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Peer Review Information

Journal: Nature Genetics
Manuscript Title: cGAS-mediated induction of type I interferon due to inborn errors of histone pre-mRNA processing
Corresponding author name(s): Dr. Yanick Crow

Editorial Notes:

N/A

Reviewer Comments & Decisions:

Decision Letter, initial version:

Date: 3rd Aug 20 17:10:22
Last Sent: 3rd Aug 20 17:10:22
Triggered By: Kyle Vogan
From: k.vogan@us.nature.com
To: yanickcrow@mac.com
Subject: Decision on Nature Genetics submission NG-A55245
Message: 3rd August 2020

Dear Yanick,

Your Article "cGAS-mediated induction of type I interferon due to inborn errors of histone pre-mRNA processing" has now been seen by two referees. You will see from their comments below that, while they find your work of interest, they have raised some relevant points. We are interested in the possibility of publishing your study in Nature Genetics, but we would like to consider your response to these points in the form of a revised manuscript before we make a final decision on publication.

To guide the scope of the revisions, the editors discuss the referee reports in detail within the team, including with the chief editor, with a view to identifying key priorities that should be addressed in revision and sometimes overruling referee requests that are deemed beyond the scope of the current study. In this case, we think both referees have provided constructive reviews aimed at strengthening the functional studies and improving the quality of the presentation, and we particularly ask that you address their technical comments with appropriate revisions to the text and display

items. We hope you will find this prioritized set of referee points to be useful when revising your study. Please do not hesitate to get in touch if you would like to discuss these issues further.

We therefore invite you to revise your manuscript taking into account all reviewer and editor comments. Please highlight all changes in the manuscript text file. At this stage we will need you to upload a copy of the manuscript in MS Word .docx or similar editable format.

We are committed to providing a fair and constructive peer-review process. Do not hesitate to contact us if there are specific requests from the reviewers that you believe are technically impossible or unlikely to yield a meaningful outcome.

When revising your manuscript:

*1) Include a "Response to referees" document detailing, point-by-point, how you addressed each referee comment. If no action was taken to address a point, you must provide a compelling argument. This response will be sent back to the referees along with the revised manuscript.

*2) If you have not done so already please begin to revise your manuscript so that it conforms to our Article format instructions, available
here.
Refer also to any guidelines provided in this letter.

*3) Include a revised version of any required Reporting Summary:
https://www.nature.com/documents/nr-reporting-summary.pdf
It will be available to referees (and, potentially, statisticians) to aid in their evaluation if the manuscript goes back for peer review.
A revised checklist is essential for re-review of the paper.

Please be aware of our guidelines on digital image standards.

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Note: This URL links to your confidential home page and associated information about manuscripts you may have submitted, or that you are reviewing for us. If you wish to forward this email to co-authors, please delete the link to your homepage.

We hope to receive your revised manuscript within 8-12 weeks. If you cannot send it within this time, please let us know.

Please do not hesitate to contact me if you have any questions or would like to discuss these revisions further.

Nature Genetics is committed to improving transparency in authorship. As part of our

efforts in this direction, we are now requesting that all authors identified as 'corresponding author' on published papers create and link their Open Researcher and Contributor Identifier (ORCID) with their account on the Manuscript Tracking System (MTS), prior to acceptance. ORCID helps the scientific community achieve unambiguous attribution of all scholarly contributions. You can create and link your ORCID from the home page of the MTS by clicking on 'Modify my Springer Nature account'. For more information please visit please visit www.springernature.com/orcid.

We look forward to seeing the revised manuscript and thank you for the opportunity to review your work.

Sincerely,
Kyle

Kyle Vogan, PhD
Senior Editor
Nature Genetics
https://orcid.org/0000-0001-9565-9665

Referee expertise:

Referee #1: Innate immunity, inflammation, nucleic acid sensing

Referee #2: Innate immunity, inflammation, nucleic acid sensing

Reviewers' Comments:

Reviewer #1:
Remarks to the Author:

In this article from Uggenti et al, the authors identify novel inborn mutations in components of the histone pre-mRNA processing complex that result in previously unidentified forms of the interferonopathy AGS. Mutations in LSM1 or Rnu71 leads to accumulation of misprocessed polyadenylated histone pre-mRNAs that disrupts the ratio of linker histone proteins resulting in access to cGAS and activation of cGAS STING dependent type I IFN and ISG signalling. The findings are very interesting and gives some much-needed physiological relevance to how cGAS localization is regulated and restricted from self-DNA. While the underlying genetic causes are very convincing, the manuscript would benefit from strengthening the findings around the contribution of RNA sensors to the phenotype. Further analysis of additional read outs of cGAS/STING activation in the experimental models should also be performed. In addition, there is little discussion in terms of severity of disease in individual patient phenotypes and how they correlate with ISG signatures and cGAMP levels. The points below aim to strengthen the manuscript prior to publication.

1. Throughout the paper there is a sense of selectivity in the ISG mRNA or protein levels analyzed. Presumably other ISGs were measures in all the experiments. It

would be important to show consistency throughout the experiments and show additional readouts. Figure 4b/supp figure 5/supp figure 8 is a good example of this where 6 ISGs are measured.

2. Figure 5c: 2 out of 10 replicates are increased. 8 replicates have little to no increase in IFNb, the authors should discuss.

3. Figure 5d: Again, there is a huge variation between experiments, some replicates look like effects are independent of cGAS and dependent on MAVS. In the shLSM11_1 group in WT the majority of the data points are comparable to cGAS-/-. Would be helpful to analyze more ISGs to show the effects are consistent across the KO lines with shLSM11_1

4. Figure 5e: Unclear if these experiments were performed at the same time. Should be ran on the same gel. Blots for cGAS STING and MAVS should be included to show KO efficiency.

5. Figure 5: An attempt should be made to show upstream markers of cGAS and STING activation in the THP1 lines such as cGAMP (like in 5G) and phosphorylated STING.

6. Figure 5f: Seems to be mislabeled there are 5 bands but only 4 labels. If second lane is indeed STING KD there is no effect on Mx1 protein levels. This is not consistent with ISG15 mRNA in the left panel of 5f. In addition, the levels of ISG mRNA and the protein levels of Mx1 the MAVS-KD seem lower compared to scrambled control.

7. Figure 6b: Again, it's difficult to compare control samples on one gel to patient samples on another. If ran on the same they should be presented as such. Densitometry of the ratios of H1.4 to H1.2 should all come from the same gel. A loading control should also be included.

