

**NUCLEAR RECEPTOR RESOURCE**  
**APPENDIX A**  
**GLUCOCORTICOID ANNOTATIONS FOR MULTIPLE SEQUENCE ALIGNMENT**

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1M - AMINO TERMINUS DOES NOT HAVE FREE -NH<sub>2</sub> BUT IS BLOCKED [8, 21]

16P - CONFLICT IN THE TAMARIN GR SEQUENCE EITHER P OR S [5, 55]

24R - R TO K HAS NO CHANGE ON AFFINITY OR TRANSACTIVATION [20]

28M - CYANOGEN BROMIDE CLEAVES AT THIS METHIONINE [8]

74V - CONFLICT IN THE TAMARIN GR SEQUENCE EITHER A OR V

98G - D NOT G (PERSONAL COMMUNICATION: SANDRO RUSCONI [FRIBOURG, SWITZERLAND])

134S - IS PHOSPHORYLATED IN STEROID TREATED CELLS [4] BUT MUTATION TO ALA HAS LITTLE TO NO EFFECT ON BIOLOGICAL ACTIVITY [48]

162S - IS PHOSPHORYLATED IN STEROID TREATED CELLS [4] BUT MUTATION TO ALA HAS LITTLE TO NO EFFECT ON BIOLOGICAL ACTIVITY [48]

171T - IS PHOSPHORYLATED IN STEROID TREATED CELLS [4] BUT MUTATION TO ALA HAS LITTLE TO NO EFFECT ON BIOLOGICAL ACTIVITY [48]

224S - IS PHOSPHORYLATED IN STEROID TREATED CELLS [4] BUT MUTATION TO ALA HAS LITTLE TO NO EFFECT ON BIOLOGICAL ACTIVITY [48]; S TO A HAS NO EFFECT ON STEROID BINDING [28]

226S - G NOT S (PERSONAL COMMUNICATION: M. GARABEDIAN AND K. YAMAMOTO [UCSF]) AND [12]

232S - IS PHOSPHORYLATED IN STEROID TREATED CELLS [4] BUT MUTATION TO ALA HAS LITTLE OR NO EFFECT ON BIOLOGICAL ACTIVITY [48]; S TO A HAS NO EFFECT ON STEROID BINDING AND AZIDE REDUCES THE AMOUNT OF PHOSPHORYLATION [28]

234W - W TO R CAUSED 4 FOLD DECREASE IN TRANSACTIVATION OF N525 (CONSTITUTIVELY ACTIVE GR) IN MAMMALIAN CELLS [30]

246S - IS PHOSPHORYLATED IN STEROID TREATED CELLS [4] BUT MUTATION TO ALA HAS LITTLE OR NO EFFECT ON BIOLOGICAL ACTIVITY [48]; S TO A HAS NO EFFECT ON STEROID BINDING AND AZIDE REDUCES THE AMOUNT OF PHOSPHORYLATION [28]

260N - D NOT N (PERSONAL COMMUNICATION: M. GARABEDIAN AND K. YAMAMOTO [UCSF]) AND [12]

276K - R NOT K (PERSONAL COMMUNICATION: M. GARABEDIAN AND K. YAMAMOTO [UCSF])

327S - IS PHOSPHORYLATED IN STEROID TREATED CELLS [4] BUT MUTATION TO ALA HAS LITTLE TO NO EFFECT ON BIOLOGICAL ACTIVITY [48]

345S - CONFLICT: T NOT S [12]

383N - N TO S HAS NO EFFECT ON DOSE-RESPONSE CURVE OR ABILITY TO TRANSACTIVATE [32]; N TO S HAS NO EFFECT [22]

409F - MAJOR CHYMOTRYPSIN CLEAVAGE ACTIVATED RS COMPLEX AFTER THIS AMINO ACID [8] BUT NO CLEAVAGE IN FUSION PROTEIN OF PROTEIN A WITH THE DNA-BINDING DOMAIN OF THE HUMAN RECEPTOR [15]

413Y - MAJOR CHYMOTRYPSIN CLEAVAGE ACTIVATED RS COMPLEX AFTER THIS AMINO ACID [8]; ONLY CLEAVAGE SITE IN FUSION PROTEIN OF PROTEIN A WITH THE DNA-BINDING DOMAIN OF THE HUMAN RECEPTOR [15]

435P - P TO R FACILITATED ACTIVATION OF AGONIST (TRIAMCINOLONE ACETONIDE), BUT NOT ANTAGONIST (RU 486), BOUND RECEPTORS [59]

439L - L TO P HAS NO EFFECT ON ACTIVITY IN VITRO OR IN VIVO [46]

440C - CO-ORDINATED WITH ZINC [35, 46]; C TO A DOES NOT ELIMINATE ZINC BINDING BUT DOES DRAMATICALLY REDUCE (<10%) DNA BINDING [1]; C TO G MAY CHANGE EFFECT OF RECEPTOR ON IL-1ALPHA INDUCTION FROM REPRESSION TO INDUCTION [54]; C TO Y ELIMINATES TRANSACTIVATION WITHOUT AFFECTING STEROID BINDING ACTIVITY AND, IN COMBINATION WITH L771F, IS RESPONSIBLE FOR THE ACTIVATION LABILE MUTANT [53]

443C - CO-ORDINATED WITH ZINC [35, 46]

444S - S TO G CAUSED 2 FOLD INCREASED TRANSACTIVATION BUT ELIMINATED ABILITY TO SUPPRESS AP-1 INDUCTION [26]

