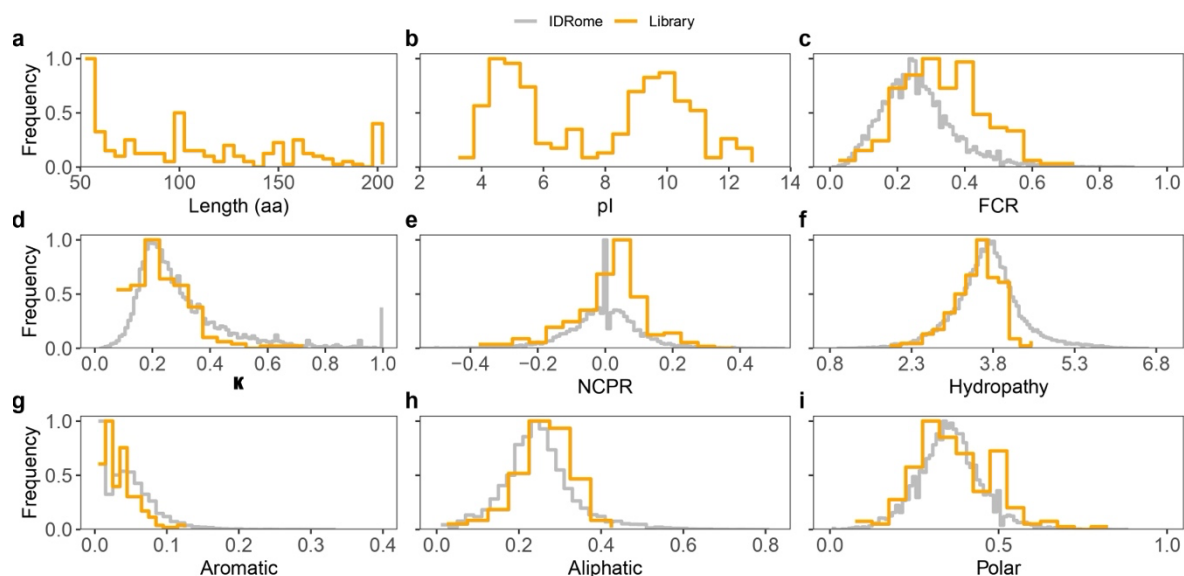
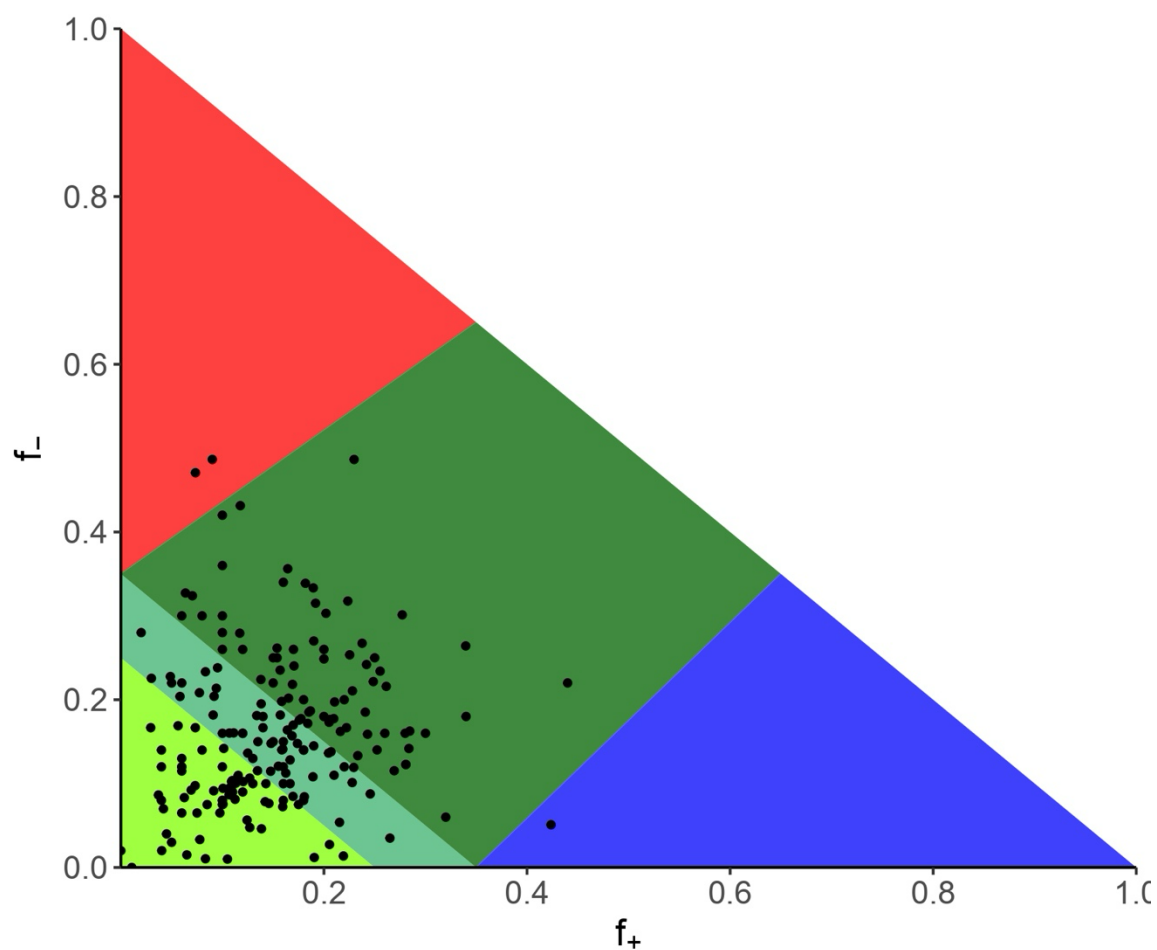


