09)	2.6×10^{-5}	1.10 (1.05–1.14)	9.9×10^{-6}
rs726288	10	*SFTPD*	T/C	1.14 (1.07–1.20)	1.6×10^{-5}	0.96 (0.86–1.06)	4.1×10^{-1}	1.22 (1.14–1.31)*	8.8×10^{-9}*
rs968567	11	*FADS1-FADS2-FADS3*	C/T	1.12 (1.07–1.16)*	1.8×10^{-8}*	1.12 (1.07–1.16)*	1.8×10^{-8}*	-	-
rs4409785	11	*CEP57*	C/T	1.12 (1.09–1.16)*	1.2×10^{-11}*	1.12 (1.08–1.16)*	3.6×10^{-9}*	1.16 (1.07–1.27)	4.3×10^{-4}
chr11:107967350	11	*ATM*	A/G	1.21 (1.13–1.29)*	1.4×10^{-8}*	1.21 (1.13–1.29)*	1.1×10^{-8}*	-	-
rs73013527	11	*ETS1*	C/T	1.09 (1.06–1.12)*	1.2×10^{-10}*	1.08 (1.05–1.11)	1.0×10^{-6}	1.14 (1.08–1.21)	4.1×10^{-6}
rs773125	12	*CDK2*	A/G	1.09 (1.06–1.12)*	1.1×10^{-10}*	1.09 (1.06–1.12)*	2.1×10^{-8}*	1.10 (1.04–1.17)	1.1×10^{-3}
rs10774624	12	*SH2B3-PTPN11*	G/A	1.09 (1.06–1.13)*	6.8×10^{-9}*	1.09 (1.06–1.13)*	6.9×10^{-9}*	-	-
rs9603616	13	*COG6*	C/T	1.10 (1.07–1.13)*	1.6×10^{-12}*	1.11 (1.07–1.14)*	2.8×10^{-11}*	1.08 (1.02–1.14)	1.0×10^{-2}
rs3783782	14	*PRKCH*	A/G	1.14 (1.09–1.18)*	2.2×10^{-9}*	1.12 (0.96–1.31)	1.4×10^{-1}	1.14 (1.09–1.19)*	4.4×10^{-9}*
rs1950897	14	*RAD51B*	T/C	1.10 (1.07–1.13)*	8.2×10^{-11}*	1.09 (1.06–1.12)*	5.0×10^{-8}*	1.16 (1.08–1.25)	1.1×10^{-4}
rs4780401	16	*TXNDC11*	T/G	1.07 (1.05–1.10)*	4.1×10^{-8}*	1.09 (1.06–1.13)*	8.7×10^{-9}*	1.03 (0.98–1.08)	2.5×10^{-1}
rs72634030	17	*C1QBP*	A/C	1.12 (1.08–1.17)*	1.5×10^{-9}*	1.12 (1.06–1.19)	2.9×10^{-5}	1.12 (1.07–1.18)	9.6×10^{-6}
rs1877030	17	*MED1*	C/T	1.09 (1.06–1.12)*	1.9×10^{-8}*	1.09 (1.05–1.13)	1.3×10^{-5}	1.09 (1.04–1.14)	3.2×10^{-4}
rs2469434	18	*CD226*	C/T	1.07 (1.05–1.10)*	8.9×10^{-10}*	1.05 (1.02–1.08)	6.7×10^{-4}	1.11 (1.07–1.15)*	1.2×10^{-8}*
chr19:10771941	19	*ILF3*	C/T	1.47 (1.30–1.67)*	8.6×10^{-10}*	1.47 (1.30–1.67)*	8.8×10^{-10}*	-	-
rs73194058	21	*IFNGR2*	C/A	1.08 (1.05–1.12)	1.2×10^{-6}	1.13 (1.08–1.18)*	2.6×10^{-8}*	1.03 (0.98–1.08)	2.9×10^{-1}
rs1893592	21	*UBASH3A*	A/C	1.11 (1.08–1.14)*	7.2×10^{-12}*	1.11 (1.07–1.15)*	9.8×10^{-9}*	1.11 (1.05–1.18)	1.3×10^{-4}
rs11089637	22	*UBE2L3-YDJC*	C/T	1.08 (1.05–1.11)*	2.1×10^{-9}*	1.10 (1.06–1.15)	2.0×10^{-7}	1.06 (1.02–1.10)	8.9×10^{-4}
rs909685	22	*SYNGR1*	A/T	1.13 (1.10–1.16)*	1.4×10^{-16}*	1.11 (1.08–1.15)*	6.4×10^{-12}*	1.23 (1.14–1.33)	2.0×10^{-7}
chrX:78464616	X	*P2RY10*	A/C	1.11 (1.07–1.15)*	3.5×10^{-8}*	1.16 (0.78–1.75)	4.6×10^{-1}	1.11 (1.07–1.15)*	3.6×10^{-8}*