445S - D TO G MAY INCREASE THE FOLD INDUCTION BY DEX [25]

449G - SOME POINT MUTANTS IN 407/556 HAD LITTLE EFFECT ON BIOLOGICAL ACTIVITY [71]; V TO G HAS WILD TYPE PROPERTIES [33]

450C - C TO G GAVE RECEPTOR WITH "40% TRANSACTIVATION BUT "10% DNA BINDING ACTIVITY OF WILD TYPE RECEPTOR [27]

451H: 451-462 SOME POINT MUTANTS (DEPENDS ON MUTANT AA) ELIMINATE OR REDUCE BIOLOGICAL ACTIVITY IN 407/556 [71]; H451N/S459G DOUBLE MUTATION IN TRUNCATED RECEPTOR OF 407-556 HAS INCREASED AFFINITY FOR DNA AND TRANSACTIVATION ACTIVITY [71]

452Y: PART OF INTERCHAIN HYDROPHOBIC INTERACTIONS HOLDING 3° STRUCTURE OF DNA BINDING DOMAIN TOGETHER [46]

455L - L TO V CAUSED 2 FOLD INCREASED TRANSACTIVATION BUT ELIMINATED ABILITY TO SUPPRESS AP-1 INDUCTION; DOUBLE MUTANT (S444G/L455V) CAUSED 2 FOLD INCREASED ACTIVATION AND 50% REDUCTION OF SUPPRESSION [26]

457C - CO-ORDINATED WITH ZINC [35, 46]

458G - INVOLVED IN SPECIFICITY OF DNA BINDING, ALONG WITH OTHER AAS [74]; NO EFFECT ON BIOLOGICAL ACTIVITY [65]; ALL RECEPTORS FROM SATURATION MUTAGENESIS (TRUNCATED GR IN YEAST) WERE ACTIVE WITH GRE OR ERE; MAIN FUNCTION OF RESIDUE WAS TO INHIBIT BINDING TO NON-COGNATE SITES [73]

459S - INVOLVED IN SPECIFICITY OF DNA BINDING, ALONG WITH OTHER AAS [74]; H451N/S459G DOUBLE MUTATION IN TRUNCATED RECEPTOR OF 407-556 HAS INCREASED AFFINITY FOR DNA AND TRANSACTIVATION ACTIVITY [71]; S TO A GIVES RECEPTOR IDENTICAL TO P493R THAT HAS NORMAL DNA BINDING, POOR TRANSACTIVATION IN EUKARYOTIC CELLS BUT GOOD ACTIVATION IN YEAST, AND 10 FOLD INCREASED AFFINITY FOR NON-SPECIFIC DNA [39]; ALL RECEPTORS FROM SATURATION MUTAGENESIS (TRUNCATED GR IN YEAST) WERE ACTIVE WITH GRE OR ERE; MAIN FUNCTION OF RESIDUE WAS TO INHIBIT BINDING TO NON-COGNATE SITES [73]

460C – CO-ORDINATED WITH ZINC [35, 46]

461K - MAKES BASE CONTACTS IN BINDING TO SPECIFIC DNA SITES [46]; K TO A HAS WILD TYPE NON-SPECIFIC DNA BINDING AFFINITY BUT <1% TRANSACTIVATION (VERSUS ~25% ACTIVITY IN F9 CELLS [63] WHILE K TO E CAUSED 10 FOLD DECREASE IN NON-SPECIFIC DNA BINDING AFFINITY [39]; K TO G CAUSES GR TO INDUCE, AS OPPOSED TO REPRESS, AP-1 REGULATED GENE EXPRESSION [4,69] AND DNA BINDING IS RETAINED BUT TRANS-ACTIVATION IS LOST [27]; K TO G AFFORDED WILD TYPE, OR ALMOST NO, INDUCTION BY DEXAMETHASONE DEPENDING ON THE GRE USED (TAT OR MMTV) [25]; K TO A CAUSED INDUCTION INSTEAD OF REPRESSION FROM GRE AND NGRE [63]

462V - INVOLVED IN SPECIFICITY OF DNA BINDING, ALONG WITH OTHER AAS [74, 46]; V TO E CAUSED 10 FOLD DECREASE IN NON-SPECIFIC DNA BINDING AFFINITY [39] AND ~60% REDUCTION OF TRANSACTIVATION [63]

463F - PART OF INTERCHAIN HYDROPHOBIC INTERACTIONS HOLDING 3° STRUCTURE OF DNA BINDING DOMAIN TOGETHER [46]

464F - PART OF INTERCHAIN HYDROPHOBIC INTERACTIONS HOLDING 3° STRUCTURE OF DNA BINDING DOMAIN TOGETHER [46]

465K - K TO G GAVE RECEPTOR WITH "40% TRANSACTIVATION BUT "10% DNA BINDING ACTIVITY OF WILD TYPE RECEPTOR [27]

466R - MAKES BASE CONTACTS IN BINDING TO SPECIFIC DNA SITES. R TO K OR G IS INACTIVE IN VIVO [46]; R TO A CAUSED 10 FOLD DECREASE IN NON-SPECIFIC DNA BINDING AFFINITY [39] AND ALMOST NO TRANSACTIVATION OF A SIMPLE GRE BUT STILL IS CAPABLE OF REPRESSION [63]

468V - 468-472 CAN TOLERATE INSERTION OF TANDEM REPEATS OF 3-9BP W/O LOSS OF BIOLOGICAL ACTIVITY AND OF 23BP WITH PARTIAL LOSS [71]