Reviewer #2:
Remarks to the Author:

In this manuscript, Uggenti et al proposes that a defect in replication-dependent histone (RDH) pre-mRNA processing causes the auto-inflammatory disease AGS. The authors found that a subset of AGS patients have rare ballelic mutations in LSM11 and RNU7-1, genes required for processing RDH pre-mRNAs. They showed that the patient fibroblasts display defects in histone mRNA processing and altered histone compositions. Knock-down of LSM11 in model cell lines results in similar defects and enhanced interferon signaling. In both patient cells and model cell lines, the enhanced interferon signaling is mediated by cGAS and STING, which led authors to propose that changes in nuclear histone composition leads to inappropriate exposure of self DNA to cGAS and aberrant activation of the interferon pathway. Overall, the findings are novel and significant. The authors' model is generally supported by the data. This reviewer has a few suggestions to further improve the manuscript.

1. While the data indirectly support the notion that the mutations in LSM11 and RNU7-1 identified in patients are loss-of-function, it was not directly tested. This is

particularly weak for RNU7-1 as all experiments with model cell lines were done by knocking down LSM11. Can the authors provide more direct evidence (for example by knocking in the patient mutations or complementing KO cells with mutant LSM11 or RNU7-1)?

2. The authors showed that the patient cells have a disproportionately low level of H1.4 compared to H1.2, and KD of H1.4 is sufficient to stimulate interferon signaling. However, H1.4 is the only RDH gene that behaves unexpectedly in Fig.2d. Does the author know whether KD of other replication-dependent linker histone also leads to hyper interferon signaling? What about H1.2, which the authors examined extensively throughout the manuscript? If the authors think that H1.4 is unique in its ability to prevent aberrant activation of cGAS, discussing why that might be the case would be helpful.

3. Figure 6g is a nice experiment, but it is unclear whether this is relevant to the paper. What is the relationship between chicken H5 and human H1.4 or other RDHs? If the purpose of the experiment was to show that the total level of the linker histones is important, then the authors should show that the total level of the chromatin-bound linker histones is lower in patient cells.

4. In several cases, data are presented in a confusing manner, and the experimental methods are not very clearly laid out in Methods.

Fig 3: why do the authors combine the data points for AGS8 and AGS9? This makes it difficult to interpret the data.

Fig 5f: the authors showed ISG15 mRNA level for AGS9, and MX1 protein level for AGS8. Can you test the ISG15 mRNA and MX1 protein levels for both AGS8 and 9? In the immunoblot for MX1, there are 5 lanes but 4 labels. If the sample order is the same as in the ISG15 mRNA plot, then the result would suggest that STING KD does not affect interferon signaling in AGS8, which is inconsistent with the model.

Fig 6a: It is unclear what the authors mean by H2A/H2B, or H3/H4? How do you combine the data for H2A and H2B, and for H3 and H4? This is confusing. The authors should display each experimental result separately.

Fig 6b: the control and AGS samples should be run on the same gel and analyzed in the same blot (same imaging & analysis method) to be able to properly compare.

qPCR: Given that the histone can globally affect transcription of multiple genes, one should make sure that internal controls for RT-qPCR is relatively stable. In Methods, the authors indicated that HPRT and/or GAPDH and/or ACTIN were used as internal controls, but this description gives an impression that the internal controls were inconsistently used throughout the manuscript. It should be also tested whether the levels of these internal control genes are constant relative to each other in all conditions under investigation.

Author Rebuttal to Initial comments

Reviewer # 1:

"*1. Throughout the paper there is a sense of selectivity in the ISG mRNA or protein levels analyzed. Presumably other ISGs were measures in all the experiments. It would be important to show consistency throughout the experiments and show additional readouts. Figure 4b/supp figure 5/supp figure 8 is a good example of this where 6 ISGs are measured.*"

Response: The concern of the reviewer applies to the data captured in Figures 5c-f.

For background, the data in Figure 4 and Supplementary figures 5 and 8 (mentioned by the reviewer) represent a 'standard' set of six interferon-stimulated genes (ISGs) that we use in our routine patient-screening assay (Rice et al. Lancet Neurology 2013;12:1159-1169). Supplementary figure 5 clearly demonstrates a consistent (all 16 patients sampled - both genotypes) and persistent (44 of 45 occasions tested - including eight patients assessed three or more times over a period of more than two years) marked increase in expression of these six ISGs in patient whole blood *ex vivo*; and the data presented in Figure 4c show that this behaviour is also observed in patient-derived fibroblasts – thereby justifying our use of this cell type in other experiments (further legitimised by the RNA-Seq data that we derived from patient fibroblasts – Supplementary figure 6).

It is important to note that Supplementary figure 8 demonstrates the expression of our complete panel of ISGs, together with interferon lambda and interferon beta, after knock-down (KD) of *LSM11* in THP-1 cells (using two different shRNAs). The figure shows that all of these ISGs behave similarly, and therefore reasonably serve as exemplar readouts in our experiments in this system. That is, the ISGs displayed in Figure 5c-f were chosen not because they give the 'best / right' results, but as a 'short-hand' (with the number of tests limited in some cases by the amount of material available). To provide reassurance relating to this point, **in Figure 5d we now include new data on the response of *IFI44L* to KD of *LSM11* by shLSM11_1 according to WT / STING / cGAS / MAVs status. We also add new data on IFIT1 expression in Figure 5f. Additionally, we provide new data on four ISGs, and interferon beta, following KD of *LSM11* using a new short-hairpin RNA, LSM11_3 (new Supplementary figure 9 - which also includes a new protein blot for ISG15**, please see below).

Please note, for clarity **we now show individual experimental points in box plots** in Figure 5c and d (and, for consistency, in Supplementary figure 8). We continue to show violin plots in Figure 5f and g, where each data point represents the average of replicate experiments in each cell line (the same is true of the data in Figure 4c).

Relating to protein expression, here – in addition to the amount of material available - we are limited by the antibodies that we have found to work in THP-1 cells and fibroblasts. To date, we have only been able to generate reliable data for MX1 and ISG15 in fibroblasts, and ISG15 in THP-1 cells. **We now provide new data for both ISG15 and MX1 in a different fibroblast cell line (AGS9) in Figure 5f (in addition to showing new data for ISG15, and the previously demonstrated MX1 blot, in our AGS8 cell line – originally the right-hand panel of Figure 5f, which figure has now been moved to Supplementary figure 12a). As mentioned above, our new Supplementary figure 9 includes a new protein blot for ISG15**.

"*2. Figure 5c: 2 out of 10 replicates are increased. 8 replicates have little to no increase in IFNb, the authors should discuss.*"

Response: The concern of the reviewer relates to the data on *IFNß* in Figure 5 panel c. The results for the ISGs *IFI27* and *IFI44l* are compelling / statistically robust (see Supplementary figure 8 and the response above).

Although variable, there is a statistical increase in the expression of *IFNß* between wild-type and *LSM11* knock-down (KD) cells. To reassure the reviewer, **we have now added new data on *IFNß* following KD of *LSM11* using a different shRNA (shLSM11_3) (Supplementary figure 9)**.

