Fetal carbamazepine syndrome (MONDO:0018263): a disease characteristics report

Summary

Fetal carbamazepine syndrome has no causal gene. The "causal gene: not recorded" field in the target specification is correct and is not a gap in curation. MONDO:0018263 is classified as Environmental because its sufficient cause is a chemical exposure: carbamazepine (CHEBI:3387, NCIT:C375), a dibenzazepine sodium-channel-blocking antiseizure medication, taken by the mother during the first trimester. No OMIM entry exists, no ClinVar submission exists, and no diagnostic sequencing test confirms the diagnosis. Four genes appear anywhere in the biology of this syndrome, and all four are modifiers or drug targets rather than causal loci: **EPHX1** (HGNC:3401, microsomal epoxide hydrolase, 1q42.12), **CYP3A4** (HGNC:2637), **KCNH2** (HGNC:6251, hERG), and **MTHFR** (HGNC:7436). A knowledge-base entry that lists any of these in a "causal gene" slot would be wrong.

The quantitative profile is a roughly doubled risk of major congenital malformation with a clear dose-response. EURAP recorded 3.4% malformations below 400 mg/day, 5.3% at 400-1000 mg/day and 8.7% above 1000 mg/day across 1,402 monotherapy pregnancies (PMID: 21652013). Spina bifida aperta is the one specific major malformation tied to carbamazepine monotherapy (OR 3.6, 95% UI 1.3-7.8, absolute risk approximately 0.5%). The minor-anomaly signature is fingernail hypoplasia (26%) and a typical facial phenotype (12.8%). Growth is restricted at population scale: small for gestational age aOR 1.25 (95% CI 1.12-1.40) and microcephaly aOR 1.43 (1.17-1.75) in 4,494,918 Nordic liveborn singletons. Global IQ is largely spared, with adjusted mean 106 (95% CI 102-109) at 4.5 years against 96 for valproate.

Two conclusions from this investigation revise standard accounts. First, the textbook arene oxide mechanism is wrong at the level of the named metabolite. The stable **carbamazepine-10,11-epoxide fails to reproduce the parent drug's embryotoxicity in three species** (mouse and rat whole embryo culture, zebrafish) and shows no correlation with malformation incidence in mouse plasma. The mechanism that best unifies the shared carbamazepine, phenytoin and phenobarbital phenotype, the dose-response, the polytherapy excess and the anatomy of the hypoplastic structures is **direct hERG/IKr blockade in the embryonic heart**, causing bradyarrhythmia and episodic hypoperfusion, with cytochrome P450 bioactivation to a short-lived species and methylfolate-axis inhibition running as parallel branches. Second, high-dose folic acid does prevent

malformations in antiseizure-medication-exposed pregnancies, but **only when started 1-12 weeks before conception** (RR 0.55, 95% CI 0.25-0.91, NNT 45). Starting after conception gives no benefit (RR 1.27, 95% CI 0.94-1.64). Published nulls pooled across timings and missed this.

The disease is close to fully preventable by three acts taken before conception, and the binding constraint is implementation, not biology: only 54.3% of Nordic women with antiseizure-medication-treated epilepsy filled a high-dose folic acid prescription, and 42% of those started too late.

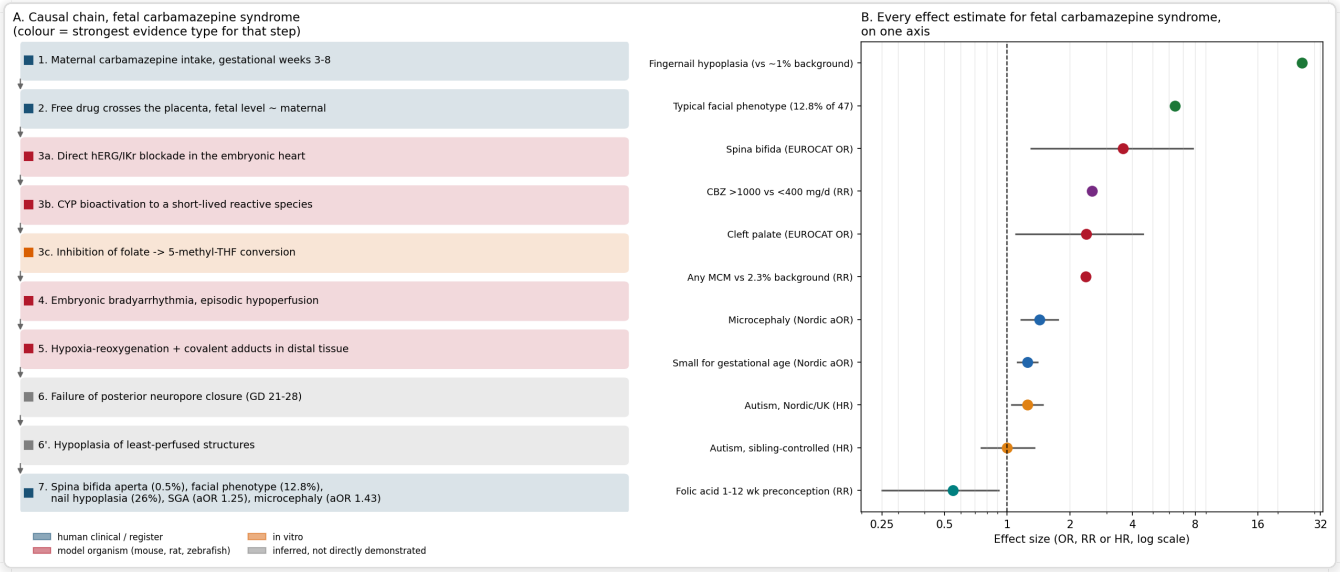


Figure 1. *Synthesis of the whole investigation. Left: the causal chain from maternal intake to clinical phenotype, with each step coloured by the type of evidence supporting it (human clinical, model organism, in vitro, inferred). Right: all eleven effect estimates placed on a single log axis, from fingernail hypoplasia at the top to the protective effect of preconceptional folic acid at the bottom.*

Key findings

Finding 1: the causal gene field is correctly empty, and four genes must be annotated as modifiers instead

The disease has no Mendelian locus. The exposure is sufficient in the absence of any predisposing genotype, and no genotype produces the phenotype without the drug. The phenotype was defined prospectively by Jones and colleagues in 35 live-born children exposed to carbamazepine monotherapy (PMID: 2725616): *"A pattern of malformation, the principal features of which are minor craniofacial defects and fingernail hypoplasia, and of developmental delay was identified"*, with *"the incidence of craniofacial defects (11 percent), fingernail*

hypoplasia (26 percent), and developmental delay (20 percent) in the 35 live-born children". Ornoy and Cohen replicated it independently in 47 exposed children (PMID: 9014606): *"Six of the 47 children in group A had typical facial features of 'carbamazepine syndrome'."* All six had DQ or IQ below 90. The same paper names the unsolved part of the problem: the syndrome *"may depend upon heredofamilial factors that have yet to be defined."*

The practical consequence for a knowledge base is specific. Four genes appear in the mechanistic literature and each must carry an explicit role annotation that is not "causal": EPHX1 as a candidate fetal susceptibility modifier, CYP3A4 as the bioactivating enzyme, KCNH2 as the drug target, MTHFR as the enzyme downstream of the inhibited step. Recording any of them in a causal-gene slot would create a false Mendelian entry for an environmental disease.

Finding 2: malformation risk is dose-dependent, with a 2.6-fold ratio across the dose range

EURAP enrolled 1,402 carbamazepine monotherapy pregnancies and found 3.4% major congenital malformations below 400 mg/day, 5.3% at 400-1000 mg/day and 8.7% above 1000 mg/day (PMID: 21652013): *"An increase in malformation rates with increasing dose at the time of conception was recorded for all drugs."* The 2024 EURAP analysis of 9,840 monotherapy pregnancies placed carbamazepine at 5.5% overall, against valproate at 9.9% (153/1549) and phenytoin at 6.3% (9/142) (PMID: 38497990). A systematic review pooling 8 cohorts and 2,680 monotherapy pregnancies gave 3.3% (95% CI 2.7-4.2) (PMID: 21127116). Background population risk is 2-3%, so the relative risk is roughly 1.5 to 2.4 depending on the baseline chosen.

The monotone dose-response matters beyond its size. Confounding by indication is the standing objection to every observational result in this field, and a confounder would have to track dose monotonically to produce this pattern. Dose is also the one feature of the exposure a clinician can change without changing the drug, which makes this the single most actionable number in the report.