470G - INSERTION OF ARG CAUSES A 2 FOLD DECREASE IN TRANSCRIPTIONAL ACTIVATION [33]

INSERT AFTER 470+ - CONFLICT IN THE TAMARIN SEQUENCE; EITHER NO AMINO ACID OR R

474Y - PART OF INTERCHAIN HYDROPHOBIC INTERACTIONS HOLDING 3° STRUCTURE OF DNA BINDING DOMAIN TOGETHER [46]; Y TO G GAVE RECEPTOR WITH "40% TRANSACTIVATION BUT "10% DNA BINDING ACTIVITY OF WILD TYPE RECEPTOR [27]

476C - CO-ORDINATED WITH ZINC [35,46]

477A - A TO T PREVENTS DNA BINDING AND TRANSACTIVATION FROM A GENE REGULATED BY A SINGLE, BUT NOT A MULTIPLE, COPY OF GRE BUT DOES NOT AFFECT REPRESSION (PERSONAL COMMUNICATION: PETER HERRILICH [KARLSRUHE, GERMANY]); A TO T IN A TRIPLE MUTANT ((A477T/R479D/D481C REDUCED TRANSACTIVATION BY GREATER THAN 90% BUT HAD NO EFFECT ON THE ABILITY TO REPRESS NF-KB ACTIVITY [40]; A TO T ELIMINATED DNA BINDING AND TRANSACTIVATION BUT NOT REPRESSION [26])

479R - THOUGHT TO FORM INTER-RECEPTOR SALT BRIDGE WITH D481 AND THUS PLAY A MAJOR ROLE IN RECEPTOR DIMERIZATION [16], ALTHOUGH MUTATION TO G HAS NO MAJOR EFFECT [27]; R479A/N491A ABOLISHED COOPERATIVE DNA BINDING IN VITRO AND TRANSACTIVATION IN VIVO [39] WITHOUT DISTURBING REPRESSION [63]; R TO D DECREASED INDUCTION FROM A SINGLE GRE BUT INCREASED SYNERGISM FROM 2 OR 3 TANDEM GRES [42]; R TO D IN A TRIPLE MUTANT ((A477T/R479D/D481C REDUCED TRANSACTIVATION BY GREATER THAN 90% BUT HAD NO EFFECT ON THE ABILITY TO REPRESS NF-KB ACTIVITY [40])

481D - D TO R CAUSES GREATLY DECREASED ACTIVATION IN N-TERMINAL DELETION OF [52]; D TO R DECREASED INDUCTION FROM A SINGLE GRE BUT INCREASED SYNERGISM FROM 2 OR 3 TANDEM GRES [42]; D TO C IN A TRIPLE MUTANT ((A477T/R479D/D481C REDUCED TRANSACTIVATION BY GREATER THAN 90% BUT HAD NO EFFECT ON THE ABILITY TO REPRESS NF-KB ACTIVITY [40]; THOUGHT TO FORM INTER-RECEPTOR SALT BRIDGE WITH R479 AND THUS PLAY A MAJOR ROLE IN RECEPTOR DIMERIZATION [16], ALTHOUGH MUTATION TO G HAS NO MAJOR EFFECT [27])

482C - CO-ORDINATED WITH ZINC [35, 46]

484I - MOST NON-CONSERVATIVE POINT MUTANTS ELIMINATE BOTH DNA BINDING AND TRANSACTIVATION [37]

486K - K TO G GAVE RECEPTOR WITH "40% TRANSACTIVATION BUT "10% DNA BINDING ACTIVITY OF WILD TYPE RECEPTOR [27]

488R - R TO Q CAUSED NORMAL DNA BINDING AND FAIR ACTIVITY IN CV-1 CELLS BUT <3% TRANSCRIPTIONAL ACTIVATION IN YEAST [57]; R TO A ABOLISHED COOPERATIVE DNA BINDING IN VITRO AND TRANSACTIVATION IN VIVO [39]; R TO Q REDUCED TRANSACTIVATION, AND REPRESSION OF NF-KB ACTIVITY, BY 80% [40]

489R - R TO K CAUSED NORMAL DNA BINDING AND GOOD ACTIVITY IN CV-1 CELLS BUT <10% TRANSCRIPTIONAL ACTIVATION, AND TEMPERATURE SENSITIVE, IN YEAST [57]

490K - K TO E REDUCED TRANSACTIVATION, AND REPRESSION OF NF-KB ACTIVITY, BY 90% [40]

491N - N TO S CAUSED NORMAL DNA BINDING AND GOOD ACTIVITY IN YEAST BUT <1% TRANSCRIPTIONAL ACTIVATION IN CV-1 CELLS [57]; N TO A HAD ESSENTIALLY WILD TYPE ACTIVITY FOR TRANSACTIVATION, AND REPRESSION OF NF-KB ACTIVITY [40]; R479A/N491A ABOLISHED COOPERATIVE DNA BINDING IN VITRO AND TRANSACTIVATION IN VIVO [39] WITHOUT DISTURBING REPRESSION [63]

492C - CO-ORDINATED WITH ZINC [35, 46]; C TO S MAY CAUSE INCORRECT FOLDING OF DNA BINDING DOMAIN [75]

493P - P493R, A494S DOUBLE MUTANT CAUSED NORMAL DNA BINDING BUT POOR TRANSCRIPTIONAL ACTIVATION [24]; P TO R SINGLE MUTANT COMPLETELY

