**Article:**
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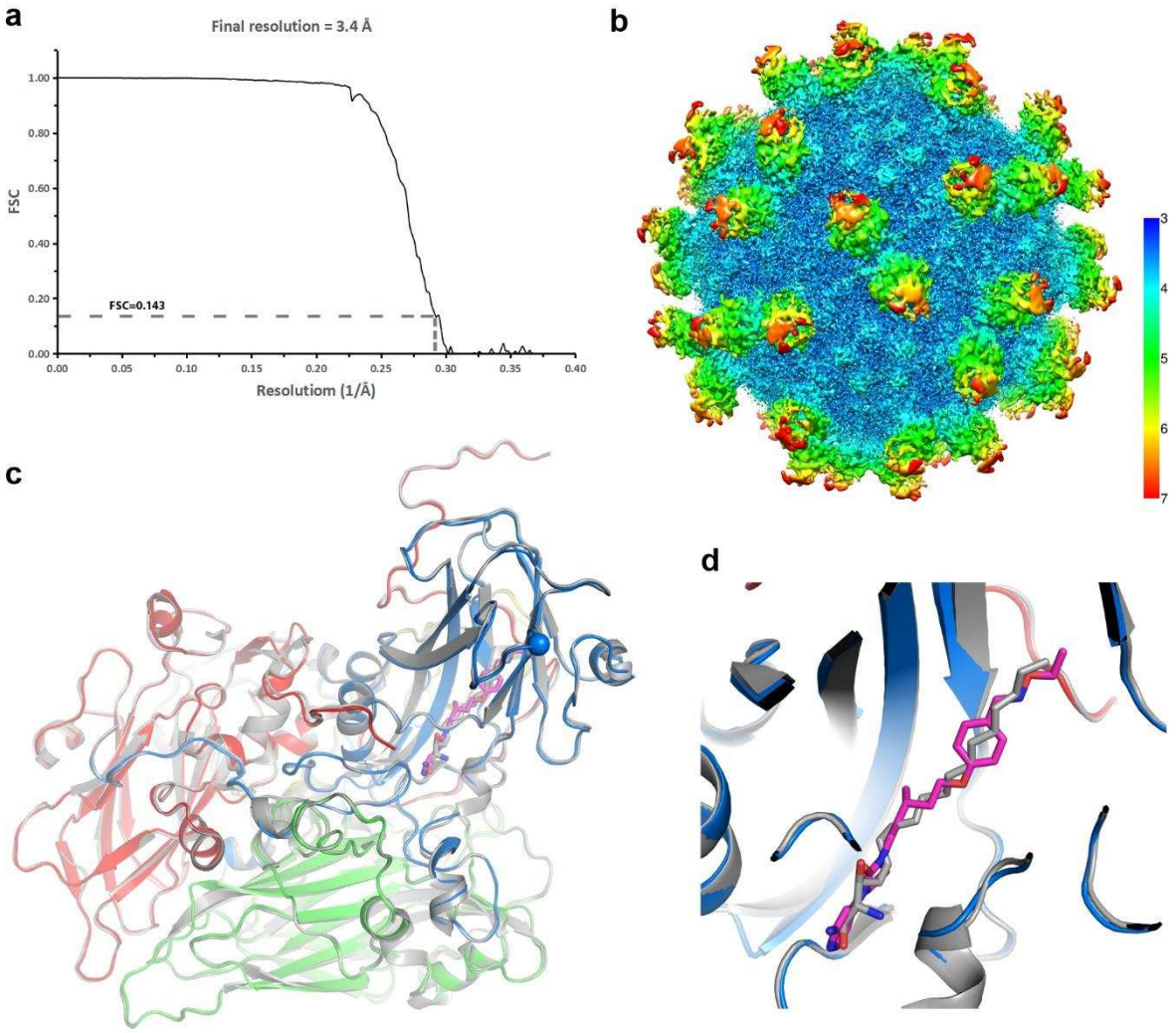
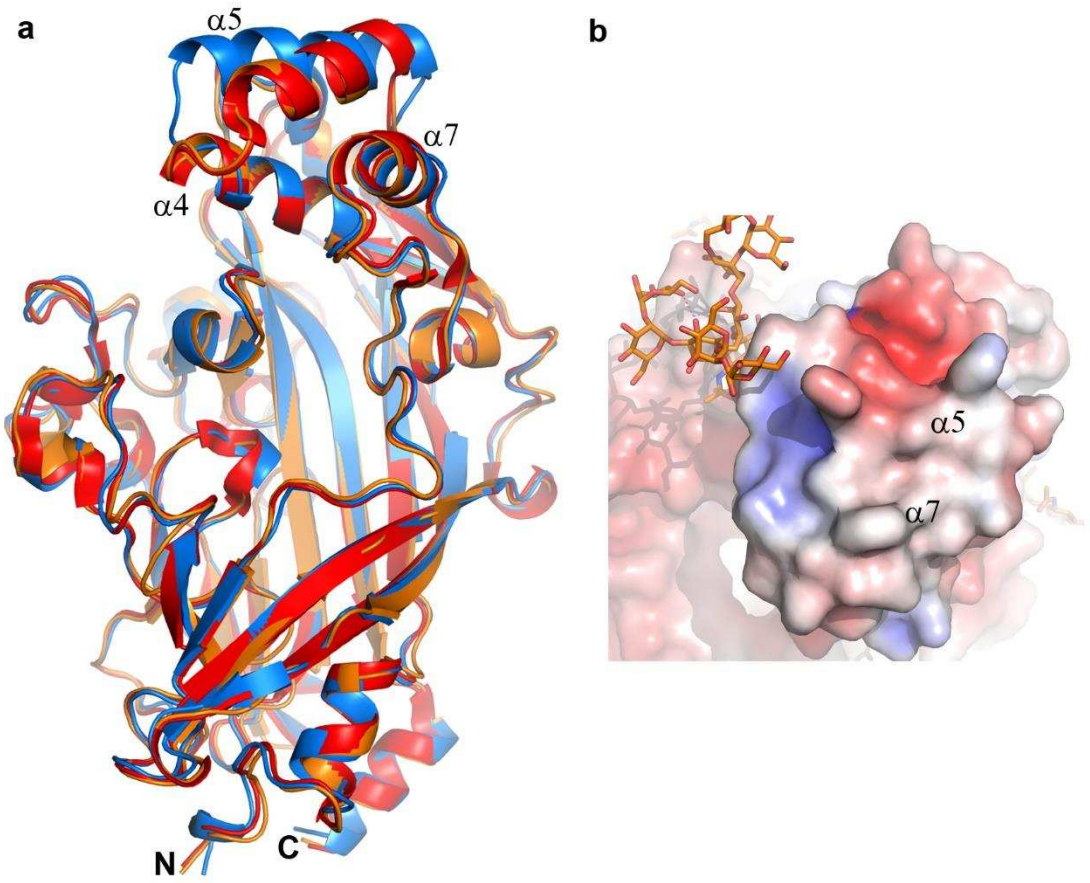
