Supplementary table legend

Table S1. Candidate causal genes identified by the SMR method. Cells with p-value < 0.05 in the table are highlighted in light blue color. The table column names are described as follows. **Gene**: Symbol representing the gene; **SNP**: ID of the most significant eQTL SNP associated with the gene; **Chrom**: ID of chromosome where the gene and SNPs are located; **Position**: Chromosomal position (base-pair) of the top eQTL SNP associated with the gene; **p_GWAS**: SLE GWAS p-value of the top eQTL SNP; **p_eQTL**: eQTL p-value of the top eQTL SNP; **alpha_SMR**: gene causal effect size estimate by SMR method; **p_SMR**: p-value for the gene causal effect size estimate by SMR method; **alpha_PMR**: gene causal effect size estimate by PMR-Egger method; **p_PMR**: p-value for the gene causal effect size estimate by PMR-Egger method; **alpha_MRAID**: gene causal effect size estimate by MRAID method; **p_MRAID**: p-value for the gene causal effect size estimate by MRAID method; **alpha_MtRobin**: gene causal effect size estimate by MR-MtRobin method; **p_MtRobin**: p-value for the gene causal effect size estimate by MR-MtRobin method. ‘NA’ in the cells: data not available because of technical issues such as ‘algorithm generated errors’ and ‘insufficient number of genetic variants at the locus to reliably estimate causal effect size’; **p_HEIDI**: p-value for HEIDI test of heterogeneity

Appendix A:

Literature evidence for disease relevance of candidate causal genes

We collected an extensive literature evidence to strengthen the association of 23 genes outside of chromosome 6 with the development of SLE. The following discussion is organized based on the MR methods utilized to identify these genes. See **Figure 14** in the main text as a guide to the discussion.

Genes identified by PMR-Egger

IRF5 and *TNPO3*:

SMR, the single-SNP Mendelian randomization method, identified these two genes as potentially causal, using the SLE risk variant, rs6467223, as an Instrumental Variable (IV) (see **Table 1**). The *IRF5-TNPO3* region harbors at least two independent SLE genetic association signals, one adjacent to the promoter of *IRF5* and a more distal signal that spans the *TNPO3* gene and includes variants within the promoter (Kottyan et al., 2015). Further, variants in the *TNPO3* promoter exhibit allele specific enhancer activity for *IRF5* independent of *TNPO3* expression (Thynn et al., 2020). A plausible role for IRF5 as a modulator of type I interferon signaling in SLE is clear (Gallucci et al., 2021). While the specific mechanism through which TNPO3 may impact SLE risk is still uncertain, it is worth mentioning that TNPO3 plays a crucial role as a host factor in facilitating the entry of various viruses into the nucleus. The most well studied of these is HIV-1 (Bhargava et al., 2018). Several lines of evidence point to Epstein-Barr virus infection as an etiologic environmental trigger of SLE (Harley et al., 2018; Harley and James, 2006; Laurynenka et al., 2022). Considering the importance of nuclear import for the proper functioning of several proteins encoded by EBV (Li et al., 2021) and the role of TNPO3 in nuclear import, it is plausible that TNPO3 could potentially influence the risk of developing SLE through this mechanism.

XKR6:

The *XKR6* gene, located near the *FAM167A-BLK* locus on chromosome 8, harbors variants whose association with SLE is influenced by the 8p23 polymorphic inversion (Namjou et al., 2014). The frequency of this ~4.5Mbp inversion variant varies significantly among human global ancestral populations (Salm et al., 2012). While the function of *XKR6* remains incompletely defined, it is a member of the XKR family of phospholipid scramblases (Kodigepalli et al., 2015). The closest orthologue of known function is Ced-8, a C. elegans gene that regulates the timing of apoptosis (Stanfield and Horvitz, 2000). Two recent studies found that some members of the XKR family promote exposure of phosphatidylserine (PS) in apoptotic cells (Suzuki et al., 2014, 2013). PS exposure is a key signal for phagocytes to clear dying cells. Inappropriate clearance of apoptotic and necrotic cellular debris is thought to be a key immunogenic context by which exposure to self-antigen breaches tolerance in SLE (Munoz et al., 2008). While it may be tempting to speculate that XKR6 plays a similar role in humans, limited investigations into its involvement in this process have not shown a conservation of this function within the XKR family (Suzuki et al., 2014).