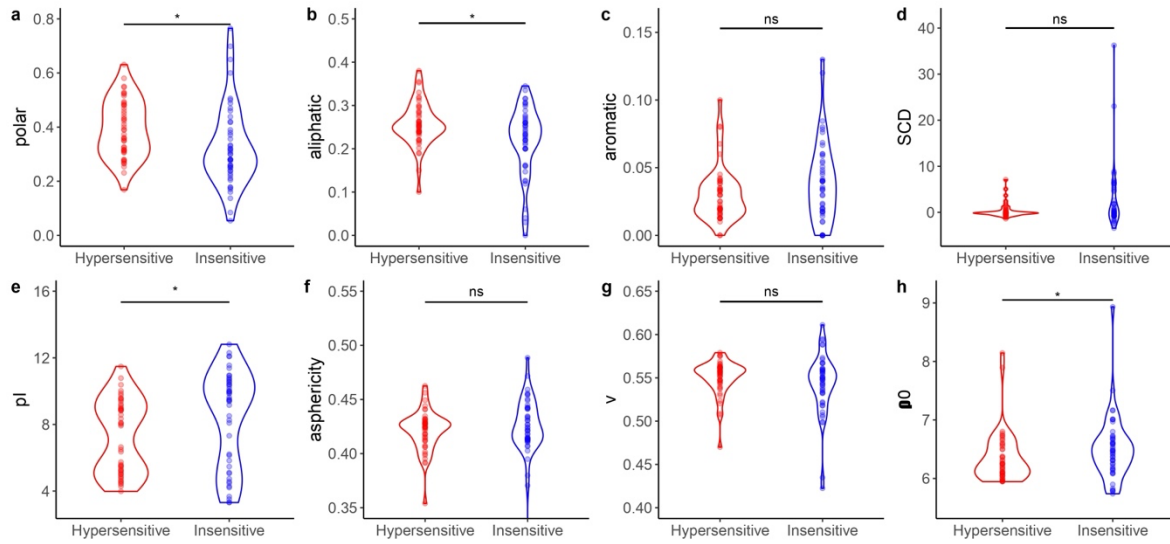
EXTENDED DATA FIGURES



Extended Data Fig. 1. Distributions of sequence-encoded properties of 188 naturally-occurring IDRs. **a**, Length distribution of IDRs in the library. **b**, Distribution of isoelectric points (pI) of IDRs in the library. **c**, Distribution of fraction of charged residues (FCR) of IDRs in the library (orange) compared to the human IDRome (gray). **d**, Distribution of kappa values (κ) of IDRs in the library (orange) compared to the human IDRome (gray). **e**, Distribution of net charge per residue (NCPR) of IDRs in the library (orange) compared to the human IDRome (gray). **f**, Distribution of Hydropathy of IDRs in the library (orange) compared to the human IDRome (gray). **g**, Distribution of fraction of aromatic residues (Aromatic) of IDRs in the library (orange) compared to the human IDRome (gray). **h**, Distribution of fraction of aliphatic residues (Aliphatic) of IDRs in the library (orange) compared to the human IDRome (gray). **i**, Distribution of fraction of polar residues (Polar) of IDRs in the library (orange) compared to the human IDRome (gray).