"*3. Figure 5d: Again, there is a huge variation between experiments, some replicates look like effects are independent of cGAS and dependent on MAVS. In the shLSM11_1 group in WT the majority of the data points are comparable to cGAS-/-. Would be helpful to analyze more ISGs to show the effects are consistent across the KO lines with shLSM11_1.*"

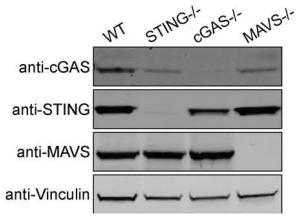
Response: Again, although we see variability, the data that we have derived have been analysed statistically (as annotated in the individual panels). We believe that the source of the variability that the reviewer refers to likely relates to differences in the efficiency of viral ('bulk') transduction of THP-1 cells across experiments, rather than a true biological effect. We do appreciate the importance of the experiment illustrated in Figure 5d and, as mentioned above, **we now include new data on the response of *IFI44L* to KD of *LSM11* by shLSM11_1 according to WT / STING / cGAS / MAVs status (Figure 5d), and on four ISGs following KD of *LSM11* by a new short-hairpin RNA, LSM11_3 (Supplementary figure 9)**.

More generally, we emphasise that mRNA results are supported by protein data (Figure 5e), the data that we present using a KD strategy in fibroblasts (Figure 5f) (i.e. a different cell type – patient material), and our measurement of cGAMP in (patient) fibroblasts (Figure 5g) (where cGAMP levels in patient cells are within the range seen when we stimulate control fibroblasts with 1ug/ml of DNA); all of these data are concordant with an induction of interferon signalling by DNA.

Please note that **we now include new data confirming the efficient knockdown of expression of *cGAS*, *STING*, *MAVs* and *MYD88* in patient fibroblasts – relevant to Figure 5f - as a new Supplementary figure 11**.

Please note also that when assessing the data derived from the different cell lines in Figure 5e (and Supplementary figures S9 and S10, it is important to compare the Scrambled and KD data within each cell line (WT, STING KO etc.) - given that they are genetically / clonally distinct – and not expression between cell lines. Rebuttal figure 1 emphasises this point, where the expression of nucleic acid sensors can differ between cell lines.

Rebuttal figure 1. Protein levels in distinct THP-1 cell lines.



"*4. Figure 5e: Unclear if these experiments were performed at the same time. Should be ran on the same gel. Blots for cGAS STING and MAVS should be included to show KO efficiency.*"

Response: We apologise to the reviewer for any concerns raised here. In our original submission, the data for the wild-type, STING KO and cGAS KO lines were from the same gel. However, we included an illustrative result for MAVS taken from a different (replicate) gel. To resolve any concerns, we now use a complete data set (wild-type / STING KO / cGAS KO / MAVS KO) in a new Figure 5e, demonstrating that these images are derived from a single blot in a **new Supplementary figure S10a**.

We have recently published a characterisation of the THP-1 cells CRISPR KO for cGAS, STING and MAVS, **which we now reference in the Methods** (Lepelley et al. J Exp Med 2020;217:e20200600). A blot confirming the absence of the relevant protein in each cell line is shown above (Rebuttal Figure 1).

"*5. Figure 5: An attempt should be made to show upstream markers of cGAS and STING activation in the THP1 lines such as cGAMP (like in 5G) and phosphorylated STING.*"

Response: We thank the reviewer for this suggestion. We have attempted to **assess phosphorylated STING** in wild-type and KO THP-1 cells, whilst also **re-assessing ISG15 expression**. Although the antibody staining is not ideal, the data are consistent with our other results, so that **we now include a new blot with these data as Supplementary figure 10b**.

"*6. Figure 5f: Seems to be mislabeled there are 5 bands but only 4 labels. If second lane is indeed STING KD there is no effect on Mx1 protein levels. This is not consistent with ISG15 mRNA in the left panel of 5f. In addition, the levels of ISG mRNA and the protein levels of Mx1 the MAVS-KD seem lower compared to scrambled control*."

Response: We do apologise to the reviewers for this error (and don't really know how we failed to spot it before submission!). The labelling was correct in the left-hand panel. In the right-hand panel we had originally run a sample following MDA5 knock-down, but then decided that this was 'redundant' considering the MAVS data that we also derived. To reassure the reviewers, **we include the gel from the original submission** (previously, right-hand side Figure 5f – derived in fibroblasts from a patient with mutations in AGS8) **and the complete blot as a new Supplementary figure 12a** (**where we also show new data for ISG15**), and **we have now derived an appropriately labelled new right-hand side Figure 5f** – this time using fibroblasts from a patient with mutations in *RNU7-1* (AGS9) (**also showing the whole blot in Supplementary figure S12b** - and, as stated above, **including new data for two ISGs**).

"*7. Figure 6b: Again, it's difficult to compare control samples on one gel to patient samples on another. If ran on the same they should be presented as such. Densitometry of the ratios of H1.4 to H1.2 should all come from the same gel. A loading control should also be included.*"

Response: These images are from the same gel, and are shown as they are simply for presentation purposes (**please see the new Supplementary figure S14 for confirmation of this fact**). Please note, we are showing one representative gel, with the densitometry calculated from the combined data derived from three experiments.

Identifying the appropriate loading control in this situation is challenging – because we cannot predict the potential effect of a disturbance of replication dependent histone (RDH) pre-mRNA processing on chromatin-bound proteins. An analysis by ratio (of H1.4 to H1.2) overcomes artefacts resulting from such a concern. This is a standard practice (e.g. see Figure 4B in Terme et al. J Biol Chem 2011;286:35347-57). The important point here is that we are assessing the ratio of H1.4 to H1.2 - derived from the same sample (quantified on the right-hand side of Figure 6b).

"*...there is little discussion in terms of severity of disease in individual patient phenotypes and how they correlate with ISG signatures and cGAMP levels.*"

Response: We do provide an extensive description of individual patient phenotypes in Supplementary table 5. In general terms, the clinical features seen in this cohort conform to 'classical' Aicardi-Goutières syndrome (AGS) – perhaps with an increased risk of liver / kidney disease and premature death (compared to patients with mutations in AGS1-7). However, our cohort of AGS8/9 patients is relatively small at this time, thus limiting the ability to draw firm conclusions relating to the breadth of phenotype, and any intra- and inter-familial differences. In regards to correlating clinical features with interferon signalling status – I think that this is not possible; we know that the type I interferonopathies are characterised by variability in phenotypic expression, and even complete clinical non-penetrance, in the face of persistently elevated ISG expression (very well illustrated by our recent paper describing a cohort of individuals with mutations in *IFH1*: Rice et al. Hum Mutat 2020;41:837-849). **Given that the focus of this manuscript is genetic/mechanistic, we have not made any changes to the text with respect to this point**.