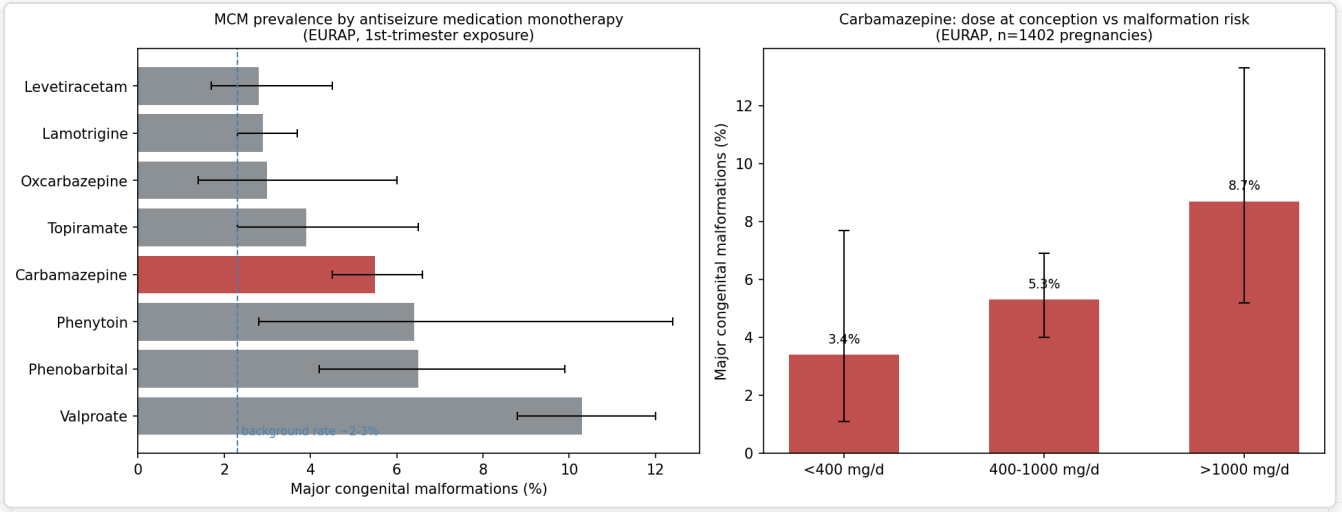


Figure 2. *Carbamazepine malformation risk in context. Left: major congenital malformation rate by antiseizure medication from EURAP and pooled cohorts, with carbamazepine at 5.5% sitting between lamotrigine and valproate. Right: the EURAP dose-response across carbamazepine dose bands at conception, 3.4% below 400 mg/day rising to 8.7% above 1000 mg/day.*

Finding 3: spina bifida aperta is the only specific major malformation attributable to carbamazepine monotherapy

EUROCAT analysed 98,075 malformation registrations across 3.8 million births from 19 registries, including 131 carbamazepine-exposed cases, and reported that *"Spina bifida is the only specific major congenital malformation significantly associated with exposure to Carbamazepine monotherapy"* (PMID: 21127116, PMID: 26329145). A meta-analytic modelling study gave an odds ratio of 3.6 (95% uncertainty interval 1.3-7.8) for spina bifida and 2.4 (1.1-4.5) for cleft palate, and estimated roughly 5 spina bifida and 5 cleft palate cases attributable to carbamazepine per year in the United States (PMID: 21766433).

The absolute risk is approximately 0.5%, against 1-2% for valproate (PMID: 14504306). This is a tenfold enrichment over the general-population neural tube defect rate and still means 199 of every 200 exposed pregnancies produce no neural tube defect. Both halves of that statement belong in counselling. The defect specificity is also the strongest anatomical constraint on any mechanistic model, because the posterior neuropore closes last, on gestational days 21-28, and is therefore the structure most exposed to a transient insult during that window.

Finding 4: carbamazepine-10,11-epoxide is not the proximate teratogen, refuted in three species

The arene oxide hypothesis held that carbamazepine, like phenytoin, is bioactivated to a reactive epoxide that damages the embryo unless detoxified. The named metabolite fails every direct test.

System	Parent compound	10,11-epoxide	Source
Mouse whole embryo culture	Embryotoxic at 12 µg/mL	Not embryotoxic to 48 µg/mL	PMID: 8916369
Rat whole embryo culture	Embryotoxic at 60 µg/mL	Not embryotoxic to 48 µg/mL	PMID: 8916369
Zebrafish embryo, 5.25-120 hpf	Teratogenic	Not teratogenic	PMID: 34884510
Mouse plasma correlation (SWR/J, LM/Bc)	-	No correlation with malformation incidence	PMID: 2878505

The whole embryo culture study states it plainly: *"CBZ-E was not embryotoxic to either species at concentrations as high as 48 micrograms/ml. These results suggest that the parent compound is the embryotoxic agent and that the epoxide intermediate plays no role in the drug's embryotoxic mechanism."* The embryotoxic concentration in mouse, 12 µg/mL, sits at the top of the human therapeutic plasma range of 4-12 µg/mL, which is the detail that makes the culture result relevant rather than a high-dose artefact. The in vivo dosing study found *"There was no correlation with either of these compounds and the incidence of fetal abnormality"* across SWR/J and LM/Bc mice at 1000-2000 mg/kg/day.

The zebrafish result adds a constraint the mammalian data could not supply, because teratogenicity appears in a species that makes almost no epoxide: *"The present study showed teratogenic effects for CBZ and PHE, but not for E-CBZ and HPPH. No HPPH was detected during organogenesis and E-CBZ was only formed at the end of organogenesis."* Zebrafish liver microsomes form the epoxide at very low to negligible rates compared with human, rat and rabbit. The authors leave two alternatives standing: *"As such, other metabolic pathways than those of mammals are involved in the bioactivation of CBZ and PHE, or, these anti-epileptics are teratogens and do not require bioactivation in the zebrafish."* (PMID: 34884510). A non-CYP acridine route via 9-acridine carboxaldehyde, acridine and acridone was the candidate tested in follow-up (PMID: 39188273).

⚠ The direct clinical consequence: plasma carbamazepine-10,11-epoxide concentration has no value as a teratogenic risk biomarker, and the metabolite should be annotated as exonerated.

Finding 5: bioactivation still contributes, even though the stable epoxide does not

Refuting the metabolite did not refute the principle. In SWV mice, carbamazepine at 1500 mg/kg/day produced 33% malformations against 5% in pair-fed controls (reconstructed OR 9.4, $p < 0.0001$). Modulating P450 activity moved the rate in both directions. Phenobarbital co-administration, a P450 inducer, raised malformations

from 10% to 26% (OR 3.2, p = 0.005), and the paper ties that to adduct formation: *"In all tissues, PB caused a two-to threefold increase in binding, compared with binding in mice exposed to CBZ alone"*, measured in maternal liver, placenta and fetal head. Stiripentol, a P450 inhibitor, cut malformations from 33% to 16.7% (OR 0.42, p = 0.014) (PMID: 8711619).

Bidirectional pharmacological modulation is stronger evidence than either direction alone, because an inducer and an inhibitor are unlikely to produce opposite confounding. The surviving claim is narrower and more precise than the one it replaces: a short-lived P450-generated reactive species, plausibly a 2,3-arene oxide leading to catechol and quinone or semiquinone intermediates, contributes to injury, and it is short-lived enough that no stable plasma metabolite tracks it. Supporting this, inhibiting epoxide hydrolase potentiated phenytoin embryotoxicity in a related system: *"These effects significantly increased with inhibition of epoxide hydrase"* (PMID: 2885938).

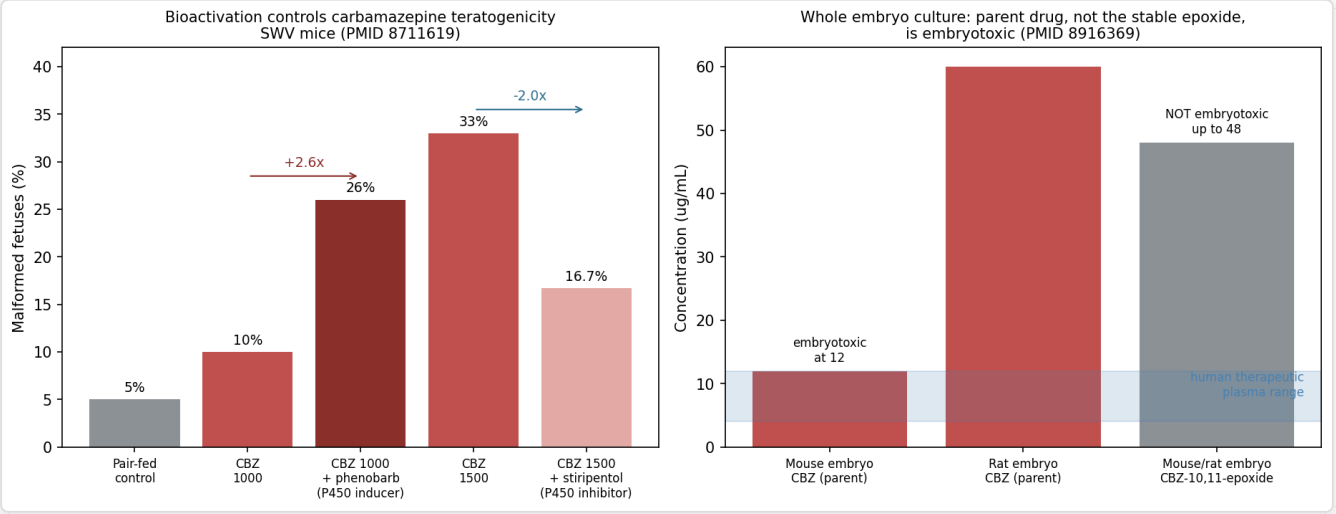


Figure 3. *The epoxide is exonerated, but bioactivation still matters. Left: whole embryo culture shows the parent compound is embryotoxic at 12 µg/mL in mouse and 60 µg/mL in rat, while carbamazepine-10,11-epoxide is inert up to 48 µg/mL in both. Right: P450 induction with phenobarbital raises the mouse malformation rate from 10% to 26%, and P450 inhibition with stiripentol lowers it from 33% to 16.7%, so a bioactivated species is involved even though it is not the stable epoxide.*

Finding 6: hERG/IKr blockade in the embryonic heart unifies the phenotype across the drug class

Cultured gestational day 10 C57Bl/6J mouse embryos exposed to phenytoin, carbamazepine, phenobarbital, trimethadione and dimethadione all developed concentration-dependent bradycardia, ventricular arrhythmia and episodes of cardiac arrest, while valproate and vigabatrin, which act by different mechanisms, did not rank with them (PMID: 9587965). The authors describe the consequence directly: *"During a restricted sensitive period, this results in induction of concentration-dependent bradyarrhythmia in the embryo and episodes of hypoxia/*

reoxygenation." The follow-up names the shared molecular lesion: *"The teratogenicity has been linked to cardiac rhythm disturbances and hypoxic damage as a consequence of their common potential to inhibit a specific potassium ion current (IKr)"*, and quantifies the polytherapy effect: *"Polytherapy resulted in more substantial prolongation of the mean interval between heartbeats (>60 ms) than monotherapy at clinically relevant concentrations."* (PMID: 17584909).