REPRODUCED THE NORMAL DNA BINDING AND POOR TRANSACTIVATION IN EUKARYOTIC CELLS, BUT GOOD ACTIVATION IN YEAST, OF THE P493R/A494S DOUBLE MUTANT LS7 AND IS IDENTICAL TO S459A, WHICH HAS 10 FOLD INCREASED AFFINITY FOR NON-SPECIFIC DNA [39]

495C - CO-ORDINATED WITH ZINC [35, 46]; C TO S MAY CAUSE INCORRECT FOLDING OF DNA BINDING DOMAIN [75]; DOUBLE MUTANT (C495W/R498Q) ELIMINATES ACTIVATION AND REPRESSION [26]

496R - R TO H IS BIOLOGICALLY INACTIVE AND HAS GREATLY REDUCED NUCLEAR TRANSLOCATION (LIKE NT-) [18, 19]; R TO S HAS NO EFFECT ON TRANSACTIVATION OR REPRESSION (PERSONAL COMMUNICATION: PETER HERRILICH [KARLSRUHE, GERMANY]); R TO S CAUSED 2 FOLD INCREASED TRANSACTIVATION AND 50% DECREASE IN REPRESSION [26]

497Y - PART OF INTERCHAIN HYDROPHOBIC INTERACTIONS HOLDING 3° STRUCTURE OF DNA BINDING DOMAIN TOGETHER[46]; Y497L/R498G DOUBLE MUTATION CAUSES 25-100% INCREASE IN TRANSACTIVATION WHILE ELIMINATING REPRESSION (PERSONAL COMMUNICATION: PETER HERRILICH [KARLSRUHE, GERMANY]);DOUBLE MUTANT (Y497L/R498G) HAS LITTLE EFFECT ON ACTIVATION BUT ELIMINATES REPRESSION [26]

498R - C495S/R498Q DOUBLE MUTATION ELIMINATES TRANSACTIVATION AND REPRESSION WHILE Y497L/R498G DOUBLE MUTATION CAUSES 25-100% INCREASE IN TRANSACTIVATION WHILE ELIMINATING REPRESSION (PERSONAL COMMUNICATION: PETER HERRILICH [KARLSRUHE, GERMANY]); R TO G CAUSED SLIGHT DECREASE IN ACTIVATION AND REPRESSION; SEE ALSO C495 AND Y497 [26]

500C - C TO S/A/M HAS LITTLE OR NO EFFECT [60] BUT MANY OTHERS GIVE INACTIVE GR; C TO R IS BIOLOGICALLY INACTIVE [57]; ONLY C IN 481/777 FRAGMENT OF E. COLI OVEREXPRESSED HGR NOT LABELED BY DEX-MES [51]

505M -M TO L OR C HAS LITTLE EFFECT BUT OTHERS ELIMINATE ACTIVITY (PERSONAL COMMUNICATION: SANDRO RUSCONI [FRIBOURG, SWITZERLAND]); M TO G GAVE RECEPTOR WITH 10% TRANSACTIVATION BUT ONLY 1% DNA BINDING OF WILD TYPE RECEPTOR [27]

517K - TRYPSIN CUTS ACTIVATED RS COMPLEX AFTER THIS AMINO ACID [8]

522A - CONFLICT IN XENOPUS SEQUENCE S OR P (P49844)

524A - CONFLICT IN XENOPUS SEQUENCE T OR A (P49844)

526V - CONFLICT IN XENOPUS SEQUENCE T OR A (P49844)

531S - CONFLICT IN XENOPUS SEQUENCE P OR N (P49844)

INSERT AFTER 534+ - ADDED A IN TAMARIN IS ONE OF 4 MUTATIONS IN STEROID BINDING DOMAIN PROPOSED TO BE RESPONSIBLE FOR 10 FOLD LOWER AFFINITY [5]

536K - TRYPSIN IS THOUGHT TO CLEAVE AFTER THIS SITE IN STEROID-FREE RECEPTORS TO FORM 16K CORE BINDING FRAGMENT [62]

538I - CONFLICT IN XENOPUS SEQUENCE L OR M (P49844)

550L - 550 OR 551 IS THE AMINO TERMINUS OF THE STEROID BINDING DOMAIN [68]; LACK OF BINDING BY HUMAN MUTANT LACKING AMINO ACIDS 489-532 [7], =507-550 IN RAT, ARGUES THAT 550 IS AMINO TERMINUS

551V - 550 OR 551 IS THE AMINO TERMINUS OF THE STEROID BINDING DOMAIN [68]

553L - L553,545G ELIMINATED TRANSCRIPTIONAL ACTIVITY (PERSONAL COMMUNICATION: MICHAEL STALLCUP [USC, CALIF.]); L553G/L554G ELIMINATED DEX BIOLOGICAL ACTIVITY AND AFFINITY LABELING BY DEX-MES [50]

554L - L553G/L554G ELIMINATED DEX BIOLOGICAL ACTIVITY AND AFFINITY LABELING BY DEX-MES [50]

555E - E TO A REQUIRES 1.7 FOLD HIGHER DEX CONCENTRATIONS FOR BIOLOGICAL ACTIVITY [50]

556V - V TO G REQUIRES 7 FOLD HIGHER DEX CONCENTRATIONS FOR BIOLOGICAL ACTIVITY [50]

557I - V TO G REQUIRES 4-100 FOLD HIGHER STEROID CONCS. FOR BIOLOGICAL ACTIVITY (PERSONAL COMMUNICATION: MICHAEL STALLCUP [USC, CALIF.])