SNPs newly associated with $P < 5.0 \times 10^{-8}$ in the combined study of the stage 1 GWAS meta-analysis and the stages 2 and 3 replication studies of trans-ethnic (Europeans and Asians), European or Asian ancestry are indicated. SNPs, positions and alleles are based on the positive (+) strand of NCBI build 37. A1 represents an RA risk allele. Chr, chromosome; OR, odds ratio; 95% CI, 95% confidence interval. Full results of the studies are available in Supplementary Table 1. Hyphens between gene names indicate that several candidate RA risk genes were included in the region.
*Association results with $P < 5.0 \times 10^{-8}$.

Fourth, we evaluated overlap with genes implicated in knockout mouse phenotypes[16]. Among the 30 categories of phenotypes[16], we observed 3 categories significantly enriched with RA risk genes ($P < 0.05/30 = 0.0017$): 'haematopoietic system phenotype', 'immune system phenotype', and 'cellular phenotype' (Extended Data Fig. 5e).

Last, we conducted molecular pathway enrichment analysis (Fig. 1c and Extended Data Fig. 5f). We observed enrichment (FDR $q < 0.05$) for T-cell-related pathways, consistent with cell-specific epigenetic marks, as well as enrichment for B-cell and cytokine signalling pathways (for example, interleukin (IL)-10, interferon, granulocyte–macrophage colony-stimulating factor (GM-CSF)). For comparison, our previous RA GWAS meta-analysis[2] did not identify the B-cell and cytokine signalling pathways, thereby indicating that as more loci are discovered, further biological pathways are identified.

On the basis of these new findings, we adopted the following 8 criteria to prioritize each of the 377 genes from the 100 non-MHC RA risk loci (Fig. 2 and Extended Data Fig. 6a–c): (1) genes with RA risk missense variant ($n = 19$); (2) *cis*-eQTL genes ($n = 51$); (3) genes prioritized by PubMed text mining[7] ($n = 90$); (4) genes prioritized by protein–protein interaction (PPI)[8] ($n = 63$); (5) PID genes ($n = 15$); (6) haematological cancer somatic mutation genes ($n = 17$); (7) genes prioritized by associated knockout mouse phenotypes ($n = 86$); and (8) genes prioritized by molecular pathway analysis[9] ($n = 35$).

Ninety-eight genes (26.0%) had a score ≥2, which we defined as 'candidate biological RA risk genes'. Nineteen loci included multiple biological RA risk genes (for example, *IL3* and *CSF2* at chromosome 5q31), whereas no biological gene was selected from 40 loci (Supplementary Table 5).