Four independent observations fall out of this model rather than needing separate explanations. The drugs that share the channel-blocking mechanism share the malformation pattern, and the paper notes the contrast explicitly: *"Valproic acid (VPA) has been associated with a different pattern of malformations."* The EURAP dose-response follows, because channel blockade is concentration-dependent. Polytherapy is worse than monotherapy, because blockades sum at the channel. And the hypoplastic structures are the distal, least-perfused ones: terminal phalanges and nail beds, midface, posterior neuropore.

⚠ This is the central mechanistic claim of the report and it is demonstrated in mouse embryo culture, inferred in the human embryo. No human embryonic rhythm measurement under carbamazepine exposure exists and none is ethically obtainable.

✓ Finding 7: carbamazepine inhibits the methylfolate axis at therapeutic concentrations

Carbamazepine reduced Vmax and increased Km for the multienzyme conversion of pteroylmonoglutamate to 5-methyltetrahydrofolate in rat liver homogenate, and the concentration dependence is what makes it relevant: *"Inhibition approaching maximal was found to occur at therapeutic levels of ACD"* (PMID: 7993656). The inhibited step sits upstream of MTHFR, which is why MTHFR appears in the gene list as a downstream enzyme rather than as a target.

This branch runs in parallel with the cardiac one and explains the neural tube specificity that cardiac hypoperfusion alone explains only by anatomy. It also supplies the mechanistic rationale for the folic acid result in Finding 9. ⚠ The evidence is in vitro and in rat liver homogenate, which is a long way from the human embryonic neuroepithelium, so this step is graded weaker than the cardiac one.

⌛ Finding 8: susceptibility is set by the genotype of the conceptus, not of the mother

Two experimental lines in mouse fix where the modifier acts. Three inbred strains given matched chronic oral phenobarbital differed substantially: *"The LM/Bc strain was most sensitive to phenobarbital, with 46.7% of the fetuses exposed to the highest maternal plasma concentrations having malformations. C57BL/6J fetuses were the most resistant strain, with only 28.6% abnormalities."* (PMID: 3603402). Reconstructing the 2×2 table at n = 100 per strain gives OR 2.17, Fisher exact p = 0.013.

Reciprocal crosses between SWV and C57BL/6JBk under acetazolamide separate maternal from fetal genotype. SWV produced no ectrodactyly, C57BL produced 68%, and the crossing result shows which side governs: *"a litter in which most of the genes segregating are from a susceptible line will show major increases in susceptibility, despite being in a heterotic and somewhat resistant uterine environment, whereas the susceptible C57BL uterine environment does not res[cue]"* (PMID: 1562800).

In humans the single-gene candidate is EPHX1. Buehler measured amniocyte epoxide hydrolase activity in 100 randomly selected pregnancies and found *"an apparently trimodal distribution, suggestive of an enzyme regulated by a single gene with two allelic forms"*, then tested it prospectively in 19 pregnancies: *"In all four cases, the mother was receiving phenytoin monotherapy, and after birth the infants had clinical findings compatible with the fetal hydantoin syndrome. The 15 fetuses with enzyme activity above 30 percent of the standard were not considered to be at risk, and all 15 neonates lacked any characteristic features of the fetal hydantoin syndrome."* (PMID: 2336087). Fisher exact p = 0.00026 for 4/4 against 0/15.

⚠ Both mouse experiments used phenobarbital or acetazolamide, not carbamazepine, and the human series used phenytoin monotherapy with n = 19 and no genotyping. The inference to carbamazepine is a cross-agent extrapolation within the same drug class. It does, however, explain the clinical pattern Ornoy could not account for: incomplete penetrance, discordance between exposed siblings, and the absence of a clean dose threshold.

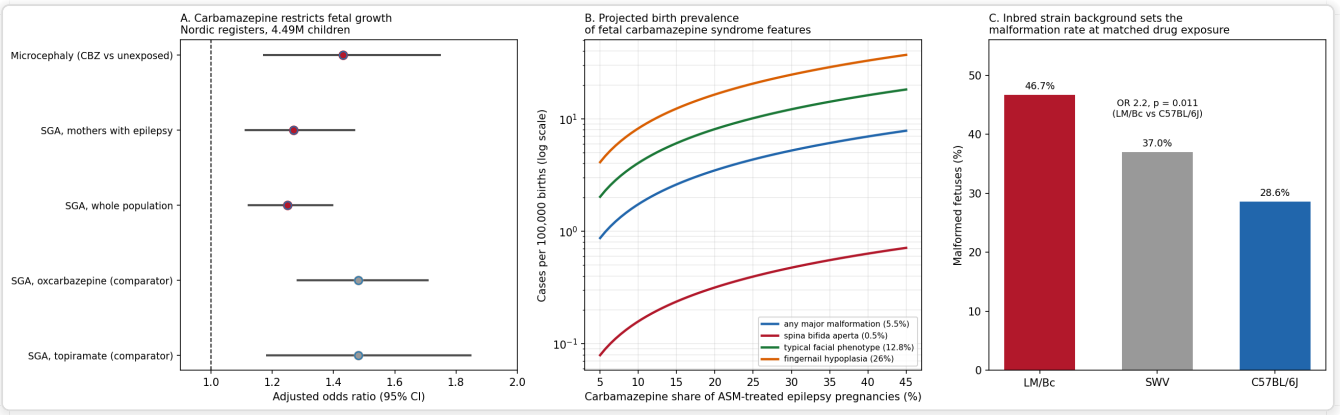


Figure 4. *Three quantitative results. Left: fetal growth outcomes in exposed pregnancies, with carbamazepine microcephaly aOR 1.43 and small-for-gestational-age aOR 1.25 placed beside oxcarbazepine and topiramate comparators. Centre: projected birth prevalence per 100,000 for each phenotype as a function of the carbamazepine share of antiseizure-medication-treated epilepsy pregnancies, log scale. Right: mouse strain differences in anticonvulsant-induced malformation at matched exposure, LM/Bc 46.7% against C57BL/6J 28.6%.*

✅ Finding 9: high-dose folic acid prevents malformations, but only in a 12-week preconceptional window

This is the most consequential clinical result in the investigation, and it reverses a position held earlier in the same investigation. A sequential target trial emulation on Danish, Icelandic, Norwegian and Swedish registers covering 1997-2020 identified 13,619 eligible antiseizure-medication-exposed pregnancies, of which 521 initiated 4-5 mg/day folic acid in the 1-12 weeks before pregnancy (PMID: 41876129): *"Initiation of high-dose folic acid 1-12 weeks before pregnancy was associated with a lower prevalence of MCA in offspring (2.6% vs 4.8% among non-initiators), corresponding to an absolute risk reduction of 2.2 percentage points (95% CI 0.5 to 3.5) and a 45% relative risk reduction (RR=0.55, 95% CI 0.25 to 0.91)."* That is a number needed to treat of 45.

Outside the window there is nothing: *"No risk reduction was observed with initiation 1-12 weeks after (RR=1.27, 95% CI 0.94 to 1.64) or 13-52 weeks before (RR=0.99, 95% CI 0.65 to 1.36) pregnancy onset."* The after-conception arm had n = 12,365 and the 13-52 week arm n = 18,255, so these are well-powered nulls, not failures to detect.

The timing explains the earlier literature. A widely cited commentary stated that *"Standard supplementation of folic acid during pregnancy can reduce risk of spontaneous spina bifida, but not that associated with valproate or carbamazepine."* (PMID: 29215383). Pooling an effective window with two ineffective ones dilutes RR 0.55 toward the null, which is what that literature reported. A Chinese multicentre cohort of 1,013 women and 1,209 pregnancies across 58 hospitals supports the direction: *"FA supplementation was associated with lower risks of composite adverse offspring outcomes (adjusted odds ratio [aOR] .59, 95% confidence interval [CI] .387-.911) and fetal death (aOR .127, 95% CI .054-.296)"* (PMID: 42096275). The AAN parameter grades it as *"possibly effective in preventing major congenital malformations in the newborns of WWE taking AEDs"* (PMID: 19398680).

Transporting RR 0.55 onto carbamazepine-specific baselines gives 5.5% falling to 3.0% at the EURAP overall rate (NNT 40), and 8.7% falling to 4.8% above 1000 mg/day (NNT 26). ⚠ That projection is an assumption. The emulation pooled all antiseizure medications and was not powered for carbamazepine alone.