558E - E TO G ELIMINATES STEROID BINDING ACTIVITY [19]

559P - P TO A REQUIRES "100 FOLD HIGHER STEROID CONCS. FOR BIOLOGICAL ACTIVITY, PRESUMABLY DUE TO DECREASED STEROID BINDING AFFINITY [6]

560E - E TO A REQUIRES,6 FOLD HIGHER DEX CONCENTRATIONS FOR BIOLOGICAL ACTIVITY [49]

561V - V TO G REQUIRES 23 FOLD HIGHER DEX CONCENTRATIONS FOR BIOLOGICAL ACTIVITY [49]

562L - L TO A REQUIRES13 FOLD HIGHER DEX CONCENTRATIONS FOR BIOLOGICAL ACTIVITY [49]

563Y - CONFLICT IN XENOPUS SEQUENCE Y OR F (P49844)

567D - D TO A REQUIRES 18 FOLD HIGHER DEX CONCENTRATIONS FOR BIOLOGICAL ACTIVITY [49]

568S - CONFLICT IN THE TAMARIN SEQUENCE EITHER T OR S; S TO A HAS WILD TYPE BIOLOGICAL ACTIVITY [49]

570V - CONFLICT IN XENOPUS SEQUENCE I OR M (P49844)

572D - D TO G GIVESRECEPTOR THAT WAS NOT STABLY EXPRESSED IN COS-7 CELLS [49]

573S - S TO A REQUIRES9 FOLD HIGHER DEX CONCENTRATIONS FOR BIOLOGICAL ACTIVITY [49]

577I - I TO N CAUSED LOSS OF DEXAMETHASONE BINDING AND GAVE A DOMINANT NEGATIVE RECEPTOR [31]

581L - L TO P CAUSES NO ACTIVITY IN YEAST OR COS-7 CELLS [23]; L TO F REQUIRES 4-100 FOLD HIGHER STEROID CONCS. FOR BIOLOGICAL ACTIVITY [M] (PERSONAL COMMUNICATION: MICHAEL STALLCUP [USC, CALIF.]); L TO F CAUSES 5-FOLD DECREASED AFFINITY AND 12 FOLD HIGHER DEX CONCENTRATIONS FOR BIOLOGICAL ACTIVITY WITH SOME LOSS OF STEROID BINDING ACTIVITY [38]; RESIDUE IS WITHIN 4.5 Å OF DEX LIGAND IN MODEL OF STEROID BINDING DOMAIN [67]

582N - RESIDUE IS WITHIN 4.5 Å OF DEX LIGAND IN MODEL OF STEROID BINDING DOMAIN [67]

583M - CYANOGEN BROMIDE CLEAVES AT THIS METHIONINE [8]; M TO R MAY CAUSE 1000 FOLD INCREASED AFFINITY FOR DEX, BUT ONLY 50 FOLD INCREASED POTENCY, WITH 5 FOLD INCREASED MAXIMAL TRANSACTIVATION [66]

584L - L TO S CAUSES NO ACTIVITY IN YEAST OR COS-7 CELLS AND DECREASED AFFINITY FOR DEX IN COS-7 CELLS [23]; RESIDUE IS WITHIN 4.5 Å OF DEX LIGAND IN MODEL OF STEROID BINDING DOMAIN [67]

585G - RESIDUE IS WITHIN 4.5 Å OF DEX LIGAND IN MODEL OF STEROID BINDING DOMAIN [67]; G TO C ELIMINATED STEROID BINDING AND TRANSACTIVATION [3]; G TO A DESTROYED STEROID BINDING AND TRANSACTIVATION [66]

588Q - RESIDUE IS WITHIN 4.5 Å OF DEX LIGAND IN MODEL OF STEROID BINDING DOMAIN [67]

591A - A TO Q MAY CAUSE 1000 FOLD INCREASED AFFINITY FOR DEX, BUT ONLY 7 FOLD INCREASED POTENCY, WITH 5 FOLD INCREASED MAXIMAL TRANSACTIVATION [66]

600L - P NOT L (PERSONAL COMMUNICATION: M. GARABEDIAN AND K. YAMAMOTO [UCSF])

602L - F NOT L (PERSONAL COMMUNICATION: M. GARABEDIAN AND K. YAMAMOTO [UCSF])

618W - W TO A HAS NO EFFECT ON BIOLOGICAL ACTIVITY (PERSONAL COMMUNICATION: MICHAEL STALLCUP [USC, CALIF.]); RESIDUE IS WITHIN 4.5 Å OF DEX LIGAND IN MODEL OF STEROID BINDING DOMAIN [67]

619M - M TO L CAUSES 2-3 FOLD REDUCED AFFINITY FOR DEX (PERSONAL COMMUNICATION: JAN CARLSTEDT-DUKE [HUDDINGE, SWEDEN])

620F - F TO S CAUSES INCREASED AFFINITY FOR DEX AND TRIAMCINOLONE ACETONIDE IN YEAST, BUT NOT IN CV-1 CELLS, AND THUS SUGGESTS SOME NON-RECEPTOR FACTOR IN STEROID BINDING [23]

622M - M TO P CAUSES REDUCED TRANSCRIPTIONAL ACTIVITY IN YEAST [23]; M TO L, C, OR S HAS NO EFFECT ON BIOLOGICAL ACTIVITY (PERSONAL COMMUNICATION: MICHAEL STALLCUP [USC, CALIF.]); PHOTO-LABELED BY TRIAMCINOLONE ACETONIDE [9, 64] AND R5020 [64]; CYANOGEN BROMIDE CLEAVES AT THIS METHIONINE (CARLSTEDT-DUKE ET AL.1987); M TO L HAS NO SIGNIFICANT EFFECT ON AFFINITY (PERSONAL COMMUNICATION: JAN CARLSTEDT-DUKE [HUDDINGE, SWEDEN]); RESIDUE IS WITHIN 4.5 Å OF DEX LIGAND IN MODEL OF STEROID BINDING DOMAIN [67]

626L - RESIDUE IS WITHIN 4.5 Å OF DEX LIGAND IN MODEL OF STEROID BINDING DOMAIN [67]

628W - W TO A REQUIRES "100 FOLD HIGHER STEROID CONCS. FOR BIOLOGICAL ACTIVITY (PERSONAL COMMUNICATION: MICHAEL STALLCUP [USC, CALIF.]