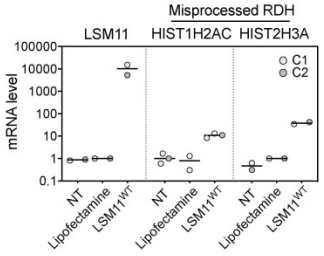
Reviewer # 2:

"*1. While the data indirectly support the notion that the mutations in LSM11 and RNU7-1 identified in patients are loss-of-function, it was not directly tested. This is particularly weak for RNU7-1 as all experiments with model cell lines were done by knocking down LSM11. Can the authors provide more direct evidence (for example by knocking in the patient mutations or complementing KO cells with mutant LSM11 or RNU7-1)?*"

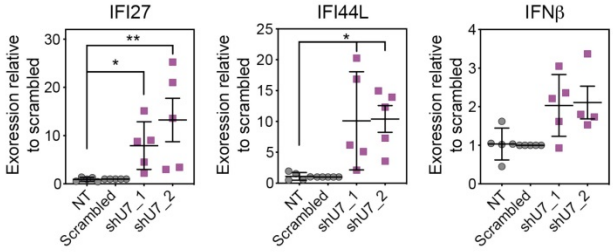
Response: We do appreciate the point raised by the reviewer. However, working with these genes poses considerable challenges that have limited the approaches that we have been able to take. Firstly, the obvious fact that *RNU7-1* is non-protein encoding means that we have not been able to perform any antibody work related to this genotype. Secondly, whilst antibodies for LSM11 exist, LSM11 protein

is expressed at levels that we have not been able to detect in fibroblasts (using either of two antibodies) (and that our collaborator Zbig Dominski, an expert in the U7 snRNP complex, confirms to be his experience also). More generally, it is known that *LSM11* and *RNU7-1* mRNAs are expressed at very low levels. Furthermore, it seems that the stoichiometry of *LSM11* / *RNU71* is very important, so that we have found that overexpression of *LSM11*, even in wild-type cells, actually results in a misprocessing of RDH (Rebuttal figure 2). Finally, for *RNU7-1*, the mRNA is so short (63 nucleotides) that we have so-far been unable to design specific primers which reliably assess *RNU7-1* expression (a problem compounded by the fact that *RNU7-1* lies in the 5' UTR of another gene - *C12ORF57*).

Rebuttal figure 2. Effect of transfection of *LSM11* on replication dependent histone (RDH) pre-mRNA processing in wild-type fibroblasts.



Taking the above difficulties into account, and given that we see similar, and robust, ISG expression and histone mRNA misprocessing profiles in patient material harbouring mutations in either *LSM11* or *RNU7-1*, we believe that our data provide very strong evidence in favour of variant pathogenicity (please note that Figure 2d shows that miss-processing of RDH pre-mRNA is not seen in fibroblasts of patients with AGS due to other genotypes). Furthermore, our histone pre-mRNA mis-processing results are consistent with those of previously published experiments investigating LSM11 / U7 loss-of-function in cell and animal systems (referenced in the manuscript). I add here that we have knocked-down *RNU7-1* in THP-1 cells, and observed a robust upregulation of ISGs and interferon beta (Rebuttal figure 3). However, since we cannot formally prove the knock-down (see point made above), we are hesitant to include these data in the manuscript.

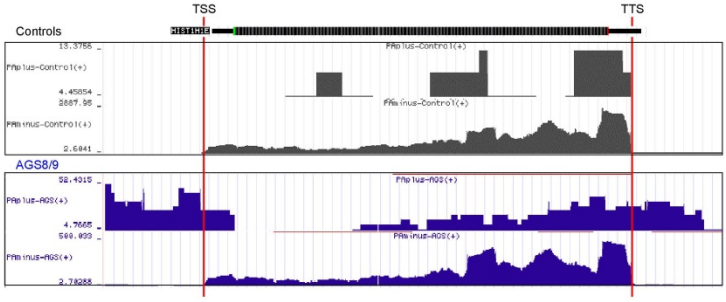


Rebuttal figure 3. Effect on interferon signalling of *RNU7-1* KD in THP-1 cells.

"*2. The authors showed that the patient cells have a disproportionately low level of H1.4 compared to H1.2, and KD of H1.4 is sufficient to stimulate interferon signaling. However, H1.4 is the only RDH gene that behaves unexpectedly in Fig.2d. Does the author know whether KD of other replication-dependent linker histone also leads to hyper interferon signaling? What about H1.2, which the authors examined extensively throughout the manuscript? If the authors think that H1.4 is unique in its ability to prevent aberrant activation of cGAS, discussing why that might be the case would be helpful.*"

Response: The differential effect on the expression of H1.4 (illustrated in Figure 2d) is interesting, seemingly related to an effect at the transcriptional level (Rebuttal figure 4), and something that we are keen to explore in the future.

Rebuttal figure 4. Screenshot of RNA-Seq data relating to *HIST1H1E* (encoding H1.4) expression in fibroblasts. Here we see reduced levels of expression in the Poly(A)- fraction of patient cells compared to those of controls. In the read-out from patients, note is made of the presence of an uncharacterised transcript sitting at the start site of *HIST1H1E*, which we predict is interfering with *HIST1H1E* transcription. Nascent RNA-Seq may throw light on the nature of this phenomenon.



It is known that different cells demonstrate different linker histone composition (e.g. Terme et al. J Biol Chem 2011;286:35347-57). In that context, we note that Izquierdo-Bouldstridge et al. (Nucleic Acids Res 2017;45:11622-116420 – cited in the original submission) found that combined depletion of H1.2 and H1.4 in T47D cells could induce an interferon signature - which was not seen when either gene was knocked down individually. We note also that neither deletion of H1.2 nor of H1.4 resulted in an interferon signature in neutrophils (Sollberger et al. eLife 2020;9:e52563). We suspect that total linker histone levels are important in regards of the AGS phenotype that we observe (noting that in fibroblasts, our RNA-Seq data indicate that *HIST1H1C* (encoding H1.2) and *HIST1H1E* (encoding H1.4) are the most highly expressed linker histone transcripts (see the Poly(A)- fraction in Supplementary figure 4)). However, we cannot rule out a relevant additive effect of core histone levels / composition. As such, at this time, we are inclined to caution in any detailed mechanistic claim(s).

"*3. Figure 6g is a nice experiment, but it is unclear whether this is relevant to the paper. What is the relationship between chicken H5 and human H1.4 or other RDHs? If the purpose of the experiment was to show that the total level of the linker histones is important, then the authors should show that the total level of the chromatin-bound linker histones is lower in patient cells*."

Response: Chicken H5 linker histone is the only linker histone in terminally differentiated chicken cells, and is a standard reagent in chromatin experimentation (e.g. see Peterson & Hansen CSH Protoc 2008;pdb.prot511200), used both for practical reasons (large quantities of pure source material readily obtainable which is stable over many weeks), and because avian histones demonstrate a very consistent pattern of post-translational modifications.