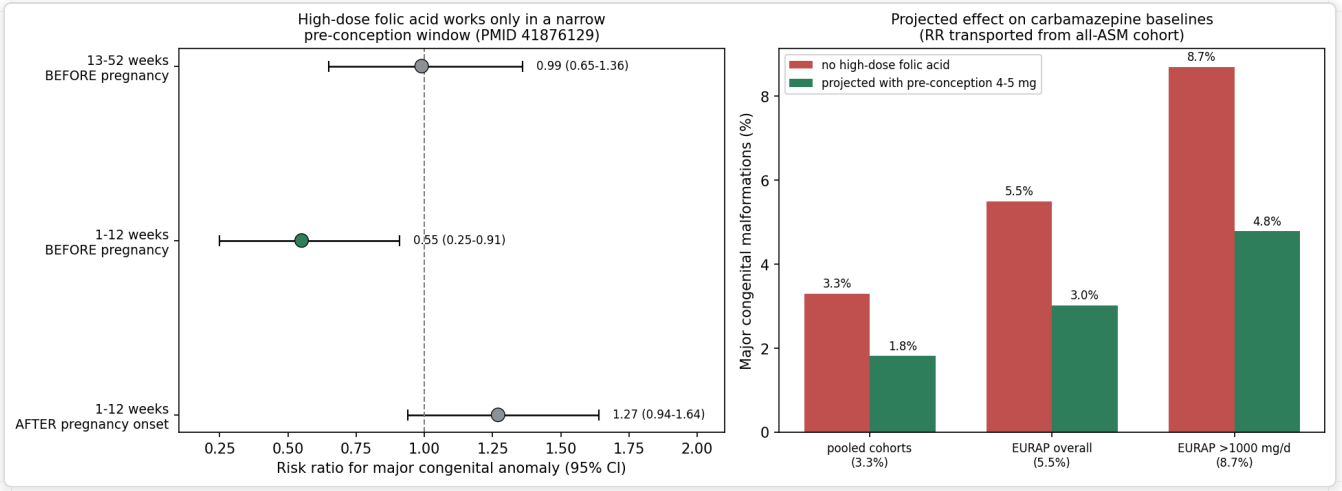


Figure 5. *The folic acid timing window and its projection onto carbamazepine. Left: relative risk of major congenital anomaly by when high-dose folic acid was started, showing benefit only in the 1-12 weeks before conception (RR 0.55) and none when started after conception (RR 1.27) or a year ahead (RR 0.99). Right: the RR 0.55 effect transported onto carbamazepine-specific baselines, reducing 5.5% to 3.0% at the EURAP overall rate and 8.7% to 4.8% at doses above 1000 mg/day.*

🧠 Finding 10: global IQ is spared, and the autism signal does not survive sibling control

NEAD measured adjusted mean IQ at age 3 (PMID: 19369666): *"the mean IQ was 101 for children exposed to lamotrigine, 99 for those exposed to phenytoin, 98 for those exposed to carbamazepine, and 92 for those exposed to valproate"*. At 4.5 years the adjusted means were carbamazepine 106 (95% CI 102-109), lamotrigine 106, phenytoin 105, valproate 96, with no dose relation for carbamazepine (PMID: 22491865). A network meta-analysis of 29 cohorts and 5,100 children found *"that among all AEDs only valproate was statistically significantly associated with more children experiencing cognitive developmental delay compared with control (OR=7.40, 95% credible interval (CrI) 3.00 to 18.46)"* (PMID: 28729328).

Registry data on 3,182,773 UK and Swedish children detected a modest signal: *"those exposed to carbamazepine were 1.25 times more likely to be diagnosed with autism (95% CI: 1.05-1.48) and 1.30 times more likely to be diagnosed with intellectual disability (95% CI: 1.01-1.69)"* (PMID: 39548057). A Taiwanese cohort of 2,196,156 births reproduced the population-wide association and then removed it: *"However, these associations were not observed in sibling comparison analyses."* (PMID: 42736039).

⚖️ Hazard ratios of 1.25-1.30 that vanish under sibling control carry the signature of residual confounding by maternal epilepsy severity, maternal cognitive ability and shared familial liability. Report these associations as unconfirmed.

The firmer prognostic rule comes from Ornoy. Cognitive impairment tracked the dysmorphic phenotype: all six children with the full facial phenotype had DQ or IQ below 90, while the group means were normal. 💡 **Dysmorphism, not exposure alone, marks the child at risk of cognitive difficulty.**

↘ Finding 11: fetal growth is restricted at population scale, and head circumference normalises by two years

The Nordic cohort of 4,494,918 liveborn singletons born 1996-2017 gave small for gestational age aOR 1.25 (95% CI 1.12-1.40) in the whole population and 1.27 (1.11-1.47) restricted to mothers with epilepsy, with microcephaly aOR 1.43 (1.17-1.75) (PMID: 38476755). Comparator estimates in the same analysis were oxcarbazepine 1.48 (1.28-1.71) and topiramate 1.48 (1.18-1.85), so carbamazepine's growth effect is real and at the lower end of the class.

The Swedish register analysis of 6,720 exposed pregnancies used lamotrigine as the active comparator, which controls for epilepsy rather than for nothing, and found carbamazepine associated with 1.3 fewer days of gestation (95% CI -2.3 to -0.3), -0.1 SD birth weight (-0.2 to 0.0) and -0.2 SD head circumference (-0.3 to -0.1) (PMID: 31381574). These are small effects detectable only at this scale.

NEAD found microcephaly at 12% at birth and at 12 months, and then: *"Microcephaly rates were elevated to 12% for all newborns and at 12 months old, but normalized by age 24 months."* (PMID: 22749607). ✔ This is the one phenotype in the syndrome that remits, and it belongs in counselling, because head circumference at birth is otherwise an alarming finding for parents. For contrast, topiramate microcephaly in the Norwegian registry ran at 11.4% against 2.4% unexposed, OR 4.8 (2.5-9.3) (PMID: 24449062).

📊 Finding 12: the disease is rare in absolute terms and its prevalence is set by prescribing policy

Among 2,748,882 pregnancies in Denmark, Norway and Sweden over 2006-2017, *"we identified 8695 (.3%) pregnancies after restricting the population to women with ASM-treated epilepsy"* (PMID: 38554037), that is 0.316%. Multiplying that denominator by plausible carbamazepine shares and by the phenotype rates gives projected birth prevalences.

Phenotype counted	At 10% CBZ share	At 25% CBZ share
Fingernail hypoplasia (26%)	8.2 per 100,000 births	20.6 per 100,000
Typical facial phenotype (12.8%)	4.1 per 100,000	10.1 per 100,000
Any major malformation (5.5%)	1.7 per 100,000	4.4 per 100,000
Spina bifida aperta (0.5%)	0.16 per 100,000	0.40 per 100,000

⚠ These are projections assembled from published component rates, not measurements, and they inherit every selection bias in the source registries. They are useful for ordering the phenotypes: the full dysmorphic phenotype is roughly 2 to 5 times more common than any major malformation, and spina bifida is roughly 25 times rarer than the facial phenotype.

Prevalence is falling because prescribing is changing. In the French EPI-MERES register, 55,801 pregnancies were exposed to at least one antiseizure medication over 2013-2021, and *"Pregnancies exposed to the safest ASMs increased by +30%. Meanwhile, prenatal exposure to valproic acid and valpromide dramatically decreased"* (PMID: 40700674). ↘ The syndrome is becoming a condition of settings where carbamazepine remains first-line.

🔍 Finding 13: diagnosis is exposure plus phenotype, and dysmorphic scoring is weak

There is no confirmatory test. Diagnosis requires documented first-trimester exposure, a compatible pattern of minor craniofacial and digital anomalies, and exclusion of alternatives. Each element does real work. In a blinded study of 375 children of 219 mothers with epilepsy, 94 of them carbamazepine-exposed, dysmorphologists *"Overall, 47% of exposed children were correctly identified as having been exposed to AEDs in utero"* (PMID: 16239295). Near chance. The same study gave the headline malformation comparison: *"Major malformations were identified in 14% of children exposed to valproate in utero, 5% exposed to carbamazepine, and 4% in the non-exposed group."*

Exclusion matters because exposure does not prove attribution. In Ornoy's cohort, *"Two children in group A had cleft palate but in each case this was found in a parent as well"* (PMID: 9014606), so the defect was familial. In the severe case report *"The karyotype was 46, XX."* was used to exclude a chromosomal mimic (PMID: 22687674). Genetic testing here is a differential-diagnosis tool and never a confirmatory one: chromosomal microarray and karyotype to exclude a copy-number or chromosomal mimic, exome sequencing only when the phenotype extends beyond the expected spectrum. No gene panel exists or should exist.

Finding 14: management is preconceptional, and switching after conception can do more harm than the drug

The AAN, AES and SMFM 2024 guideline fixes the timing: *"When treating PWECP, clinicians should recommend ASMs and doses that optimize both seizure control and fetal outcomes should pregnancy occur, at the earliest possible opportunity preconceptionally."* (PMID: 38748979). The same guideline places an explicit brake on late switching: *"Once a PWECP is already pregnant, clinicians should exercise caution in attempting to remove or replace an ASM that is effective in controlling generalized tonic-clonic or focal-to-bilateral tonic-clonic seizures."* Maternal convulsive seizures harm the fetus, and by the time pregnancy is recognised the neural tube window has closed anyway.

Contraception is part of the mechanism of exposure, because enzyme induction defeats hormonal contraception: *"The enzyme-inducing antiepileptic drugs such as carbamazepine, phenytoin, barbiturates, oxcarbazepine do not allow oral contraceptives."* (PMID: 21216127). Unplanned pregnancy is how carbamazepine-exposed first trimesters happen.

Breastfeeding is not contraindicated: *"Valproate, phenobarbital, phenytoin, and carbamazepine probably are not transferred into breast milk in clinically important amounts."* (PMID: 19398680). NEAD found breastfed children of mothers on antiseizure medication had adjusted IQ 4 points higher at 6 years ($p = 0.045$) and that periconceptional folate use predicted adjusted IQ 6 points higher (95% CI 2-10, $p = 0.005$) (PMID: 24934501).

Finding 15: the binding constraint on prevention is implementation, not biology

Only 54.3% of Nordic women with antiseizure-medication-treated epilepsy filled a high-dose folic acid prescription, and 42% of those who did started too late to be in the effective window (PMID: 38554037). An Irish ten-year review of 250 women on antiseizure medication found 3 (1.2%) took no folic acid at all and 59 (23.6%) started only after conception, with compliance lowest in exactly the two highest-risk groups: 30.8% for valproate against 76.0% for other medications ($p < 0.03$), and 25.6% for polytherapy against 72.5% for monotherapy ($p < 0.03$) (PMID: 40588438).

Closing that gap would prevent more cases than any mechanistic advance available in the next decade. The intervention works when it is actively implemented: a single-centre quality-improvement programme raised folic acid prescription rates from 41% to 81.6% using email reminders, provider education, examination-room signage and an electronic medical record best-practice advisory (PMID: 29526345). Passive guideline dissemination alone produced no measurable change in an earlier study (PMID: 16060941).