RP11-148O21.2, *RP11-148O21.4* and *RP11-148O21.6*:

These three genes, located in the *FAM167A-BLK* locus, have been identified as causal using two distinct variants, rs2736345 (*RP11-148O21.2* & *RP11-148O21.4*) and rs11250144 (*RP11-148O21.6*), as Instrumental Variables by the SMR method (see **Table 1**). While *BLK* and *FAM167A* exhibit functional effects that could plausibly impact the etiology of SLE (see below: Genes identified by MRAID), it is noteworthy the other three genes within the locus are classified as long interspersed non-coding RNA (lincRNA) and their specific functions remain unknown. Identification of two lincRNAs as causal for SLE risk at this locus does not *ipso facto* invalidate

dysregulated expression of *FAM167A* and/or *BLK* as causal at this locus. This is because lincRNAs can act to regulate expression of nearby genes. A notable example is the association of *IRF8* with SLE. At that locus, the SLE risk variant alters expression of the long non-coding RNA AC092723.1. AC092723.1, in turn, recruits TET1 to the *IRF8* promoter and regulates its expression. Thus, the nomination by PMR-Egger of *RP11-148O21.2*, *RP11-148O21.4* and *RP11-148O21.6* as causal remains consistent with dysregulation of *FAM167A* and/or *BLK* ultimately mediating disease risk. Further, *RP11-148O21.2*, *RP11-148O21.4* and *RP11-148O21.6* all exhibit increased expression in B cells relative to other immune cells [DICE database, https://dice-database.org/genes, (Schmiedel et al., 2018)]. This finding aligns with the importance of B cells in SLE etiopathogenesis (Parodis et al., 2022). Consistent with the predictions of the PMR-Egger method, these genes have also been described to be co-regulated by SLE– and RA-associated risk variants (Lodde et al., 2020).

PHRF1 and *IRF7*:

These two genes are adjacent to one another, but the two IV genetic variants used by SMR to identify these genes are different (see **Table 1**). The SLE relevance of *IRF7* function is clear as related to IRF7 impacting the type I interferon signaling pathway (Fu et al., 2011). Importantly, one of the proposed mechanisms of the SLE drug, mycophenolate mofetil, is through IRF7 (Shigesaka et al., 2020). In contrast, the role of *PHRF1* is not immediately obvious, since few publications address the role of this gene [Plant HomeoDomain (PHD) and Ring Finger 1]. *PHRF1* encodes an E3-ubiquitin ligase similar to another SLE risk gene, *TNFAIP3*, which encodes A20. Whereas TNFAIP3 modulates NF-kB signaling (Ma and Malynn, 2012), PHRF1 has been shown to modulate Non-homologous end joining (NHEJ) of double stranded DNA breaks (Chang et al., 2015). A functional NHEJ pathway is necessary for class switch recombination (CSR) to IgA, IgG and IgE (Xu et al., 2022). Thus, modulation of NHEJ provides a plausible mechanism through which *PHRF1* expression may impact SLE risk. Specifically, class switch from IgM to IgG is

characteristic of the pathogenic autoantibodies of SLE patients, in whom CSR appears to be dysregulated (Liu et al., 2004).

ORMDL3, *GSDMB* and *RP11-94L15.2*:

The same IV genetic variant, rs12936231, was used by SMR to identify these three genes. In addition to association with SLE, this variant has been associated with several SLE related immune traits [GWAS Atlas PheWAS: https://atlas.ctglab.nl/PheWAS (Watanabe et al., 2019)]. Curiously, there are cell-state specific expression quantitative trait loci (eQTL) at this locus that show an association with *ORMDL3* expression (Nathan et al., 2022). Plausible immune cell mechanisms for ORMDL3 include the modulation of sphingolipid synthesis leading to skewed CD4+ T cell development (Luthers et al., 2020). Several mechanisms that link *GSDMB* (Gasdermin B) function to immune phenotypes, which are expected to have an impact on SLE, have been described (Ivanov et al., 2023). However, there is some controversy regarding its role compared to other better studied members of the pore-forming gasdermin family. This is partly attributed to the absence of a *GSDMB* orthologue in mice, which limits *in vivo* studies and further complicates the understanding of its specific function (Ruan, 2023). *RP11-94L15.2* encodes a long interspersed non-coding RNA (lincRNA) of unknown function. Notably, it is immediately adjacent to/overlapping with *IKZF3*, which encodes Aiolos, an SLE candidate in its own right and the target (together with Ikaros) of iberdomide, an SLE therapy currently in clinical trials (Merrill et al., 2022, p. 2).