Extended Data Fig. 2. Das-Pappu diagram-of-states for 188 naturally-occurring IDRs. Each dot represents an individual IDR. f_+ is the fraction of positively charged residues. f_- is the fraction of negatively charged residues. R1 (green yellow) weak polyampholytes and polyelectrolytes (globules and tadpoles). R2 (light green): boundary region. R3 (dark green): strong polyampholytes (coils, hairpins and chimeras). R4 (red): negatively charged strong polyampholytes (swollen coils). R5 (blue): positively charged strong polyampholytes (swollen coils).



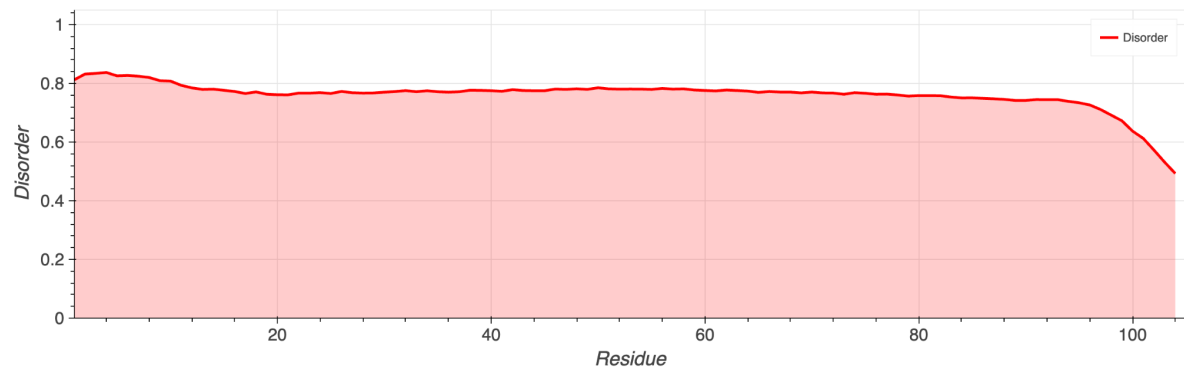
Extended Data Fig. 3. Sequence features and predicted IDR ensemble properties of hypersensitive and insensitive IDRs. **a-e**, Sequence features of IDRs belonging to the hypersensitive (red) or insensitive (blue) groups. **a**, fraction of polar residues (polar); **b**, fraction of aliphatic residues (aliphatic); **c**, fraction of aromatic residues (aromatic); **d**, sequence charge decoration (SCD); **e**, isoelectric point (pI). **f-h**, predicted ensemble properties for IDRs of the hypersensitive (red) or insensitive (blue) groups. **f**, predicted asphericity (asphericity); **g**, predicted polymer scaling exponent (ν). **h**, predicted prefactor (p_0). Each point represents the corresponding value for an IDR. Color intensity indicates the representation of values within the same range. Mann-Whitney U test * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$.