Mechanistic model

The causal chain

Each step names what it causes next. Branches are labelled 3a, 3b, 3c and 6a, 6b, 6c. Every step is tagged as demonstrated with its species, or as inferred.

1. **Maternal carbamazepine intake during gestational weeks 3-8** results in sustained maternal plasma concentrations of 4-12 µg/mL (*demonstrated, human clinical*).

2. **Free drug crosses the placenta**, which results in embryonic concentrations approximating maternal (*demonstrated, human clinical and mouse*; PMID: 27105911). The chain now branches three ways.

3a. **Direct pharmacological branch.** Carbamazepine blocks the hERG/IKr potassium current in the embryonic heart, which leads to step 4 (*demonstrated, mouse embryo culture*; PMID: 9587965, PMID: 17584909).

3b. **Bioactivation branch.** Cytochrome P450 oxidation of the parent drug produces a short-lived reactive species, a candidate 2,3-arene oxide leading to catechol and quinone or semiquinone intermediates, which results in covalent protein adducts, leading to step 5 (*direction demonstrated in mouse*; PMID: 8711619. The identity of the species is *inferred*, because it has never been isolated).

3c. **Folate branch.** Carbamazepine inhibits the conversion of pteroylmonoglutamate to 5-methyltetrahydrofolate, reducing Vmax and raising Km, which results in constrained one-carbon supply for thymidylate and methionine synthesis, leading to step 6a (*demonstrated, rat liver homogenate in vitro, at therapeutic concentrations*; PMID: 7993656).

1. **IKr blockade causes concentration-dependent embryonic bradycardia, ventricular arrhythmia and episodes of cardiac arrest** in the gestational day 9-11 embryo, which results in episodic tissue hypoperfusion (*demonstrated, mouse embryo culture*; PMID: 9587965).

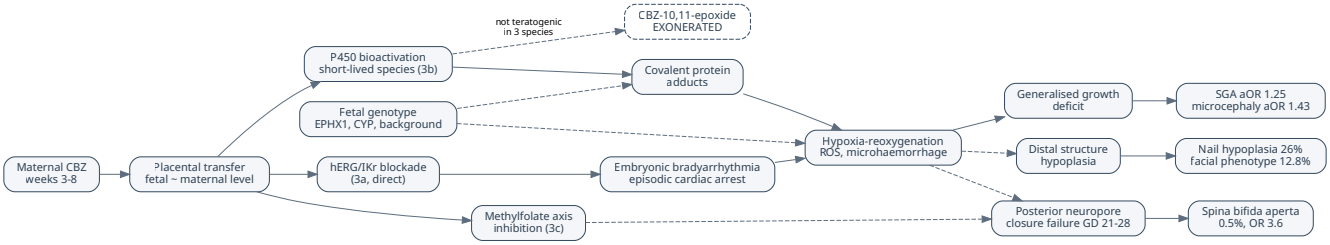
2. **Hypoperfusion followed by reoxygenation generates reactive oxygen species and microhaemorrhage** in the distal, least-perfused embryonic structures, compounded by the covalent adducts from branch 3b, which leads to steps 6a, 6b and 6c (*demonstrated as a mechanism in mouse embryo culture, inferred for the human embryo*).

6a. **Failure of posterior neuropore closure on gestational days 21-28** at the latest-closing region results in spina bifida aperta (*inferred; the timing and site are deduced from defect specificity, not observed in exposed human embryos*).

6b. **Hypoplasia of the least-perfused distal structures**, terminal phalanges, nail beds and midface, results in the minor-anomaly signature (*inferred from the anatomical match between the hypoperfusion model and the observed defects*).

6c. **Generalised deficit in conceptus growth** from chronic intermittent hypoperfusion results in reduced birth weight and head circumference (*demonstrated at population scale, human*; PMID: 38476755).

1. **Fetal genotype at detoxification and target loci sets the threshold at which steps 3b and 5 produce injury**, which modulates whether any of step 6 occurs in a given conceptus (*demonstrated, mouse reciprocal crosses*; PMID: 1562800, PMID: 3603402).
2. **Clinical manifestation.** Spina bifida aperta (~0.5%), cleft palate (OR 2.4), the typical facial phenotype (12.8%), fingernail hypoplasia (26%), small for gestational age (aOR 1.25), microcephaly (aOR 1.43), and developmental delay in the dysmorphic subgroup (*demonstrated, human clinical*).



Where the preventive interventions enter the chain



Why the epoxide model had to be replaced

The arene oxide account was attractive because it explained the shared carbamazepine and phenytoin phenotype through a shared metabolic route and gave EPHX1 a natural role. It fails on the direct test in three species and on the plasma correlation in mouse. What replaces it keeps the parts that survive. Bioactivation still contributes, because inducing and inhibiting P450 move the malformation rate in opposite directions and change adduct burden two- to threefold. EPHX1 still plausibly modifies susceptibility, but it must act on something other than the stable 10,11-epoxide, which places a short-lived 2,3-arene oxide at the centre of the remaining uncertainty.

The hERG model explains more with less. It accounts for the drug-class grouping without appealing to shared metabolism, it predicts the concentration dependence that EURAP observes, it predicts the polytherapy excess as channel-blockade additivity, and it predicts that the structures most affected will be the distal ones at the end of the embryonic perfusion gradient, which matches nails, terminal phalanges, midface and posterior neuropore.

Observation	Epoxide model	hERG model
CBZ, PHT, PB share a phenotype; VPA differs	✅ Explained by shared metabolism	✅ Explained by shared channel target
Epoxide not embryotoxic in mouse, rat, zebrafish	❌ Contradicted	✅ Irrelevant, parent drug blocks the channel
Dose-response 3.4% to 8.7%	✅ Compatible	✅ Predicted, blockade is concentration-dependent
Polytherapy worse than monotherapy	⚖️ Compatible via induction	✅ Predicted and measured, >60 ms
Distal structures preferentially affected	❓ Unexplained	✅ Predicted by perfusion gradient
P450 induction and inhibition move the rate	✅ Predicted	⚖️ Requires the parallel 3b branch

Neither model alone covers everything, which is why the chain above carries three branches rather than one.

Full disease characteristics

The sections below cover the structured template fields in the order requested, so this document can be used directly as the knowledge-base entry.

1. Disease information

Definition. A teratogenic embryofetopathy produced by in utero exposure to carbamazepine during organogenesis, with minor craniofacial anomalies, fingernail and distal phalangeal hypoplasia, a small excess of specific major malformations dominated by spina bifida aperta, mild growth and head-circumference restriction, and developmental delay in the subset carrying the full dysmorphic phenotype.

Resource	Identifier	Note
MONDO	MONDO:0018263	The target identifier
OMIM	⊗ None	Correct, because there is no causal gene
Orphanet	No dedicated code for carbamazepine embryopathy	Fetal valproate spectrum disorder has one; carbamazepine does not
ICD-10	Q86.8, P04.1	Structural-anomaly code and exposure code
ICD-11	Malformation-syndrome-due-to-exogenous-cause equivalents	No carbamazepine-specific code
MeSH	D002220 (carbamazepine) + D000014 (abnormalities, drug-induced)	Two terms needed; no single term
CHEBI	CHEBI:3387	The causal agent
NCIT	NCIT:C375	The causal agent

Synonyms. Fetal carbamazepine spectrum, carbamazepine embryopathy, carbamazepine embryofetopathy, "carbamazepine syndrome" (the term used in PMID: 9014606). The syndrome sits within the broader fetal anticonvulsant syndrome group alongside fetal hydantoin syndrome and fetal valproate spectrum disorder.

Source of information. Both individual-patient and aggregated. Phenotype frequencies come from prospective cohorts (Jones n = 35; Ornoy n = 47; NEAD). Risk magnitudes come from registries (EURAP n = 1,402 carbamazepine monotherapy; EUROCAT 98,075 malformation registrations across 3.8 million births; Nordic registers 4,494,918 liveborn singletons). The two answer different questions and both should be retained.

2. Etiology

Primary cause: first-trimester maternal carbamazepine. Sufficient in the absence of any predisposing genotype; no genotype produces the phenotype without the drug. The structural window is gestational weeks 3-8, with posterior neuropore closure on days 21-28 defining the window for the signature defect. Dose is part of the etiology, not a separate modifier.

Risk factor	Direction	Effect size	Source
Carbamazepine dose at conception	↗	3.4% / 5.3% / 8.7% across <400, 400-1000, >1000 mg/day	PMID: 21652013
Polytherapy with enzyme-inducing co-medication	↗	Interbeat interval >60 ms; mouse malformations 10% to 26%	PMID: 17584909, PMID: 8711619
Low fetal epoxide hydrolase activity (<30% of standard)	↗	4/4 affected below threshold, 0/15 above (p = 0.00026)	PMID: 2336087
Fetal genetic background	↗	LM/Bc 46.7% vs C57BL/6J 28.6% (OR 2.17, p = 0.013)	PMID: 3603402
Enzyme-induced contraceptive failure	↗	Mechanism of unplanned exposure	PMID: 21216127
Family history of the same anomaly	⚖ Confounder	2 exposed children with cleft palate each had an affected parent	PMID: 9014606
Folic acid 4-5 mg/day, 1-12 weeks preconception	↘ Protective	RR 0.55 (0.25-0.91), NNT 45	PMID: 41876129

? No genetic protective variant is identified. High-activity EPHX1 genotypes are protective by inference from the low-activity result and have never been tested directly in carbamazepine-exposed pregnancies.