TYK2:

In addition to its association with SLE, the top eQTL variant, rs11085725, used in the identification of this gene through the SMR method, has also been associated with several SLE related immune traits [GWAS Atlas PheWAS: https://atlas.ctglab.nl/PheWAS (Watanabe et al., 2019)]. Curiously,

several variants altering the amino acid sequence of TYK2 are also associated with SLE, RA and IBD with limited effect on non-immune mediated traits (Diogo et al., 2015). The association at *TYK2* may be similar to that observed at *ITGAM*, another SLE associated gene. The *ITGAM* risk variant that alters the amino acid sequence has also been shown to act as an enhancer for *ITGAM* mRNA expression (Maiti et al., 2014). Indeed, since exonic transcription factor binding sites (Stergachis et al., 2013) are relatively common, this may represent a more general genetic risk mechanism than one might appreciate. Regardless, Tyk2 is a Janus Kinase immediately downstream of several cytokine receptors. This notably includes IL-12/23 and type I interferon signaling pathways. Recent FDA approval has been granted for deucravacitinib, a selective Tyk2 inhibitor for treatment of psoriasis (Hoy, 2022). Furthermore, a recent phase II clinical trial of this agent in SLE showed increased response rates over placebo and phase III trials are underway (Morand et al., 2023).

UBE2L3:

Along with its association with SLE, the top eQTL variant, rs2070512, utilized in identifying this gene through the SMR method, has also shown associations with multiple immune traits relevant to SLE [GWAS Atlas PheWAS: https://atlas.ctglab.nl/PheWAS (Watanabe et al., 2019)]. Prior work has shown increased mRNA (UBE2L3) and protein (UBCH7) level expression in SLE patients bearing the risk haplotype (Wang et al., 2012). This increase in expression appears to depend on YY1-mediated enhancement of an interaction between the *UBE2L3* and adjacent *YDJC* promoter (Gopalakrishnan et al., 2022). The lead SLE risk variant at this locus has been shown to regulate basal NF-kB in monocytes and B cells. This variant also regulates responsiveness to TNF-family signals: TNF in myeloid cells and CD40 in B cells. (M. J. Lewis et al., 2015). Genotype-associated correlates in B cell subsets of SLE patients and controls and a predilection for expression in plasma cells (M. Lewis et al., 2015). In addition to CD40– and TNF–

stimulus induced NF-kB activity, TLR7– stimulus induced NF-kB activity has been attributed to UBE2L3 (Mauro et al., 2023). In addition to this, UBE2L3 is a proposed target of dimethyl fumarate (DMF), a therapy approved for both multiple sclerosis and psoriasis. Several additional proposed mechanisms of DMF include modulation of Nrf2-dependent, Nrf2-independent, Th2, type 2 myeloid and Th17 pathways (Ebihara et al., 2016; Tollenaere et al., 2021; Yadav et al., 2019). The relative contribution of each of these mechanisms in current clinical indications remains incompletely clear.

Genes identified by MRAID

AF131215.9 and *AF131215.2*:

These two genes are lncRNAs of unknown function located within intron 1 of the canonical [according to the MANE project (Morales et al., 2022)] transcript of *XKR6*. The specific functions of these genes and their impact on SLE-related immune phenotypes remains to be determined. However, the SLE association near *IRF8* (see below) provides a potential general mechanism for variants that impact lncRNA expression. In this scenario, lncRNA expression modulates expression of one or more nearby genes in close physical proximity to the lncRNA. Applying this model to *AF131215.9* and *AF131215.2,* it may be that they regulate expression of *XKR6* or another nearby SLE risk gene, such as *FAM167A* or *BLK.* Alternatively, they may modify SLE risk through another mechanism.

FAM167A, *BLK* and *RP11-148O21.4*:

RP11-148O21.4 was also identified by PMR-Egger (see discussion above). As for *BLK* and *FAM167A*, previous studies have demonstrated that the SLE risk variants reciprocally regulate the expression of these two genes (Hom et al., 2008; Saint Just Ribeiro et al., 2022). At first glance, decreased expression or activity of *BLK* seems paradoxical in light of the B cell hyperactivity observed in SLE patients (Peng, 2009) and the observation that increased BLK