>V1
 ILLT**EE**IEETD**Y**Q**E**DEQ**E**SI**A**K**Q**Q**E**REME**E**KE**K**T**Y**RE**K**TAA**A**E**K**AE**K**LE**K**Q**H**AREM**K**E**F**RD**L**AD**S**Q**I**D**K**Q**E**KE
 AK**L**E**A**RM**A**KE**R**EL**D**R**G**Q**V**R**A**VR**S**RRL**R**ARR

>V2
 EALIEEQ**EE**IEE**E**EDQ**E****Y**Q**E**Q**E**SE**I**A**Q**Q**E**ME**E**KE**K**T**Y**RE**K**TAA**A**E**K**AE**K**LE**K**Q**H**ARD**V**K**D**F**R**DAME**S**T**I**D**R**
 Q**D**R**V**K**L**ARK**M**AK**R**RRRL**R**GT**K**LAK**R**AL**S**RLARR

>V3
 AAMT**E**EDQ**E**EQ**E**SQ**E**EM**E**E**A**EE**A**EEED**V**ED**L**ESDE**V**D**L**E**A**ED**E**AE**E**LLGAAL**A**Q**I**HAT**I**Q**A**F**Y**RR**K**RR**A**K**Q**
 R**K**T**Y**R**K**T**K**IR**K**Q**R**K**R**K**I**R**Q**K**R**K**M**K**R**LAK**R**S**R**LA

Extended Data Fig. 5. Amino acid sequences of HeCAHS8 LR κ variants. Positively charged residues in blue, negatively charged residues in red, polar residues in green, aliphatic residues in black, aromatic residues in yellow.



Extended Data Fig. 6. Syn1 disorder prediction. Disorder prediction across the sequence of Syn1 with Metapredict. The red shaded region indicates reliable disorder prediction.

```

>FL_HeCAHS8
MSGGRNVESHMERNEKVVVNNSGHADVKKQQQQVEHTEFTHTEVKAPLIHP
APPIISTGAAGLAEEIVGQGFASAARISGGTAEVHLQPSAAMTEEARRD
QERYRQEQESIAKQQEREMKKTEAYRKTAEEAEKIRKELEKQHARDVE
FRKDLIESTIDRQKREVDLEAKMAKRELDREGQLAKEALERSRLATNVEV
NFDSAAGHTVSGGTTVSTSDKMEIKRN

>LR
AAMTEEARRDQERYRQEQESIAKQQEREMKKTEAYRKTAEEAEKIRKE
LEKQHARDVEFRKDLIESTIDRQKREVDLEAKMAKRELDREGQLAKEALE
RSRLA

>2X_LR
MSGGRNVESHMERNEKVVVNNSGHADVKKQQQQVEHTEFTHTEVKAPLIHP
APPIISTGAAGLAEEIVGQGFASAARISGGTAEVHLQPSAAMTEEARRD
QERYRQEQESIAKQQEREMKKTEAYRKTAEEAEKIRKELEKQHARDVE
FRKDLIESTIDRQKREVDLEAKMAKRELDREGQLAKEALERSRLATNMTE
EARRDQERYRQEQESIAKQQEREMKKTEAYRKTAEEAEKIRKELEKQH
ARDVEFRKDLIESTIDRQKREVDLEAKMAKRELDREGQLAKEALERSRLA
TNVEVNFDSAAGHTVSGGTTVSTSDKMEIKRN

>FL_Proline
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QERYRQEQESIAKQQEREMKKTEAYRKTAEEAEKIRKELEKQHARDVE
FRKDLIESTIDRQKREVDLEAKMAKRELDREGQLAKEALERSRLATNVPV
NFPSAAGHTVSGGTPSTSDKMPIKRN

>NLN
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FRKDLIESTIDRQKREVDLEAKMAKRELDREGQLAKEALERSRLAMSGRN
VESHMERNEKVVVNNSGHADVKKQQQQVEHTEFTHTEVKAPLIHPAPPII
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>CLC
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QESIAKQQEREMKKTEAYRKTAEEAEKIRKELEKQHARDVEFRKDLIE
STIDRQKREVDLEAKMAKRELDREGQLAKEALERSRLATNVEVNFDSAAG
HTVSGGTTVSTSDKMEIKRN

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Extended Data Fig. 7. Amino acid sequences of HeCAHS8 variants. Positively charged residues in blue, negatively charged residues in red, polar residues in green, aliphatic residues in black, aromatic residues in yellow, prolines in magenta.