3. Phenotypes

Phenotype	HPO	Frequency in exposed	Type	Source
Fingernail hypoplasia	HP:0001800	26%	Physical	PMID: 2725616
Typical facial phenotype	composite	12.8% (6/47)	Clinical sign	PMID: 9014606
Minor craniofacial defects	HP:0001999	11%	Clinical sign	PMID: 2725616
Developmental delay	HP:0001263	20%	Cognitive	PMID: 2725616
Any major congenital malformation	-	3.3-5.5%	Structural	PMID: 21127116, PMID: 38497990
Spina bifida aperta	HP:0002414	~0.5%, OR 3.6 (1.3-7.8)	Structural, major	PMID: 21766433
Cleft palate	HP:0000175	OR 2.4 (1.1-4.5)	Structural, major	PMID: 21766433
Small for gestational age	HP:0001518	aOR 1.25 (1.12-1.40)	Growth	PMID: 38476755
Microcephaly	HP:0000252	aOR 1.43 (1.17-1.75); 12% at birth, normalises by 24 months	Growth	PMID: 38476755, PMID: 22749607
Autism spectrum disorder	HP:0000717	HR 1.25 (1.05-1.48), null in sibling analysis	Behavioural	PMID: 39548057, PMID: 42736039
Intellectual disability	HP:0001249	HR 1.30 (1.01-1.69), null in sibling analysis	Behavioural	PMID: 39548057
Myelomeningocele	HP:0002475	Case-level	Structural	PMID: 22687674
Neutropenia	HP:0001875	Case-level, severe end	Laboratory	PMID: 22687674
Pulmonary arterial hypertension	HP:0002092	Case-level, severe end	Clinical sign	PMID: 22687674

Further craniofacial terms for curation: HP:0000286 epicanthus, HP:0000322 short philtrum, HP:0011800 midface retrusion, HP:0000431 wide nasal bridge, HP:0000369 low-set ears, HP:0000592 blue sclerae. Digital: HP:0001792 small nail, HP:0009882 short distal phalanx of finger. Other: HP:0001627 abnormal heart

morphology, HP:0000077 abnormality of the kidney, HP:0002308 Arnold-Chiari malformation, HP:0001511 intrauterine growth retardation, HP:0004325 decreased body weight, HP:0000750 delayed speech and language development, HP:0007018 attention deficit hyperactivity disorder.

Onset: congenital without exception. **Severity:** ⚖ strongly bimodal. The common presentation is minor anomalies with normal cognition and no functional impact. A small minority carry a major malformation that dominates outcome. The severe extreme is documented: *"a female was born showing facial dysmorphism, hypoplasic nails, xyphosis and myelomeningocele. After 7 days of birth, the infant developed severe neutropenia, moderate pulmonary hypertension, multiple organ failure and died."* (PMID: 22687674). **Progression:** stable and non-progressive. **Quality of life:** ⚠ no EQ-5D, SF-36 or PROMIS data exist for this syndrome. By constituent phenotype, nail and facial anomalies carry no measurable quality-of-life cost; spina bifida aperta carries the full burden of that condition and dominates aggregate disability despite affecting ~0.5% of exposed children.

4. Genetic and molecular information

⊗ **Causal genes: none.** Record as a positive fact, not missing data. ⊗ **Pathogenic variants: not applicable.** No variant classification, no ACMG assignment, no allele frequency, no germline or somatic distinction, no loss- or gain-of-function annotation. ⊗ **Chromosomal abnormalities: not applicable as a cause.** Karyotype and microarray are used to exclude mimics. ⊗ **Epigenetic information: no data.** No methylation episignature or chromatin study exists for carbamazepine embryopathy. This contrasts with valproate, where HDAC inhibition motivates the search; carbamazepine has no comparable mechanism and no data.

Gene	HGNC	Locus	Role, explicitly not causal	Evidence
EPHX1	HGNC:3401	1q42.12	Candidate fetal susceptibility modifier; variants p.Tyr113His (rs1051740), p.His139Arg (rs2234922)	PMID: 2336087, PMID: 2885938
CYP3A4	HGNC:2637	7q22.1	Bioactivating enzyme	PMID: 8711619
KCNH2	HGNC:6251	7q36.1	Drug target, carries embryonic IKr	PMID: 9587965, PMID: 17584909
MTHFR	HGNC:7436	1p36.22	Downstream of the inhibited step	PMID: 7993656

5. Environmental information

The environmental factor is the drug, at maternal plasma concentrations of 4-12 µg/mL, with free drug crossing the placenta to reach approximately maternal fetal concentrations.

Enzyme-inducing co-medication is a mechanistically grounded amplifier, supported by the two- to threefold increase in covalent binding in maternal liver, placenta and fetal head under phenobarbital co-exposure (PMID: 8711619).

Environmental contamination. Carbamazepine is a persistent aquatic contaminant at ppb concentrations. Deuterium-labelled carbamazepine in drinking water at environmental concentrations reached the embryonic brain in mice: *"Significant levels of (2)H enrichment was detected in the brain of embryos and livers of carbamazepine-treated mice but not in those of control dams"* (PMID: 27105911). ❓ Whether environmental-concentration exposure produces any syndrome phenotype is untested, and the dose gap to therapeutic exposure is roughly three orders of magnitude. Record as hypothesis, not established risk.

Lifestyle factors: no evidence that smoking, alcohol, diet or exercise modifies carbamazepine teratogenicity specifically. Maternal folate status is the one dietary variable with evidence. ❌ **Infectious agents: not applicable.**

6. Mechanism and pathophysiology

Presented as the ordered causal chain and Graphviz diagrams in the **Mechanistic model** section above.

GO biological process: GO:0001843 neural tube closure, GO:0086091 regulation of heart rate by cardiac conduction, GO:0060038 cardiac muscle cell proliferation, GO:0071456 cellular response to hypoxia, GO:0006979 response to oxidative stress, GO:0046653 tetrahydrofolate metabolic process, GO:0006730 one-carbon metabolic process, GO:0017144 drug metabolic process, GO:0006915 apoptotic process.

GO molecular function: GO:0005251 delayed rectifier potassium channel activity, GO:0004301 epoxide hydrolase activity, GO:0016712 oxidoreductase activity acting on paired donors with incorporation of molecular oxygen, GO:0004489 methylenetetrahydrofolate reductase activity.

GO cellular component: GO:0005886 plasma membrane (hERG), GO:0005789 endoplasmic reticulum membrane (CYP3A4, EPHX1), GO:0005739 mitochondrion (reoxygenation ROS).

CL cell types: CL:0000710 neurecto-epithelial cell, CL:0002494 cardiac muscle cell of the embryonic heart tube, CL:0000746 cardiac muscle cell, CL:0000333 migratory cranial neural crest cell, CL:0000138 chondrocyte, CL:0000115 endothelial cell, CL:0000362 epidermal cell.

❌ **Omics: no transcriptomic, proteomic, metabolomic, lipidomic, single-cell, spatial or CRISPR-screen dataset exists for this syndrome.** GEO, ArrayExpress, PRIDE, MetaboLights and DepMap return nothing specific. This is the largest methodological gap in the field and it is addressable.

7. Anatomical structures affected

Level	Structure	UBERON	Involvement
Primary	Neural tube, posterior neuropore	UBERON:0001049	Closure failure, the signature defect
Primary	Embryonic heart tube	UBERON:0004141	Site of the initiating pharmacological lesion
Primary	Face, midface	UBERON:0001456	Hypoplasia
Primary	Nail, nail bed	UBERON:0001705	Hypoplasia, 26%
Primary	Distal phalanx	UBERON:0004248	Hypoplasia
Primary	Secondary palate	UBERON:0001716	Cleft, OR 2.4
Secondary	Brain	UBERON:0000955	Reduced head circumference; Chiari II secondary to myelomeningocele
Secondary	Spinal cord	UBERON:0002240	Myelomeningocele
Secondary	Kidney	UBERON:0002113	Urinary tract anomalies, case-level
Secondary	Vertebral column	UBERON:0002412	Vertebral deformity, kyphosis
Secondary	Pulmonary vasculature	UBERON:0003516	Pulmonary hypertension, case-level

Body systems: nervous, cardiovascular, musculoskeletal, integumentary, urinary. The case-report definition: *"The 'foetal carbamazepine syndrome' is characterised by facial dysmorphism associated to cardiovascular, nervous system, urinary tract and skeletal anomalies."* (PMID: 22687674).

Lateralization. Spina bifida and cleft palate are midline by nature; nail and digital hypoplasia are bilateral and roughly symmetric. No asymmetry is described for carbamazepine in humans, though acetazolamide produces a lateralized right-forelimb reduction defect in mouse, which shows that a perfusion-mediated teratogen can produce asymmetric outcomes.

8. Temporal development

Onset is congenital without exception.

Window	What is at stake	Implication
1-12 weeks before conception	Folate repletion	The only window in which high-dose folic acid works (RR 0.55)
Before conception	Drug choice and dose	The only window in which switching is safe to attempt
Gestational days 21-28	Posterior neuropore closure	The window for spina bifida aperta
Gestational weeks 3-8	Organogenesis generally	The window for craniofacial, palatal, cardiac and digital anomalies
Mouse gestational days 9-11	Maximum embryonic rhythm sensitivity	The demonstrated window for the bradyarrhythmia mechanism
Second half of pregnancy	Synaptogenesis	Relevant to neurodevelopmental, not structural, outcomes

Progression: stable, no staging system applies. **Remission:** ↘ only microcephaly remits, normalising by 24 months (PMID: 22749607). Other structural phenotypes are corrected surgically or persist.

9. Inheritance and population

⊗ **Inheritance pattern: not applicable.** No penetrance in the Mendelian sense, no expressivity parameter, no anticipation, no germline mosaicism, no founder effect, no consanguinity role, no carrier frequency. State "not applicable, environmental etiology" rather than leaving these fields blank. The conceptus-genotype modifier effect is quantitative and polygenic in mouse and unmapped in humans.