activity enhances B cell receptor-signaling (DeFranco, 1997). Nonetheless, *BLK* also remains a strong candidate causal gene for the associated autoimmune diseases. First, the correspondence of decreased *BLK* expression in B cell lines and primary B cells and disease risk variants has been described in SLE, SS and RA (Guthridge et al., 2014; Lindén et al., 2017; Simpfendorfer et al., 2012; Thalayasingam et al., 2018). Second, despite the decreased *BLK* expression in B cells bearing autoimmune disease risk alleles, B cells from individuals carrying the risk haplotype are more responsive to B cell receptor stimulus (Simpfendorfer et al., 2012). This increased responsiveness in the presence of decreased *BLK* expression/function is paralleled in marginal zone and follicular B cell subsets *Blk*-deficient mice (Samuelson et al., 2012). Third, Blk-deficiency and/or haploinsufficiency leads to worsened disease phenotypes in murine models of lupus-like disease (Samuelson et al., 2014; Wu et al., 2015). Fourth, rare, loss-of-function variants in *BLK* causing reduced kinase activity have been observed SLE patients and introduction of one such orthologous *Blk* variant increases pathogenic lymphocyte accumulation in the MRL.Fas^{lpr} murine lupus-like disease model (Jiang et al., 2019). Finally, in parallel to the accumulation of splenic B1a cells in murine Blk-deficiency, healthy persons carrying the SLE/RA risk allele at rs2736340 were found to have increased B1-like cells and IgG anti-dsDNA in their peripheral blood (Wu et al., 2015). Taken together, these data support the hypothesis that *BLK* is a causal gene contributing to autoimmune disease risk at this risk locus. While the long-standing observation that BLK contributes to B cell receptor signaling (Burkhardt et al., 1991; DeFranco, 1997) makes this support seem paradoxical, data clearly demonstrate differential requirement for *Blk* and effect on signaling at various stages of B cell development, whether at the pre-B cell stage (Saijo et al., 2003) or in mature B cells (Samuelson et al., 2015).

As for how *FAM167A* might impact SLE risk, recent data implicate the product of this gene, DIORA-1, in NF-kB signaling (Mentlein et al., 2018; Yang et al., 2022), a pathway of some importance in the generation of lupus-autoimmunity (Mauro et al., 2023). Thus, both of these

genes impact biological pathways of relevance to the development of SLE. The impact of both genes on relevant biological pathways in SLE, along with the findings from MRAID and MR-MtRobin, strengthens the causal connection between the *FAM167A-BLK* gene dyad and SLE.

PHRF1 and *UBE2L3*:

These genes were also identified by PMR-Egger and the impact of both on pathways relevant to SLE risk is discussed above.

Genes identified by MR-MtRobin

Altogether, the 16 non-chromosome 6 genes identified by MR-MtRobin comprise five areas of the genome.

GPX3:

This gene encodes glutathione peroxidase 3 and is located adjacent to *TNIP1*. The product of this gene is a plasma selenoprotein that regulates oxidative stress by reducing lipid peroxides and hydrogen peroxide. How glutathione peroxidase 3 might impact SLE risk is not immediately obvious to us. However, *NCF1* (Zhao et al., 2017) and *NCF2* (Jacob et al., 2012), are both SLE risk genes where nonsynonymous variants have been implicated as causal. The enzymes encoded by these genes act upstream of glutathione peroxidase by generating superoxide that is converted to hydrogen peroxide by superoxide dismutase. Thus, *GPX3* could act in the same pathway as these other two SLE risk genes.

IRF5, *RP11-128A6.2*, *SMO*:

IRF5 was identified as causal by PMR-Egger (see discussion above). As for *RP11-128A6.2* it encodes an ornithine decarboxylase pseudogene located within one of the exons of *TNPO3*. In

contrast, *SMO* encodes smoothened, a G-protein coupled receptor that becomes activated when sonic hedgehog (Shh) or another ligand binds Patched Homologue 1 (PTCH1) (Zhang and Beachy, 2023). How this core developmental pathway might impact SLE-relevant biology is not directly apparent. However, hedgehog signaling is important at several lymphocyte developmental stages, including B lymphopoiesis (Cooper et al., 2012), germinal center formation (Sacedón et al., 2005), during the process of positive selection of T cell clones in the thymus (Outram et al., 2000), and during the activation (Lowrey et al., 2002) and proliferation (Chan et al., 2006) of CD4+ T lymphocytes.

XKR6, AF131215.9, AF131215.2, FAM167A, BLK, RP11-148O21.6, RP11-148O21.4, RP11-148O21.2:

These genes were identified as causal by either PMR-Egger or MRAID (see discussion above).

PHRF1 and *TMEM80*:

PHRF1 was identified as causal by both PMR-Egger and MRAID (see discussion above). As for *TMEM80*, the product of this gene is associated with the MKS signaling module of the primary cilia (Li et al., 2016). Mechanistic links to SLE etiology for this gene are also unclear.

RP11-542M13.3 and *RP11-542M13.2*:

These genes are implicated as causal by SMR method using two distinct variants as IV variables. The genes encode two adjacent lncRNAs in the SLE risk region near *IRF8*. Prior work has demonstrated that the lncRNA encoded by the gene *RP11-542M13.2*, also known as *AC092723.1*, regulates *IRF8* expression by recruiting a cell-type-specific enhancer complex (Zhou et al., 2022).

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