629R - R TO A ELIMINATES TRANSCRIPTIONAL ACTIVITY (PERSONAL COMMUNICATION: MICHAEL STALLCUP [USC, CALIF.]); RESIDUE IS WITHIN 4.5 Å OF DEX LIGAND IN MODEL OF STEROID BINDING DOMAIN [67]

634S - S TO A IN MARMOSET IS ONE OF 4 MUTATIONS IN STEROID BINDING DOMAIN PROPOSED TO BE RESPONSIBLE FOR 10 FOLD LOWER AFFINITY [5]

636G - A TO S IN MARMOSET IS ONE OF 4 MUTATIONS IN STEROID BINDING DOMAIN PROPOSED TO BE RESPONSIBLE FOR 10 FOLD LOWER AFFINITY [5]

640C - FORMS AN INTRAMOLECULAR DISULFIDE WITH C656 OR C661 [11]; C TO S CAUSES 3 FOLD LOSS IN BINDING AFFINITY [10]; C TO A HAS NO EFFECT ON BIOLOGICAL ACTIVITY [14]; RESIDUE IS WITHIN 4.5 Å OF DEX LIGAND IN MODEL OF STEROID BINDING DOMAIN [67]; LABELED BY DEX-MES IN 481/777 OF HGR OVEREXPRESSED IN E. COLI [51]

641F - F TO A REQUIRES 4-100 FOLD HIGHER STEROID CONCS. FOR BIOLOGICAL ACTIVITY (PERSONAL COMMUNICATION: MICHAEL STALLCUP [USC, CALIF.]); RESIDUE IS WITHIN 4.5 Å OF DEX LIGAND IN MODEL OF STEROID BINDING DOMAIN [67]

643P - P TO A REQUIRES "100 FOLD HIGHER STEROID CONCS. FOR BIOLOGICAL ACTIVITY (PERSONAL COMMUNICATION: MICHAEL STALLCUP [USC, CALIF.]

656C - COVALENTLY LABELED BY DEX-MES [61, 9]; COVALENTLY LABELED BY DEX-MES [64]; FORMS AN INTRAMOLECULAR DISULFIDE WITH C661 OR C640 [11]; FORMS A SPECIFIC COMPLEX WITH ARSENITE [44, 11]; RESIDUE IS WITHIN 4.5 Å OF DEX LIGAND IN MODEL OF STEROID BINDING DOMAIN [67]; C TO G OR S YIELDS "SUPER" RECEPTOR [10]; C TO Y HAS NO EFFECT ON AFFINITY OF RECEPTORS EXPRESSED IN COS-7 CELLS (CHAKRABORTI AND SIMONS, UNPUBLISHED RESULTS) BUT REDUCES TRANSCRIPTIONAL ACTIVITY IN YEAST [23]; C TO W HAS NO EFFECT ON TRANSCRIPTIONAL ACTIVITY [34]; C TO S HAS NO EFFECT ON AFFINITY (PERSONAL COMMUNICATION: JAN CARLSTEDT-DUKE [HUDDINGE, SWEDEN]); C TO S CAUSES ABOUT 15 FOLD HIGHER AFFINITY [70]; C TO S HAS NO EFFECT ON BIOLOGICAL ACTIVITY [14]

657M - RESIDUE IS WITHIN 4.5 Å OF DEX LIGAND IN MODEL OF STEROID BINDING DOMAIN [67]

659D - D TO G CAUSES NO ACTIVITY IN YEAST OR COS-7 CELLS AND DECREASED AFFINITY FOR DEX IN COS-7 CELLS [23]; D TO V REDUCED AFFINITY 3 FOLD AND TRANSACTIVATION 25 FOLD BUT HAD NO EFFECT ON REPRESSION [20]; D TO V CAUSES 3 FOLD DECREASED STEROID AFFINITY AND 7 FOLD REDUCED GLUCOCORTICOID SENSITIVITY [29]

661C - FORMS AN INTRAMOLECULAR DISULFIDE WITH C656 OR C640 [11]; FORMS A SPECIFIC COMPLEX WITH ARSENITE [44, 11]; C TO S CAUSES 4 FOLD LOSS IN BINDING AFFINITY [10]; C TO R IS TRANSCRIPTIONALLY ACTIVE IN YEAST ONLY WITH DEACYLCORTIVAZOL [23]; C TO G REQUIRES 2-3 FOLD HIGHER STEROID CONCENTRATIONS FOR BIOLOGICAL ACTIVITY [14]; LABELED BY DEX-MES IN 481/777 OF HGR OVEREXPRESSED IN E. COLI [51]; C TO S HAS WILD TYPE AFFINITY IN CELL-FREE ASSAY [70]