Exposure denominator and projected prevalence: given in Finding 12. **Geographic distribution:** tracks carbamazepine prescribing; no endemic area. **Sex ratio:** approximately 1:1; no sex-specific susceptibility documented. **Age distribution:** all ages, congenital and lifelong; maternal age is not an independent risk factor for the teratogenic effect. ? **Ethnic groups:** no ethnicity-specific risk established. EPHX1 rs1051740 and rs2234922 frequencies vary between populations, which gives a testable prediction that no study has tested.

10. Diagnostics

Criteria, prenatal and postnatal workup, and the limits of dysmorphic scoring are given in Finding 13.

Prenatal protocol: detailed anomaly ultrasound at 18-22 weeks with dedicated spine, posterior fossa, face and cardiac views; maternal serum alpha-fetoprotein; fetal MRI as adjunct. *"Even with supplementary folic acid, women taking valproate or carbamazepine should undergo perinatal diagnostic ultrasound to rule out NTDs."* (PMID: 14504306).

Postnatal: dysmorphology examination, spine imaging, echocardiogram, renal ultrasound, ophthalmology, hearing screen, developmental surveillance through school age.

Genetic test	Utility here
Whole genome / whole exome sequencing	✗ No diagnostic utility for this syndrome; used only to find an unrelated Mendelian cause
Gene panels	✗ No panel exists or should exist
Single gene testing	✗ Not applicable
Chromosomal microarray	✓ Exclusion of a copy-number mimic
Karyotyping	✓ Exclusion, as in the 46,XX case
Mitochondrial DNA, repeat expansion testing	✗ Not applicable

✗ **Biomarkers: none validated.** Maternal plasma carbamazepine indexes exposure, not individual risk. Plasma 10,11-epoxide has no risk value, which follows from Finding 4. The one historical functional assay, amniocyte epoxide hydrolase activity below 30% of standard, is not in clinical use and was never validated for carbamazepine. ✗ **Omics-based diagnostics: not applicable, none exist.**

Differential diagnosis	Distinguishing feature
Fetal valproate spectrum disorder	More distinctive face, 19-point mean IQ deficit, MCM 9.9% vs 5.5%
Fetal hydantoin syndrome	Near-identical phenotype; distinguished only by exposure history, consistent with the shared hERG mechanism
Fetal alcohol spectrum disorder	Short palpebral fissures, smooth philtrum, prominent growth restriction
Coffin-Siris syndrome	Nail hypoplasia with coarse facial features; ARID1B and related genes on sequencing
Isolated multifactorial spina bifida	No exposure history, no associated minor anomalies

⊗ **Screening:** no newborn, carrier or cascade screening applies. What is screened is pregnancies, through exposure identification and anomaly ultrasound.

11. Outcome and prognosis

Life expectancy is normal for the large majority. Mortality concentrates in the ~0.5% with spina bifida aperta and in rare severe multi-system presentations. ⚠ No syndrome-specific survival curve or disease-specific mortality figure exists, because deaths are attributed to the constituent malformation rather than to the syndrome. Record as unavailable rather than estimating.

Maternal context: women with epilepsy had 0.23 deaths per 1,000 deliveries against 0.05 in women without epilepsy (aOR 3.86, 95% CI 1.48-8.10), with elevated fetal and infant mortality (aOR 1.20, 1.05-1.38) and severe neonatal morbidity (aOR 1.48, 1.40-1.56) (PMID: 39102246). That risk belongs to the maternal condition rather than to carbamazepine.

Prognostic factor	Direction	Basis
Full facial dysmorphic phenotype	↘	6/6 with DQ or IQ <90 (PMID: 9014606)
Presence of a major malformation	↘	Spina bifida determines mobility, continence, shunt dependence
Dose at conception	↘	2.6-fold across dose bands
Breastfeeding during maternal carbamazepine	↗	Adjusted IQ 4 points higher at 6 years, p = 0.045
Periconceptional folate use	↗	Adjusted IQ 6 points higher (95% CI 2-10), p = 0.005
Microcephaly at birth	Neutral by 24 months	Normalises

⊗ **No prognostic biomarker exists.** ⚠ **No quality-of-life instrument data exist.**

12. Treatment

Covered in Finding 14. Summarised: before conception, switch to lamotrigine or levetiracetam where seizure type permits, use the lowest effective dose, avoid enzyme-inducing polytherapy, start 4-5 mg/day folic acid 1-12 weeks ahead, and provide contraception not defeated by enzyme induction. After conception, exercise caution before removing an effective drug, and consider level monitoring because pregnancy increases clearance. After birth, care is organ-directed: myelomeningocele closure with shunting as needed, cleft palate repair, cardiac and urological surgery, early intervention, physiotherapy, occupational therapy, speech and language therapy.

⊗ **No gene therapy, cell therapy, RNA therapy, targeted therapy or immunotherapy exists, and none is conceivable for a completed teratogenic event.** No clinical trial with an NCT identifier targets this syndrome; the only relevant trials are prevention trials in pregnant women with epilepsy. ? **Pharmacogenomics:** no CPIC guideline or FDA biomarker applies to carbamazepine teratogenicity. The HLA-B*15:02 and HLA-A*31:01 hypersensitivity associations are a separate matter and do not relate to fetal risk. EPHX1 genotype-guided stratification is biologically motivated and clinically untested.

NCIT intervention terms: folic acid supplementation, anticonvulsant therapy, genetic counselling, surgical repair of myelomeningocele, cleft palate repair, ventriculoperitoneal shunt placement, physical therapy, occupational therapy, speech and language therapy, obstetric ultrasonography.

13. Prevention

✅ **Primary prevention is the whole of management** and is described in Findings 9, 14 and 15. **Secondary prevention** is the 18-22 week anomaly ultrasound, which detects rather than prevents and informs decisions about continuing the pregnancy and about delivering at a centre with neurosurgical capability. **Tertiary prevention** is surgical correction, shunt surveillance and early intervention for the dysmorphic subgroup.

❌ **Counselling:** genetic counselling for Mendelian recurrence risk does not apply. Teratogen counselling does, and it carries the single most useful message available here: recurrence risk in a subsequent pregnancy depends on whether the exposure is repeated, so it is modifiable to near zero by changing the medication. That distinguishes this syndrome from every genetic condition in the differential.

❌ Immunization, vector control and sanitation: not applicable. The relevant public health lever is prescribing policy, which is already producing a measurable decline (PMID: 40700674).

14. Other species and natural disease

❌ **No naturally occurring equivalent exists in any species, and none can,** because the condition requires deliberate administration of a human pharmaceutical during pregnancy. OMIA has no entry, because OMIA catalogues inherited conditions. VetCompass has no relevant record. There is no breed predisposition and no VBO term.

Species	NCBI Taxon	What was shown
Mus musculus	NCBI:txid10090	Full phenotype recapitulation, strain differences, P450 modulation, embryo culture bradyarrhythmia
Rattus norvegicus	NCBI:txid10116	Whole embryo culture embryotoxicity at 60 µg/mL
Danio rerio	NCBI:txid7955	Teratogenicity of parent compound and not of the epoxide, with LC-MS metabolite quantification
Oryctolagus cuniculus	NCBI:txid9986	Liver microsome comparison for epoxide formation

Orthologues: mouse *Ephx1* (13849), *Kcnh2* (16509), *Mthfr* (17769), *Cyp3a11* (13112, functional analogue of CYP3A4); zebrafish *kcnh6a* and *ephx1* orthologues.

Comparative pathology. Mouse recapitulates the craniofacial and skeletal components: *"Various malformations were detected such as brachygnathia, calvarial deformity, vertebral deformity, short tail, and brachydactyly."* (PMID: 19895254). At the highest doses mice also develop spina bifida, anencephaly, meromelia and oligodactyly (PMID: 25553681), which exceeds the human spectrum and reflects dose rather than species difference.

Conservation of the mechanism. The hERG/IKr current is conserved from zebrafish to human, which is why the cardiac mechanism transfers. Epoxide formation is not conserved to the same degree, and that contrast is what makes the zebrafish result informative. ✖ **Zoonotic potential: not applicable.**

15. Model organisms

System	Type	Good for	Limitation
Mouse chronic oral gavage (SWV, LM/Bc, C57BL/6J, CD-1)	Mammalian, induced	Dose-response, strain genetics, full structural phenotype	Doses of 1000-2000 mg/kg/day far exceed human therapeutic exposure
Mouse whole embryo culture, GD 9-10	Mammalian, ex vivo	Isolating direct drug effects from maternal metabolism; the bradyarrhythmia assay	Cannot model maternal pharmacokinetics or chronic exposure
Rat whole embryo culture	Mammalian, ex vivo	Species comparison of embryotoxic threshold	Same
Zebrafish embryo, 5.25-120 hpf	Non-mammalian, induced	High throughput; LC-MS metabolite quantification in the same embryo; no mammalian CYP confound	Different metabolic repertoire, no placenta, different neural tube closure sequence
Reciprocal mouse crosses (SWV × C57BL/6JBk)	Mammalian, genetic	Separating conceptus from maternal genotype	Performed with acetazolamide, not carbamazepine

✖ **No knockout, knock-in, transgenic, conditional or humanized genetic model of this syndrome exists, and none is meaningful,** because there is no gene to knock out. The informative genetic models would be *Ephx1*-null or variant-knock-in mice exposed to carbamazepine, which test the modifier hypothesis rather than the disease. MGI, IMPC, KOMP and IMSR hold *Ephx1* and *Kcnh2* alleles, none crossed to a carbamazepine exposure protocol.

Recapitulation. ✔ Good for craniofacial hypoplasia, skeletal and vertebral defects, digit anomalies, growth restriction and high-dose neural tube defects. ✖ Poor or absent for the human nail hypoplasia phenotype, for the cognitive phenotype, and for the human therapeutic dose range.