The reasoning behind this particular assay was to determine if the presence or absence of linker histone might affect the 'immunogenicity' of chromatin – which appears to be the case. Ideally, we would like to show that ('pure') chromatin extracted from patient fibroblasts is more immunogenic (i.e. induces more cGAMP production) than chromatin from control cells. However, these are extremely challenging experiments, requiring considerable amounts of starting material which we have not been able to achieve to date - and likely necessitating the future development of a novel protocol for chromatin extraction from (relatively) small number of cells. The same issue is relevant to our ability to interrogate the total level of chromatin-bound linker histone, with our current experiments using chromatin-enriched fractions. Furthermore, antibodies are not available to all linker histone subtypes (and, to our knowledge, no effective pan-H1 antibody exists). However, we now include data from an initial experiment where we first isolated protein from the nuclear fraction of control and patient fibroblasts. By Coomassie gel staining, we observed an overall reduction of linker histones in patient compared to control cells, whilst the level of core histones was not obviously affected (**new Supplementary figure S13**). We subsequently went on to perform the experiment described in Figure 6. Again, we observed no difference in the total level of core histones (Fig. 6a), whilst our examination of chromatin-bound histone revealed a marked reduction in the ratio of linker histone H1.4 compared to H1.2 in patient cells (Fig. 6b; **new fig. S14**). Given that *HIST1H1E* (encoding H1.4) and *HIST1H1C* (encoding H1.2) together represent the majority of linker histone transcripts expressed in fibroblasts (fig. S4; **new table S7**), we

think that our suggestion of a reduction in overall chromatin-bound linker histone is justified. **We have adjusted the text accordingly**.

"*Fig 3: why do the authors combine the data points for AGS8 and AGS9? This makes it difficult to interpret the data*."

Response: The data are pooled for statistical reasons, comparing RNA-Seq data from fibroblasts of one patient with mutations in *LSM11* (AGS8) and two patients with mutations in *RNU7-1* (AGS9) (i.e. three patients in total) to three controls. Given the similar ISG expression and histone mRNA misprocessing profiles in patient material with mutations in either *LSM11* or *RNU7-1*, we consider it reasonable to combine the data. **We ask then that we might leave the figure as-is**.

"*Fig 5f: the authors showed ISG15 mRNA level for AGS9, and MX1 protein level for AGS8. Can you test the ISG15 mRNA and MX1 protein levels for both AGS8 and 9? In the immunoblot for MX1, there are 5 lanes but 4 labels. If the sample order is the same as in the ISG15 mRNA plot, then the result would suggest that STING KD does not affect interferon signaling in AGS8, which is inconsistent with the model*."

Response: We thank the reviewer for these points, which were also raised by Reviewer #1 and have been addressed above.

"*Fig 6a: It is unclear what the authors mean by H2A/H2B, or H3/H4? How do you combine the data for H2A and H2B, and for H3 and H4? This is confusing. The authors should display each experimental result separately*."

Response: We apologise for any confusion. Here, we are referring to the ratio of H2A to H2B, and of H3 to H4 (given that these histone pairs act as dimers / tetramers in the nucleosome), normalised to the ratio in control cells. As above, such an analysis overcomes artefacts resulting from difficulties in choosing a control protein. **For clarity, we have changed the label on the Y axis in Figure 6a**.

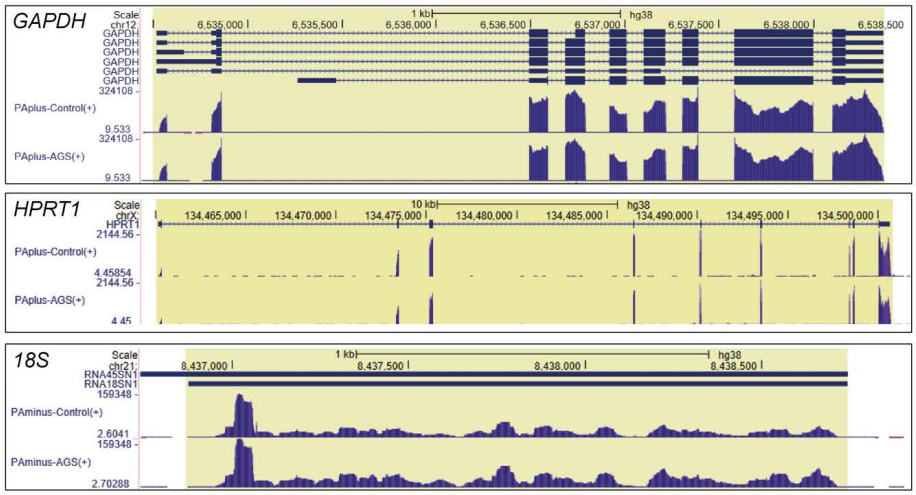
"*Fig 6b: the control and AGS samples should be run on the same gel and analyzed in the same blot (same imaging & analysis method) to be able to properly compare*."

Response: Again, this important point was also raised by Reviewer #1, and responded to above.

"*qPCR: Given that the histone can globally affect transcription of multiple genes, one should make sure that internal controls for RT-qPCR is relatively stable. In Methods, the authors indicated that HPRT and/or GAPDH and/or ACTIN were used as internal controls, but this description gives an impression that the internal controls were inconsistently used throughout the manuscript. It should be also tested whether the levels of these internal control genes are constant relative to each other in all conditions under investigation*."

Response: We apologise for any confusion, **leading us to clarify our use of house-keeping genes for our qPCR experiments in the Methods**. Specifically, *HPRT1* was used for all THP-1 cell experiments, *GAPDH* and / or *HPRT1* used for experiments in fibroblasts, and *18S* and *HPRT1* used to normalise ISG expression in blood. That the expression of these genes is similar between patient and control cells is corroborated by our RNA-Seq data (Rebuttal figure 5). There was a misunderstanding relating to the use of *ACTB* (as a control for the experiment detailed in Supplementary figure S9 of the original submission), so that we have removed mention of this gene from the Methods (again, we apologise for this error).

Rebuttal figure 5. Expression of *GAPDH1*, *HPRT1* and *18s* in patient and control fibroblasts.



Decision Letter, first revision:

Date: 31st Aug 20 16:57:35
Last Sent: 31st Aug 20 16:57:35
Triggered By: Kyle Vogan
From: k.vogan@us.nature.com
To: yanickcrow@mac.com
Subject: Decision on Nature Genetics submission NG-A55245R
Message: 31st August 2020

Dear Yanick,

Your revised Article "cGAS-mediated induction of type I interferon due to inborn errors of histone pre-mRNA processing" has been seen by the two original referees. You will see from their comments below that, while Reviewer #1 has no remaining requests, Reviewer #2 has raised two ongoing concerns. We remain very interested in the possibility of publishing your study in Nature Genetics, but we would like to consider your response to these points in the form of a further revision before we make a final decision on publication.