664M - CYANOGEN BROMIDE CLEAVES AT THIS METHIONINE [8]

671L - L TO S CAUSES REDUCED TRANSCRIPT; ACTIVITY IN YEAST OR COS-7 CELLS AND DECREASED AFFINITY FOR DEX IN COS-7 CELLS [23]

673R - CONFLICT IN XENOPUS SEQUENCE S OR R (P49844); TRYPSIN IS THOUGHT TO CLEAVE AFTER THIS SITE IN STEROID-FREE RECEPTORS TO FORM 16K CORE BINDING FRAGMENT [62]

682L - L TO F REQUIRES 4-100 FOLD HIGHER STEROID CONCS. FOR BIOLOGICAL ACTIVITY [M] (PERSONAL COMMUNICATION: MICHAEL STALLCUP [USC, CALIF.]); L TO F CAUSES ACTIVATION LABILE PHENOTYPE WITH NO LOSS IN DEX AFFINITY (BUT 200 FOLD HIGHER DEX CONCENTRATIONS ARE REQUIRED FOR BIOLOGICAL ACTIVITY) AND CHANGES IN RELATIVE AFFINITY ONLY FOR DAC [38]

683C - C TO S OR A REQUIRES 4-100 FOLD HIGHER STEROID CONCS. FOR BIOLOGICAL ACTIVITY [14]; C683S/C754S DOUBLE MUTANT CAUSED A 300 FOLD INCREASE IN THE DEX CONCENTRATION REQUIRED FOR INDUCTION [14]; BOTH C TO S AND C683S/M684L DOUBLE MUTANT HAVE NO EFFECT ON AFFINITY [70]; LABELED BY DEX-MES IN 481/777 OF HGR OVEREXPRESSED IN E. COLI [51]; C TO S HAS NO EFFECT ON AFFINITY (PERSONAL COMMUNICATION: JAN CARLSTEDT-DUKE [HUDDINGE, SWEDEN])

684M - CYANOGEN BROMIDE CLEAVES AT THIS METHIONINE [8]; M TO I REQUIRES 4-100 FOLD HIGHER STEROID CONCS. FOR BIOLOGICAL ACTIVITY (PERSONAL COMMUNICATION: MICHAEL STALLCUP [USC, CALIF.]); M TO I CAUSES ABOUT 3 FOLD LOWER DEX AFFINITY (10 FOLD HIGHER DEX CONCENTRATIONS ARE REQUIRED FOR BIOLOGICAL ACTIVITY) AND SOME LOSS OF BINDING SPECIFICITY [38]; C683S/M684L DOUBLE MUTANT HAS NO EFFECT ON AFFINITY [70]

706E - E TO K CAUSES NO ACTIVITY IN YEAST OR COS-7 CELLS AND DECREASED AFFINITY FOR DEX IN COS-7 CELLS [23]

715L - L TO V HAS NO EFFECT IN YEAST [23]

732R - R TO Q CAUSED ABOUT A 5 FOLD A RIGHT SHIFT IN THE DEXAMETHASONE DOSE-RESPONSE CURVE IN FULL LENGTH RECEPTOR AND ELIMINATED STEROID BINDING IN CONTEXT OF DEL 550-795 (XU AND SIMONS, PERSONAL COMMUNICATION).

747V - V TO I IN PATIENT WITH 1° CORTISOL RESISTANCE CAUSES 2-FOLD DECREASED AFFINITY AND 4-FOLD DECREASED EC<sub>50</sub> [47]; V TO I REDUCED AFFINITY BY 2 FOLD AND TRANSACTIVATION 10 FOLD BUT ONLY MARGINALLY REDUCED REPRESSION [20]

754C - PHOTOLABELED BY TRIAMCINOLONE ACETONIDE [9] AND R5020 [64]; C TO G REQUIRES >100 FOLD HIGHER STEROID CONCS. FOR BIOLOGICAL ACTIVITY, APPARENTLY DUE TO DECREASED PROTEIN STABILITY AND DEGRADATION TO A 68 KDA SPECIES (NO 98 KDA SEEN) [6] AND C TO S REQUIRES 4-100 FOLD MORE STEROID FOR BIOLOGICAL ACTIVITY [14]; C683S/C754S DOUBLE MUTANT CAUSED A 300 FOLD INCREASE IN THE DEX CONCENTRATION REQUIRED FOR INDUCTION [14]; LABELED BY DEX-MES IN 481/777 OF HGR OVEREXPRESSED IN E. COLI [51]; RESIDUE IS WITHIN 4.5 Å OF DEX LIGAND IN MODEL OF STEROID BINDING DOMAIN [67]; SATURATION MUTAGENESIS REVEALED THAT ONLY 3 CHANGES ( TO A, S. OR T) ARE COMPATIBLE WITH BINDING, WITH S AND T MUTATIONS DIFFERENTLY AFFECTING THE BINDING OF TRIAMCINOLONE ACETONIDE AND CORTISOL [41]

757T - RESIDUE IS WITHIN 4.5 Å OF DEX LIGAND IN MODEL OF STEROID BINDING DOMAIN [67]

579L - CONFLICT IN XENOPUS SEQUENCE L OR M (P49844)

761K - RESIDUE IS WITHIN 4.5 Å OF DEX LIGAND IN MODEL OF STEROID BINDING DOMAIN [67]

762T - T TO I CAUSES REDUCED TRANSCRIPT. ACTIVITY IN YEAST [23]