To provide empirical evidence of the pipeline, we evaluated relationships of the gene scores to independent genomic or epigenetic information. Genes with higher biological scores were more likely to be the nearest gene to the risk SNP (18.6% for gene score <2 and 49.0% for gene score ≥2; $P = 2.1 \times 10^{-8}$), and also to be included in the region where RA risk SNPs were overlapping with H3K4me3 T_{reg} peaks (41.9% for gene score <2 and 57.1% for gene score ≥2; $P = 0.034$). Further, T_{reg} cells demonstrated the largest increase in overlapping proportions with H3K4me3 peaks for increase of biological gene scores compared with other cell types (Extended Data Fig. 6d).

Finally, we evaluated the potential role of RA genetics in drug discovery. We proposed that if human genetics is useful for drug target validation, then it should identify existing approved drugs for RA. To test this 'therapeutic hypothesis'[1], we obtained 871 drug target genes corresponding to approved, in clinical trials or experimental drugs for human diseases[17,18] (Supplementary Table 6). We evaluated whether any of the protein products from the identified biological RA risk genes, or any genes from a direct PPI network with such protein products

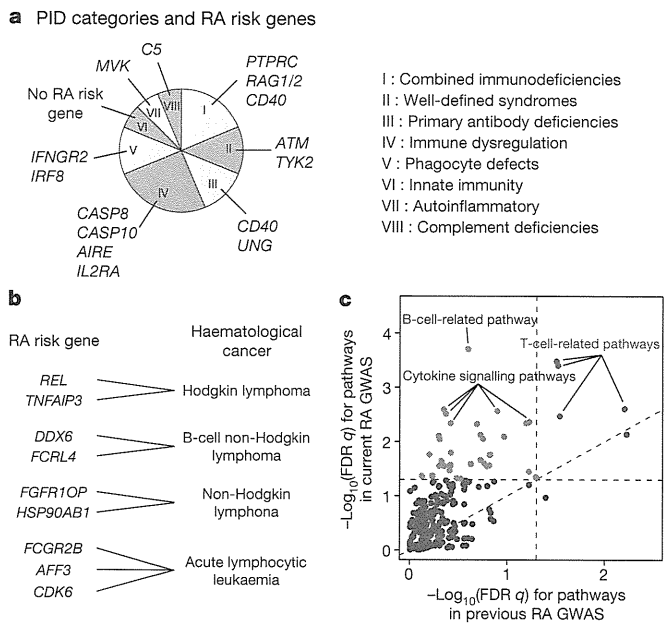

Figure 1 | Overlap of RA risk loci with PID genes, haematological cancer somatic mutations and molecular pathways. **a**, Overlap of RA risk genes with PID genes, subdivided by PID categories (I–VIII). **b**, Examples of overlap of haematological cancer somatic mutation genes with RA risk genes. **c**, Comparisons of molecular pathway analysis results between the current trans-ethnic meta-analysis (*y*-axis) and the previous meta-analysis for RA (*x*-axis)[2]. Each dot represents a molecular pathway. Dotted line represents FDR $q = 0.05$ or $y = x$.

(Fig. 3a), are the pharmacologically active targets of approved RA drugs (Extended Data Fig. 7a).

Twenty-seven drug target genes of approved RA drugs demonstrated significant overlap with 98 biological RA risk genes and 2,332 genes from the expanded PPI network (18 genes overlapped; 3.7-fold enrichment by permutation analysis, $P < 1.0 \times 10^{-5}$; Fig. 3b). For comparison, all drug target genes (regardless of disease indication) overlapped with 247 genes, which is 1.7-fold more enrichment than expected by chance, but less than 2.2-fold enrichment compared with overlap of the target genes of RA drugs ($P = 0.0035$). Examples of approved RA therapies identified by this analysis include tocilizumab[19,20] (anti-IL6R), tofacitinib[21] (JAK3 inhibitor) and abatacept[21] (CTLA4–immunoglobulin; Fig. 3c and Extended Data Fig. 8).

We also assessed how approved drugs for other diseases might be connected to biological RA risk genes. We highlight *CDK6* and *CDK4*, targets of three approved drugs for different types of cancer[22] (Fig. 3d).