In particular, as requested by Reviewer #2, we ask that you provide additional evidence to support the claim that the overall level of linker histones is reduced in patients and that you add a Supplementary Note outlining the technical challenges you faced in performing functional studies with LSM11 and RNU7-1. We again hope that you will find this prioritized set of referee points to be useful when revising your study. Please do not hesitate to get in touch if you would like to discuss these issues further.

We therefore invite you to revise your manuscript again taking into account all reviewer and editor comments. Please highlight all changes in the manuscript text file. At this stage we will need you to upload a copy of the manuscript in MS Word .docx or similar editable format.

We are committed to providing a fair and constructive peer-review process. Do not hesitate to contact us if there are specific requests from the reviewers that you believe are technically impossible or unlikely to yield a meaningful outcome.

When revising your manuscript:

*1) Include a “Response to referees” document detailing, point-by-point, how you addressed each referee comment. If no action was taken to address a point, you must provide a compelling argument. This response will be sent back to the referees along with the revised manuscript.

*2) If you have not done so already please begin to revise your manuscript so that it conforms to our Article format instructions, available here. Refer also to any guidelines provided in this letter.

*3) Include a revised version of any required Reporting Summary:

https://www.nature.com/documents/nr-reporting-summary.pdf
It will be available to referees (and, potentially, statisticians) to aid in their evaluation if the manuscript goes back for peer review.
A revised checklist is essential for re-review of the paper.

Please be aware of our guidelines on digital image standards.

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Note: This URL links to your confidential home page and associated information about manuscripts you may have submitted, or that you are reviewing for us. If you wish to forward this email to co-authors, please delete the link to your homepage.

We again hope to receive your revised manuscript within 4-8 weeks. If you cannot send it within this time, please let us know.

Please do not hesitate to contact me if you have any questions or would like to discuss these revisions further.

Nature Genetics is committed to improving transparency in authorship. As part of our efforts in this direction, we are now requesting that all authors identified as 'corresponding author' on published papers create and link their Open Researcher and Contributor Identifier (ORCID) with their account on the Manuscript Tracking System (MTS), prior to acceptance. ORCID helps the scientific community achieve unambiguous attribution of all scholarly contributions. You can create and link your ORCID from the home page of the MTS by clicking on 'Modify my Springer Nature account'. For more information please visit please visit www.springernature.com/orcid.

We look forward to seeing the revised manuscript and thank you for the opportunity to review your work.

Sincerely,
Kyle

Kyle Vogan, PhD
Senior Editor
Nature Genetics
https://orcid.org/0000-0001-9565-9665

Referee expertise:

Referee #1: Innate immunity, inflammation, nucleic acid sensing

Referee #2: Innate immunity, inflammation, nucleic acid sensing

Reviewers' Comments:

Reviewer #1:
None

Reviewer #2:
Remarks to the Author:

In general, the authors' response is appropriate, but I have one suggestion and a remaining concern.

In response to the reviewer 2's first point, the authors described several major technical challenges, which are understandable. However, there was no change in the manuscript text to explain these challenges. I would strongly suggest that the authors address these technical challenges and limitation in the text so that the readers can understand these issues.

In response to the reviewer 2's 3rd point, the authors argued that the skewed ratio of H1.4 to H1.2 supports the argument that the total linker histone is reduced. As shown in Fig S14, one cannot draw this conclusion simply by looking at the ratio. The authors also argued that the other piece of data supporting this argument is Fig S13, which is a Coomassie stained SDS gel image, where the identity of the bands indicated as H1 are unclear. Since overall reduction of the linker histones in patients is one of the major arguments in the manuscript, this needs to be addressed more clearly.

Author Rebuttal, first revision:

igmm
INSTITUTE OF GENETICS
& MOLECULAR MEDICINE

MRC Institute of Genetics and Molecular Medicine
The University of Edinburgh
Crewe Road
Edinburgh
EH4 2XU

1st September 2020

Dr Kyle Vogan
Senior editor
Nature Genetics

Dear Kyle

Re: cGAS-mediated induction of type I interferon due to inborn errors of histone pre-mRNA processing (NG-A55245R)

Once again, thank you to your expert reviewers for their further consideration of our work, and to you for your original (yesterday evening) and follow-up (this morning) emails (and, without wishing to be presumptive, your positive slant on our manuscript). I wasn't quite sure of how formal I should be at this point, but I decided that it might be most appropriate to respond in letter form.

Reviewer # 1:

No further requests.

Reviewer # 2:

"*In general, the authors' response is appropriate, but I have one suggestion and a remaining concern*."

"*1. In response to the reviewer 2's first point, the authors described several major technical challenges, which are understandable. However, there was no change in the manuscript text to explain these challenges. I would strongly suggest that the authors address these technical challenges and limitation in the text so that the readers can understand these issues*."

Response: Although the difficulties related to this point, outlined in our rebuttal (dated 14th August), are important, I can't quite see how to incorporate what would be, essentially, a set of negative statements about things that we can't do (!) - without spoiling the flow of the text / the logical description of our work-flow that we have crafted. I wonder then if we might not take up this suggestion if you do not mind. If you do feel that we should include text relating to this, I will make adjustments of course.

2. "*In response to the reviewer 2's 3rd point, the authors argued that the skewed ratio of H1.4 to H1.2 supports the argument that the total linker histone is reduced. As shown in Fig S14, one cannot draw this conclusion simply by looking at the ratio. The authors also argued that the other piece of data supporting this argument is Fig S13, which is a Coomassie stained SDS gel image, where the identity of the bands indicated as H1 are unclear. Since overall reduction of the linker histones in patients is one of the major arguments in the manuscript, this needs to be addressed more clearly*."

Response: I am extremely grateful to you for allowing us to proceed without further experimentation in this regard – taking into account the issues/challenges that we previously highlighted in our rebuttal (and my email of last night). However, as a response to the reviewer's comment, I would argue that our Coomassie gel (Supplementary figure 13) is helpful in illustrating a (clear) reduction of overall linker histones (in lanes marked F1 and F8 – see the bottom panel in particular).

Editorial comment:

"*....we are comfortable moving forward with the paper without additional data to assess linker histone levels, provided the interpretations are presented with a sufficient degree of caution*."

Response: Once more, thank you very much indeed for this Kyle. In brief, I consider that we have been suitably circumspect in the text relating to the relative importance (or otherwise) of linker histones. Thus, in the *Abstract* we end by saying (underlined here only for emphasis):

"*We conclude that nuclear histones, as key constituents of chromatin, are essential in suppressing the immunogenicity of self-DNA*."

Whilst, at the end of the manuscript, we say:

"*These mutations lead to a dysregulation of histone mRNA transcripts, a disturbance of histone protein composition, and the induction of an interferon response through a cGAS-stimulator of interferon genes (STING) dependent pathway*."