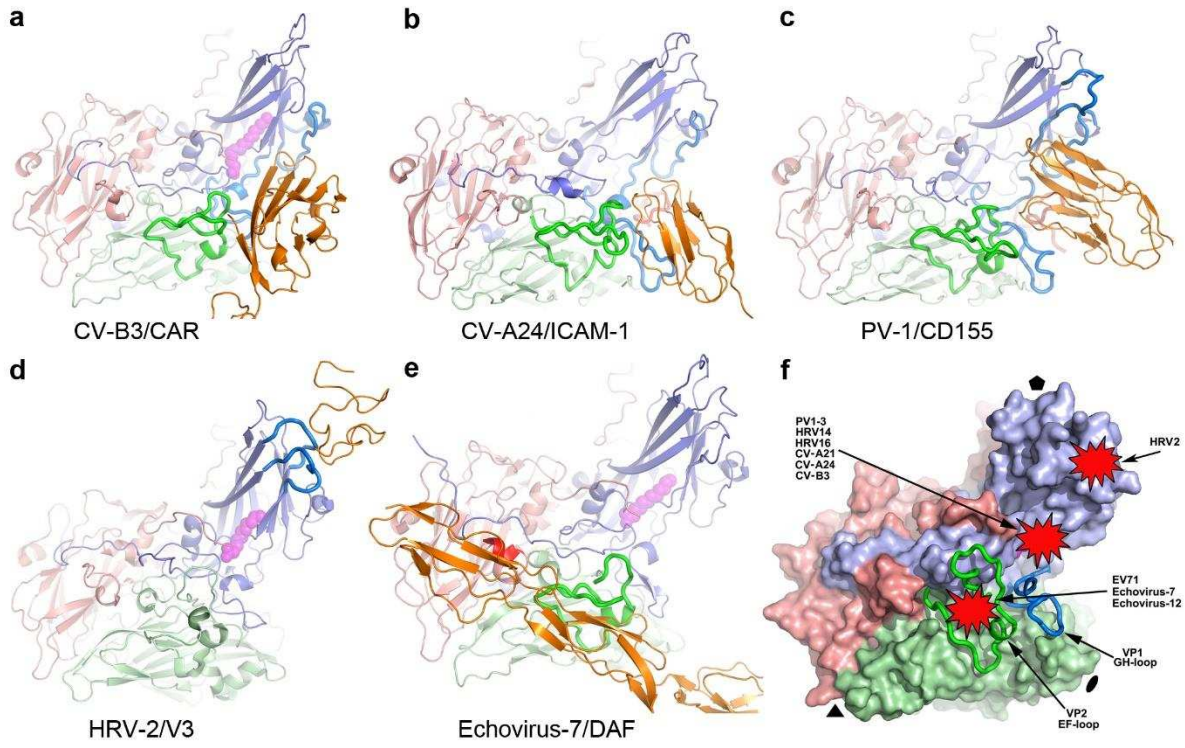
**Extended Data**