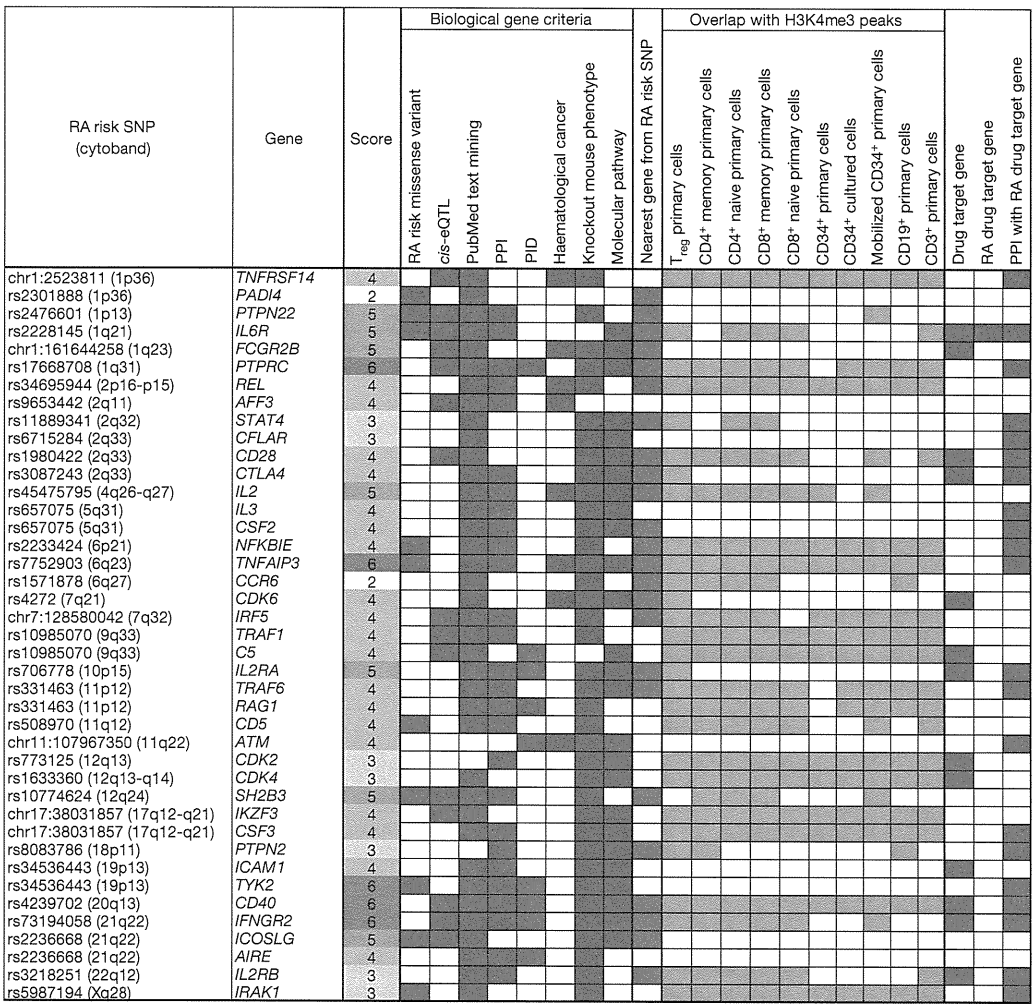

Figure 2 | Prioritized biological RA risk genes. Representative biological RA risk genes. We list the summary gene score derived from individual criteria (filled red box indicates criterion satisfied; 98 genes with a score ≥2 out of 377 genes included in the RA risk loci were defined as 'biological candidate genes'; see Extended Data Fig. 6). Filled blue boxes indicate the nearest gene to the RA risk SNP. Filled green boxes indicate overlap with H3K4me3 peaks in immune-related cells. Filled purple boxes indicate overlap with drug target genes. For full results, see Supplementary Table 5.