Where we do highlight linker histone(s) in the final section, we do so very precisely in relation to the specific experiment that was performed, but then end with a (suitably) cautious interpretation:

"*Altogether, these data support the possibility that chromatin-bound histone stoichiometry plays an essential physiological role in limiting cGAS activation in the nucleus*."

I look forward to hearing if you now think that the manuscript is acceptable for publication.

Yours sincerely

Yanick Crow

Decision Letter, second revision:

Date: 22nd Sep 20 09:58:20

Last Sent: 22nd Sep 20 09:58:20

Triggered By: Kyle Vogan

From: k.vogan@us.nature.com

To: yanickcrow@mac.com

CC: carolina.uggenti@igmm.ed.ac.uk,alice.lepelley@institutimagine.org,Marine.mdepp@gmail.com, andrew.badrock@iggm.ed.ac.uk,m.rodero@uq.edu.au,Marie-therese.el-daher@igmm.ed.ac.uk,Gillian.Rice@manchester.ac.uk,somdutta.dhir@igmm.ed.ac.uk,Ann.Wheeler@igmm.ed.ac.uk,ashish.dhir@igmm.ed.ac.uk,w.albawardi@ed.ac.uk,marie-louise.fremond@aphp.fr,luis.seabra@institutimagine.org,j.doig@ed.ac.uk,natalie.blair@ed.ac.uk,maria.martin-niclos@institutimagine.org,e.dellamina@garvan.org.au,alejandro.rubio@genyo.es,Jose.Garcia-Perez@igmm.ed.ac.uk,Duncan.Sproul@igmm.ed.ac.uk,jan.rehwinkel@imm.ox.ac.uk,Jonny.hertzog@kellogg.ox.ac.uk,boland@cng.fr,robert.olaso@cng.fr,deleuze@cng.fr,julien.baruteau@gosh.nhs.uk,brochard.k@chu-toulouse.fr,drjonbuck@yahoo.co.uk,cavallerav@gmail.com,cristina.cereda@mondino.it,liesbeth.dewaele@uzleuven.be,angus.dobbie@nhs.net,diane.doummar@aphp.fr,frances.elmslie@nhs.net,m.koch-hogrebe@kinderklinik-datteln.de,ram16k@yahoo.com.au,k.lamb@nhs.net,jh.livingston@nhs.net,Anirban.Majumdar@UHBristol.nhs.uk,charles.lourenco@estacio.br,simona.orcesi@mondino.it,sylviane.peudenier@chu-brest.fr,K.rostasy@kinderklinik-datteln.de,c.salmon@nhs.net,christiaanscott@gmail.com,davidetondu@hotmail.com,touati.g@chu-toulouse.fr,marialuisa.valente@mondino.it,vanderlindenh@yahoo.com.br,hilde.vanesch@uzleuven.be,marie.vermelle@ch-dunkerque.fr,kate.webb@uct.ac.za,andrew.jackson@ed.ac.uk,martin.reijns@igmm.ed.ac.uk,nick.gilbert@ed.ac.uk

Subject: Decision on Nature Genetics submission NG-A55245R1

Message:

Our ref: NG-A55245R1

22nd September 2020

Dear Yanick,

Thank you for submitting your revised manuscript "cGAS-mediated induction of type I interferon due to inborn errors of histone pre-mRNA processing" (NG-A55245R1). In light of your responses to the referees' comments, we will be happy in principle to publish your work in Nature Genetics as an Article pending final revisions to comply with our editorial and formatting guidelines.

Note that we will send you a checklist detailing these editorial and formatting requirements in about a week. Please do not finalize your revisions or upload the final materials until you receive this additional information.

In recognition of the time and expertise our reviewers provide to Nature Genetics's editorial process, we would like to formally acknowledge their contribution to the external peer review of your manuscript entitled "cGAS-mediated induction of type I interferon due to inborn errors of histone pre-mRNA processing". For those reviewers who give their assent, we will be publishing their names alongside the published article.

While we prepare these instructions, we encourage the Corresponding Author to begin to review and collect the following:

-- Confirmation from all authors that the manuscript correctly states their names, institutional affiliations, funding IDs, consortium membership and roles, author or collaborator status, and author contributions.

-- Declarations of any financial and non-financial competing interests from any author. For the sake of transparency and to help readers form their own judgment of potential bias, the Nature Research Journals require authors to declare any financial and non-financial competing interests in relation to the work described in the submitted manuscript. This declaration must be complete, including author initials, in the final manuscript text.

If you have any questions as you begin to prepare your submission please feel free to contact our Editorial offices at genetics@us.nature.com. We are happy to assist you.

Thank you again for your interest in Nature Genetics.

Sincerely,
Kyle

Kyle Vogan, PhD
Senior Editor
Nature Genetics
https://orcid.org/0000-0001-9565-9665

ORCID

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Date: 28th Sep 20 11:30:47
Last Sent: 28th Sep 20 11:30:47
Triggered By: Kyle Vogan
From: k.vogan@us.nature.com
To: yanickcrow@mac.com
Subject: Final formatting instructions for NG-A55245R1
Message: Our ref: NG-A55245R1

28th September 2020

Dear Yanick,

Thank you for your patience as we've prepared the guidelines for final submission of your Nature Genetics manuscript "cGAS-mediated induction of type I interferon due to inborn errors of histone pre-mRNA processing" (NG-A55245R1). Please follow the instructions provided here and in the attached files.

When you upload your final materials, please:

A) Fill out and upload the attached ***Publishing Policy Worksheet For Authors***, which contains information on how to comply with our legal guidelines for publication and links to the files that you will need to upload prior to final acceptance. You must initial the relevant portions of this checklist, sign it and return it with your final files. We will not be able to proceed further without these files:

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d) Competing Interests Statement (if applicable)

e) Author Approval List (if applicable)

f) Third Party Rights Table (if applicable, either Third Party Rights for Original Research or Third Party Rights if Commissioned by Journal)

g) Institutional Open Access Waiver (if applicable)

h) Inventory of Supporting Information (required)

B) Include a tracked-changes Word file of your revised article.

C) Include a point-by-point response to the points below:

General formatting:

1. Please revise the sentence in the main text describing the assessment of overall levels of linker histones as follows: "By Coomassie gel staining, we observed suggestive evidence that the overall level of linker histones is reduced in patient compared to control cells…"

2. Please revise the Supporting Information to follow the formatting guidelines outlined below and in the accompanying files (see attached "NRG Formatting Guide" and "Inventory of Supporting Information" for detailed instructions on formatting), and revise headings and text callouts accordingly. In particular, please reformat up to 10 Supplementary Figures as Extended Data Figures, and present any additional Supplementary Figures and their accompanying legends together with the Supplementary Tables as a single merged PDF file.

3. Please present the Author Contributions and Competing Interests statement as standalone sections separate from the Acknowledgments.

4. Please include the Online Methods and accompanying references in the main text file.

5. Please clarify the Data Availability statement by explicitly noting which data or materials are under controlled access and how requests for these data and materials can be submitted.