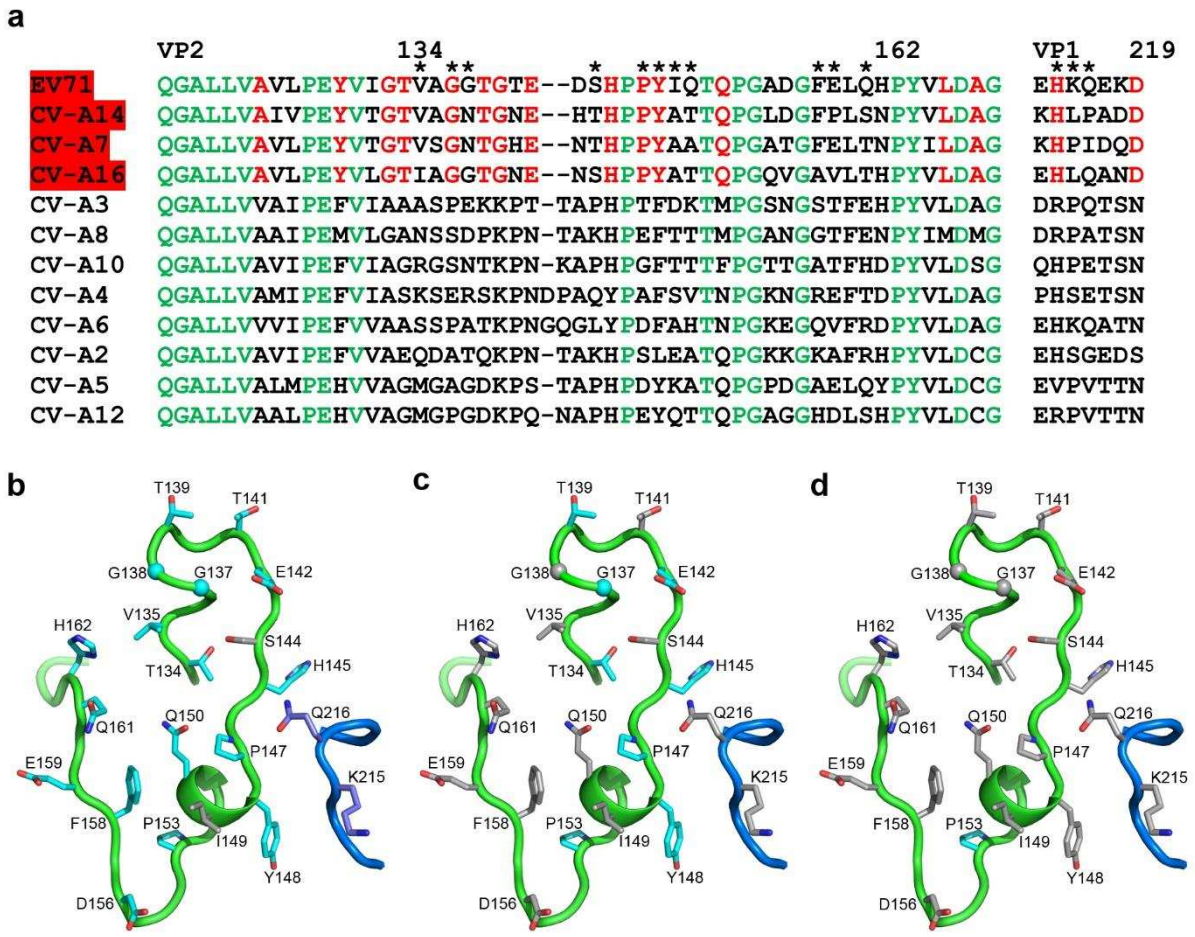

**Extended Data Fig. 1 | Overall structure of EV71/SCARB2 complex. a,** The gold standard FSC curve of the final map with a resolution of 3.4 Å at FSC = 0.143. **b**, The final density map coloured by local resolution. **c**, Overlay of receptor bound EV71 (coloured in blue, green, red and yellow for VP1-4, respectively; pocket inhibitor, NLD, shown as magenta sticks) and the mature virus (grey, pocket factor, sphingosine, shown as grey sticks). The blue sphere indicates the position of the acid resistant mutation N104S. **d**, close-up of VP1 pocket factor binding region of (**c**).




**Extended Data Fig. 2 | The EV71 bound SCARB2 adopts a higher pH conformation. a,** Superposition of the EV71 bound SCARB2 (orange) with its apo forms at pH6.5 (red) and at pH4.6 (blue). **b**, Electrostatic surface of EV71 bound SCARB2 showing the hydrophobic nature of α5 and α7. The oligosaccharides linked to residue N325 are shown as orange sticks.




**Extended Data Fig. 3 | Receptor binding modes of enteroviruses. a,** CV-B3/CAR (Coxsackievirus and adenovirus receptor) complex (PDB ID, 3J6N). **b,** CV-A24/ICAM-1 complex (PDB ID, 6EIT). **c**, PV-1/CD155 complex (PDB ID, 3J8F). d**,** HRV-2/V3 complex (very-low-density lipoprotein module V3; PDB ID, 3DPR ). **e**, echovirus-7/DAF (decay-accelerating factor) complex (PDB ID, 3IYP). In each of the panels **a**-**e**, a protomer of virus capsid is shown as ribbons with VP1-4 coloured in blue, green, red and yellow, respectively; loops involved in interactions with receptor are shown as thick brightly coloured coils, and pocket factor as magenta spheres; receptor is shown as orange ribbons. **f**, Summary of receptor attachment areas (marked by red stars) shown on a protomer of EV71 which is drawn as surface representations with VP1 in blue, VP2 in green and VP3 in red. VP1 GH loop and VP2 EF loop, which interact with receptor SCARB2, are shown as thick bright coils.