765I - I TO T REDUCED AFFINITY FOR DEX OR CORTISOL BY LESS THAN OR EQUAL TO 2 FOLD BUT CAUSED A 100 FOLD RIGHT SHIFT IN THE DOSE RESPONSE CURVE AND IS ESSENTIALLY INACTIVE WITH NATURAL GLUCOCORTICOID [56]

767F - RESIDUE IS WITHIN 4.5 Å OF DEX LIGAND IN MODEL OF STEROID BINDING DOMAIN [67]

770M - CYANOGEN BROMIDE CLEAVES AT THIS METHIONINE [8]; DOUBLE MUTATION TO A (770/771) HAS NO MAJOR AFFECT ON STEROID BINDING BUT ELIMINATES TRANSCRIPTIONAL ACTIVATION [17]. HOWEVER, IN RAT RECEPTORS, THIS MUTATION HAS EITHER A THREE FOLD LOWER AFFINITY FOR STEROID [58] OR NO AFFINITY AT ALL [37]; M770A/L771A CAUSED LOSS OF BINDING OF DEX, BUT NOT RU 486, WHICH DISPLAYED PARTIAL AGONIST ACTIVITY OF WILD TYPE RECEPTOR [36]

771L - M770A/L771A CAUSED LOSS OF BINDING OF DEX, BUT NOT RU 486, WHICH DISPLAYED PARTIAL AGONIST ACTIVITY OF WILD TYPE RECEPTOR [36]; DOUBLE MUTATION TO A (770/771) HAS NO MAJOR AFFECT ON STEROID BINDING BUT ELIMINATES TRANSCRIPTIONAL ACTIVATION [17]. HOWEVER, IN RAT RECEPTORS, THIS MUTATION HAS EITHER A THREE FOLD LOWER AFFINITY FOR STEROID [58] OR NO AFFINITY AT ALL [37]; L TO F GIVES RISE TO ACTIVATION LABILE OR R- PHENOTYPE, DEPENDING ON THE CELLULAR ENVIRONMENT [2]; THIS SAME MUTATION GIVES RECEPTORS WITH UNSTABLE BINDING AT 37°C BUT NOT AT 0°C AND, IN COMBINATION WITH C440Y, WILL ALSO GIVE AN ACTIVATION LABILE PHENOTYPE [53]; RESIDUE IS WITHIN 4.5 Å OF DEX LIGAND IN MODEL OF STEROID BINDING DOMAIN [67]

773E - E TO A DOES NOT AFFECT STEROID BINDING BUT DECREASES TRANSCRIPTIONAL ACTIVATION BY 40% [17]

774I - I774A/I775A DOUBLE MUTANT HAS NO MAJOR AFFECT ON STEROID BINDING BUT ELIMINATES TRANSCRIPTIONAL ACTIVATION [17]; HOWEVER, LANZ ET AL. FOUND THAT THESE MUTATIONS DID NOT BIND STEROID [37]. I774A/I775A CAUSED LOSS OF BINDING OF DEX, BUT NOT RU 486, WHICH DISPLAYED PARTIAL AGONIST ACTIVITY OF WILD TYPE RECEPTOR [36]

775I - I774A/I775A DOUBLE MUTANT HAS NO MAJOR AFFECT ON STEROID BINDING BUT ELIMINATES TRANSCRIPTIONAL ACTIVATION [17]. HOWEVER, LANZ ET AL. FOUND THAT THESE MUTATIONS DID NOT BIND STEROID [37]; I774A/I775A CAUSED LOSS OF BINDING OF DEX, BUT NOT RU 486, WHICH DISPLAYED PARTIAL AGONIST ACTIVITY OF WILD TYPE RECEPTOR [36]; RESIDUE IS WITHIN 4.5 Å OF DEX LIGAND IN MODEL OF STEROID BINDING DOMAIN [67]

779I - CONFLICT IN THE TAMARIN SEQUENCE EITHER L OR I.

780P - P780/K781 DOUBLE DELETION HAS NO EFFECT ON ACTIVITY WITH EITHER DEX OR RU486 [36]

781K - P780/K781 DOUBLE DELETION HAS NO EFFECT ON ACTIVITY WITH EITHER DEX OR RU486 [36]

782Y -Y TO N NEEDS 3 TO 4 FOLD MORE DEX FOR EQUAL BIOLOGICAL ACTIVITY, PRESUMABLY DUE TO 3-4 FOLD LOWER AFFINITY [19]; Y TO N CAUSED 2-10 FOLD RIGHT SHIFT IN DOSE-RESPONSE CURVES OF NUMEROUS AGONISTS AND PARTIAL ANTAGONISTS THAT IS SIMILAR TO OBSERVED INCREASE IN KD [72]

787I - CONFLICT IN XENOPUS SEQUENCE S OR P (P49844)

788K - K TO R IN MARMOSET IS ONE OF 4 MUTATIONS IN STEROID BINDING DOMAIN PROPOSED TO BE RESPONSIBLE FOR 10 FOLD LOWER AFFINITY [5]

792F - F TO A CAUSED 7 FOLD DECREASED ACTIVITY AND AFFINITY WITH TA AND INCREASED REDUCTIONS WITH OTHER STEROIDS; F TO L CAUSED A 5 FOLD DECREASED AFFINITY IN CELL FREE TRANSLATED RECEPTOR

793H - H TO L HAS NO EFFECT ON BIOLOGICAL ACTIVITY (PERSONAL COMMUNICATION: MICHAEL STALLCUP [USC, CALIF.]); H TO L HAS NO EFFECT ON TRANSCRIPTIONAL ACTIVITY [13]

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