6. Please add a Code Availability statement.

7. Only papers that have been published or accepted by a named publication or recognized preprint server should be in the numbered reference list. Published conference abstracts, numbered patents and research data sets that have been assigned a digital object identifier may be included in the reference list.

8. Unpublished meeting abstracts, personal communications and manuscripts under consideration (and not formally accepted) may be cited only internally within the text and should not be added to the reference list. Please provide the names of the first five authors of unpublished data. If you cite personal communications or unpublished data of any individuals who are not authors of your manuscript, you must supply copies of written (including email) permission from the primary investigator of each

group cited.

9. All references must be cited in numerical order. Place Methods-only references after the Methods section and continue the numbering of the main reference list (i.e., do not start at 1). Ensure the reference list is up to date for the final submission.

10. Equations and symbols that will be set apart from the text must be in an editable format. Do not use embedded images for equations or symbols.

11. Genes must be clearly distinguished from gene products (e.g., "gene Abc encodes a protein kinase," not "gene Abc is a protein kinase"). For genes, provide database-approved official symbols (for human genes throughout the paper use http://varnomen.hgvs.org/). For the relevant species, use NCBI Gene: http://www.ncbi.nlm.nih.gov/gene. Italicize gene symbols and functionally defined locus symbols; do not use italics for proteins, noncoding gene products and spelled-out gene names.

12. For descriptions of variants, use HGVS notation according to the guidelines at http://varnomen.hgvs.org/. Include the accession code for the corresponding reference sequence at first mention of a variant.

Figures and Tables:

13. Please upload each figure as a separate file.

14. All figures and tables, including Extended Data figures, must be cited in the text in numerical order.

15. Figure legends should be concise. Begin with a brief title and then describe what is presented in the figure and detail all relevant statistical information (as described and declared in the supplied checklist), avoiding inappropriate methodological detail.

16. Shadings or symbols in graphs must be defined in some fashion. We prefer that you use a key within the image; do not include colored symbols in the legend.

17. All relevant figures must have scale bars (rather than numerical descriptions of magnification).

18. All relevant figures must have a definition for any error bars.

19. Graph axes should start at zero and not be altered in scale to exaggerate effects. A 'broken' graph can be used if absolutely necessary due to sizing constraints, but the break must be visually evident and should not impinge on any data points.

20. Cropping of gel and/or blot images must be mentioned in the figure legend. Gel pieces should be separated with white space (do not add borders). Please ensure that all blots and gels are accompanied by the locations of molecular weight/size markers; at least one marker position must be present in all cropped images. Please also supply full scans of all blots and gels as Source Data and reference the source data from the main paper.

21. Bar graphs should be converted to a dot-plot format or to a box-and-whisker format to show data distribution. All box-plot elements (center line, limits, whiskers, points) should be defined.

22. When submitting the revised version of your manuscript, please pay close attention to our href="https://www.nature.com/nature-research/editorial-policies/image-integrity">Digital Image Integrity Guidelines. and to the following points below:

- That unprocessed scans are clearly labelled and match the gels and western blots presented in figures.

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24. Reporting Guidelines– Attached you will find an annotated version of the Reporting Summary you submitted, along with a Word document indicating revisions that need to be made in compliance with our reproducibility requirements. These documents detail any changes that will need to be made to the text, and particularly the main and supplementary figure legends, including (but not limited to) details regarding sample sizes, replication, scale and error bars, and statistics. Please use these documents as a guide when preparing your revision and submit an updated Reporting Summary with your revised manuscript. The Reporting Summary will be published as supplementary material when your manuscript is published.

Supporting Information:

25. All Supporting Information must be submitted in accordance with the instructions in the attached Inventory of Supporting Information and should fit into one of three categories:

a. EXTENDED DATA FIGURES: Extended Data figures are an integral part of the paper, and only data that directly contribute to the main message should be presented. These figures will be integrated into the full-text HTML version of your paper and will be appended to the online PDF. There is a limit of 10 Extended Data figures, and each must be referred to in the main text. Each Extended Data figure should be of the same quality as the main figures and should be supplied at a size that will allow both the figure and legend to be presented on a single legal-sized page. Each figure should be submitted as an individual .jpg, .tif or .eps file with a maximum size of 10 MB each. All Extended Data figure legends must be provided in the attached Inventory of Supporting Information, not in the figure files themselves.

b. SUPPLEMENTARY INFORMATION: Supplementary Information is material that is essential background to the study but that is not practical to include in the printed version of the paper (for example, video files, large data sets, and calculations). Each item must be referred to in the main manuscript and detailed in the attached Inventory of Supporting Information. Tables containing large data sets should be in Excel format, with the table number and title included within the body of the table. All textual information and any additional Supplementary Figures (which should be presented with the legends directly below each figure) should be provided as a single, combined PDF. Please note that we cannot accept resupplies of Supplementary Information after the paper has been formally accepted unless there has been a critical scientific error.

All Extended Data figures must be called out in your manuscript and cited as Extended Data Figure 1, Extended Data Figure 2, etc. Additional Supplementary Figures and other items are not required to be called out in your manuscript text, but should be numbered, starting at one, as Supplementary Figure 1 (not Figure S1), Supplementary Table 1 (not Table S1), etc.

c. SOURCE DATA: We encourage you to provide source data for your figures whenever possible. Full-length, unprocessed gels and blots must be provided as source data for any relevant figures and should be provided as individual PDF files for each figure containing all supporting blots and/or gels with the linked figure noted directly in the file. Statistics source data should be provided in Excel format, one file for each relevant figure, with the linked figure noted directly in the file. For imaging source data, we encourage deposition to a relevant repository, such as figshare (https://figshare.com/) or the Image Data Resource (https://idr.openmicroscopy.org).

TRANSPARENT PEER REVIEW

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If you have any further questions, please feel free to contact me.

Best wishes,
Kyle

Kyle Vogan, PhD
Senior Editor
Nature Genetics
https://orcid.org/0000-0001-9565-9665

Final Decision Letter:

Date: 9th Oct 20 12:53:24
Last Sent: 9th Oct 20 12:53:24
Triggered By: Kyle Vogan
From: k.vogan@us.nature.com
To: yanickcrow@mac.com
CC: rjsproduction@springernature.com
Subject: Decision on NG-A55245R2 Crow
Message: In reply please quote: NG-A55245R2 Crow

9th October 2020

Dear Yanick,

I am delighted to say that your manuscript "cGAS-mediated induction of type I interferon due to inborn errors of histone pre-mRNA processing" has been accepted for publication in an upcoming issue of Nature Genetics.

Prior to setting your manuscript, we may make minor changes to enhance the lucidity of the text and with reference to our house style. We therefore ask that you examine the proofs

most carefully to ensure that we have not inadvertently altered the sense of your text in any way.

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Sincerely,
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