**Extended Data Fig. 4 | Comparison of residues in the receptor attachment area of EV71 with other type A enteroviruses that cause HFMD. a,** Sequence alignment of the receptor binding region of EV71 with the HFMD causing type A enteroviruses. Virus names with red background are SCARB2 dependent, and the others SCARB2 independent. Conserved residues are in green, residues conserved in SCARB2 dependent viruses in red. Residue numbers of EV71 are indicated, and those having direct contacts with SCARB2 are marked with an asterisk. **b-d**, The structure of VP1 GH and VP2 EF loops that form the receptor-binding platform of EV71. The backbone of VP1 GH loop is coloured in blue, and VP2 EF loop in green. Side chains which contact the receptor directly or fold towards the receptor are shown as sticks and coloured in cyan (EF loop) or blue (GH loop), but in grey if not conserved. Residues among 11 EV71 genotypes (A, B1-B5, C1-C5) are highly conserved (**b**), less

conserved among the 4 SCARB2 dependent viruses (**c**), and only VP2 P153 is conserved among the HFMD type A enteroviruses (**d**).

| **EV71-SCARB2 complex** | |
|---|---|
| **Data collection and reconstruction** | |
| Voltage (kV) | 300 |
| Frames | 32 |
| Dose rate ($e^-$/ Å $^2$/ s) | 4 |
| Total dose ($e^-$/ Å $^2$) | 35 |
| Pixel size (Å) | 1.35 |
| Defocus (μm) | 0.5 - 2.5 |
| Movies | 757 |
| Particles used in the final reconstruction | 10443 |
| Map resolution (Å) | 3.4 |
| Map sharpening B-factor (Å$^2$) | -150.4 |
| **Model refinement** | |
| Total number of atoms | 10075 |
| Protein residues | 1244 |
| Model-to-map fit, CC_mask | 0.748 |
| R.m.s.d., bonds (Å) | 0.01 |
| R.m.s.d., angles (°) | 0.956 |
| All-atom Clash score | 4.89 |
| Rotamer outliers (%) | 0.38 |
| Ramachandran plot | |
| Favored (%) | 93.91 |
| Allowed (%) | 5.93 |
| Outliers (%) | 0.16 |

**Extended Data Table 1 | Cryo-EM data collection, reconstruction and refinement statistics**

| Residue in EV71 | Residue in SCARB2 | Distance (Å) |
|---|---|---|
| **Potential hydrogen bonds** | | |
| A214 HIS | E163 TYR | 3.76 |
| B78 TRP | E154 GLU | 3.95 |
| B148 TYR | E163 TYR | 3.38 |
| B161 GLN | E192 ARG | 3.42 |
| **Hydrophobic interactions** | | |
| A216 GLN | E186 SER | 3.99 |
| A216 GLN | E187 LEU | 3.30 |
| B135 VAL | E190 VAL | 3.45 |
| B135 VAL | E193 PRO | 3.84 |
| B137 GLY | | 3.59 |
| B138 GLY | | 3.69 |
| B144 SER | E190 VAL | 3.99 |
| B147 PRO | E187 LEU | 3.67 |
| | E190 VAL | 3.71 |
| | E191 PHE | 3.93 |
| B148 TYR | E163 TYR | 2.94 |
| B149 ILE | E158 ALA | 3.69 |
| | E159 MET | 2.80 |
| | E162 ALA | 3.72 |
| | E163 TYR | 3.84 |
| B150 GLN | E191 PHE | 3.66 |
| B156 ASP | E161 LYS | 3.88 |
| B158 PHE | B191 PHE | 3.42 |
| B161 GLN | E155 ILE | 3.51 |
| | E191 PHE | 3.77 |
| | E192 ARG | 3.93 |
| **Potential Charged interactions** | | |
| A217 GLU | E181 LYS | 3.16 |
| B156 ASP | E161 LYS | 3.83 |

**Extended Data Table 2 | list of interactions between EV71 and SCARB2.** The protein chain names for the viral proteins are as VP1, A; VP2, B; and the receptor, E.