Resources: MGI, IMSR, MMRRC, EMMA (mouse); RGD (rat); ZFIN (zebrafish); Alliance of Genome Resources for orthology.

Evidence base

86 papers were reviewed across five iterations. They divide into five groups, and the strength of what each group can support differs sharply.

📖 **Registry epidemiology: strongest for magnitude, weakest for mechanism.** EURAP (PMID: 21652013, PMID: 38497990) supplies the dose-response and the comparative ranking. EUROCAT via the systematic review and case-control study (PMID: 21127116, PMID: 26329145) supplies the defect specificity. The US modelling study supplies odds ratios and attributable burden (PMID: 21766433). Nordic registers supply growth effects at a scale where 0.2 SD effects become detectable (PMID: 38476755, PMID: 31381574, PMID: 24449062). None of these can separate drug effect from epilepsy effect without an active comparator, which is why the Swedish lamotrigine-reference design carries more weight for that question than an unexposed-reference design.

📖 **Prospective clinical cohorts: strongest for phenotype definition.** Jones (PMID: 2725616), Ornoy (PMID: 9014606), NEAD (PMID: 19369666, PMID: 22491865, PMID: 22749607, PMID: 24934501) and the blinded dysmorphology study (PMID: 16239295). Sample sizes of 35 to 375 give these frequency estimates wide implicit confidence intervals, and they remain definitive for what the phenotype consists of.

🔬 **Experimental embryology: strongest for mechanism.** Whole embryo culture (PMID: 8916369), P450 modulation (PMID: 8711619), the plasma correlation study (PMID: 2878505), the bradyarrhythmia studies (PMID: 9587965, PMID: 17584909), the zebrafish studies (PMID: 34884510, PMID: 39188273), the strain and crossing genetics (PMID: 3603402, PMID: 1562800), the methylfolate enzymology (PMID: 7993656) and the epoxide hydrolase inhibition study (PMID: 2885938). This group carries both revisions in this report.

📖 **Prevention and guideline literature.** The target trial emulation (PMID: 41876129) is the most consequential clinical paper reviewed, because it converts a disputed null into a timing-conditional benefit. The AAN, AES and SMFM guideline (PMID: 38748979) and the AAN parameter (PMID: 19398680) define practice. Implementation studies (PMID: 38554037, PMID: 40588438, PMID: 29526345, PMID: 16060941) quantify the gap between guideline and practice.

⚖ **Papers that challenge findings in this report.** The commentary stating that folic acid cannot reduce carbamazepine-associated spina bifida risk (PMID: 29215383) grounded an earlier position in this investigation that the target trial emulation overturned. The sibling-comparison study (PMID: 42736039) challenges the registry neurodevelopmental findings (PMID: 39548057), and the challenge is accepted here. A US claims-based cohort reporting a modest ADHD and behavioural disorder signal with second-half-of-pregnancy exposure (HR 1.23-1.40) (PMID: 41813017) neither confirms nor contradicts the first-trimester structural findings, because it addresses a different exposure window. The Australian Pregnancy Register found untreated pregnancies in women with epilepsy tending to a lower malformation rate than treated ones (RR 0.48, 95% CI 0.23-1.00, n = 128 untreated) (PMID: 42085975), a relevant comparison with too few events to settle anything.

Supported and refuted hypotheses

Hypothesis	Verdict	Evidence
Fetal carbamazepine syndrome has a causal gene	✗ Refuted	No OMIM, no ClinVar, no linkage; exposure is sufficient
Risk rises with carbamazepine dose	✓ Supported	3.4% / 5.3% / 8.7%, n = 1,402
Spina bifida aperta is the signature major malformation	✓ Supported	OR 3.6 (1.3-7.8); only specific MCM in EUROCAT
Carbamazepine-10,11-epoxide is the proximate teratogen	✗ Refuted in 3 species	Mouse, rat, zebrafish; no plasma correlation
P450 bioactivation contributes	✓ Supported	Induction 10%→26%, inhibition 33%→16.7%, adducts up 2-3×
hERG/IKr blockade is the unifying mechanism	✓ Supported in mouse, ? inferred in human	Class specificity, dose-response, polytherapy additivity, defect anatomy
Carbamazepine inhibits the methylfolate axis at therapeutic levels	✓ Supported in vitro	Reduced Vmax, increased Km
Folic acid does not protect against carbamazepine malformations	✗ Refuted, with a timing condition	RR 0.55 preconception, RR 1.27 after
Carbamazepine lowers global IQ	✗ Refuted	Adjusted mean 106 (102-109) at 4.5 years vs 96 for valproate
Carbamazepine causes autism and intellectual disability	⚖ Unconfirmed	HR 1.25 and 1.30 in 3.18M children, null in sibling comparison of 2.20M births
Susceptibility is set by fetal rather than maternal genotype	✓ Supported in mouse	Reciprocal crosses; cross-agent extrapolation to carbamazepine
Low EPHX1 activity predicts anticonvulsant embryopathy	✓ Supported, n = 19, phenytoin	4/4 below threshold affected, 15/15 above unaffected

Two self-corrections during this investigation

Correction 1. An early finding endorsed the arene oxide and 10,11-epoxide mechanism as the leading explanation. Later findings overturned the metabolite's identity across three species while preserving the bioactivation principle. The surviving claim is weaker and more precise: a short-lived P450-generated species contributes, the stable epoxide does not, and the direct pharmacological branch may be sufficient on its own.

Correction 2. An early finding stated that folic acid does not protect against carbamazepine-associated spina bifida, following PMID: 29215383. A later finding explained that null as a pooling-across-timings artefact and replaced it with a timing-conditional benefit. This changes clinical advice, so it is the more consequential of the two.

Limitations and knowledge gaps

The hERG mechanism is demonstrated in mouse embryo culture and inferred in the human embryo. No human embryonic cardiac rhythm measurement under carbamazepine exposure exists and none is ethically obtainable. The inference rests on four concordances, which is strong circumstantial evidence and not direct demonstration.

The identity of the reactive bioactivated species is unknown. The 2,3-arene oxide leading to catechol and quinone intermediates is inferred from the direction of P450 modulation and from the absence of any plasma correlation. It has never been isolated.

The conceptus-genotype result is a cross-agent extrapolation. The reciprocal crosses used acetazolamide and the strain panel used phenobarbital. Neither used carbamazepine. The same applies to the EPHX1 prediction result, which used phenytoin monotherapy in 19 pregnancies without genotyping.

The folic acid effect size is pooled across all antiseizure medications. RR 0.55 comes from 521 initiators among 13,619 exposed pregnancies across all drugs, so the carbamazepine-specific projection is an assumption the study was not powered to test. The inverted-U shape, with no benefit from starting 13-52 weeks ahead, most likely reflects adherence decay and confounding by pregnancy planning rather than a biological window that reopens.

The prevalence figures are projections, not measurements. They multiply a published exposure denominator by published outcome rates and inherit every selection bias in both.

Residual confounding by indication is unresolvable in observational data. Maternal epilepsy itself carries risk, as does seizure occurrence during pregnancy, and the untreated-epilepsy comparison has too few events to settle the question.

Field	Status	Why
Epigenetic changes	✖ No data	No methylation or chromatin study for carbamazepine embryopathy
Transcriptomics, proteomics, metabolomics, lipidomics	✖ No data	No GEO, PRIDE or MetaboLights dataset
Single-cell and spatial transcriptomics	✖ No data	Not attempted in any model
CRISPR or RNAi functional screens	✖ No data	No screen targets teratogenic susceptibility
Quality of life instruments	✖ No data	No EQ-5D, SF-36 or PROMIS study
Survival and disease-specific mortality	✖ No data	Deaths attributed to the constituent malformation
Ethnicity-specific risk	? Untested	EPHX1 variant frequencies vary; no study has tested the prediction
Prognostic biomarker	✖ None exists	The one candidate is refuted

Proposed follow-up experiments

Ranked by expected value, combining the size of the gap, feasibility, and what would change if the experiment succeeded.

1. ⏳ **QTL mapping of carbamazepine teratogenic susceptibility in the LM/Bc, SWV and C57BL/6J panel.** The highest-value unexecuted experiment in the field. Strain differences are established (46.7% vs 28.6%) and fetal-genotype dependence is established, but the loci have never been mapped for this drug. Design: F2 intercross or Collaborative Cross lines, chronic oral carbamazepine at a dose giving ~30% malformation in the reference strain, genotype and phenotype 300-500 conceptuses, map to the malformation trait. A hit at *Ephx1* or *Kcnh2* would convert two inferred modifiers into demonstrated ones; a hit elsewhere would be new biology.
2. 💓 **Genetic rescue test of the hERG model.** Expose *Kcnh2*-heterozygous and wild-type mouse embryos to matched carbamazepine. The model predicts heterozygotes are sensitised, because they begin with less reserve IKr current. A null result would weaken the central mechanistic claim of this report, which is the reason to run it.

3. **EPHX1 genotype association in a carbamazepine-exposed registry cohort.** Genotype rs1051740 and rs2234922 in stored samples from EURAP or a Nordic register, using child rather than maternal genotype, with any major congenital malformation as the outcome. This is the direct human test of the 1990 amniocyte result with modern methods, it uses existing samples, and a positive result would support preconceptional risk stratification.
4. **Single-cell transcriptomic time course of carbamazepine-exposed mouse embryos, gestational days 8-11.** The hypoperfusion model predicts a hypoxia-response signature appearing first in the distal, least-perfused tissues and in the neuroepithelium of the posterior neuropore, with timing that tracks the arrhythmia. This fills the largest methodological gap and tests a specific spatial prediction.
5. **Trap and identify the short-lived reactive species.** Use glutathione and N-acetylcysteine trapping with LC-MS/MS in a human embryonic microsomal system under CYP3A4 induction, comparing adduct profiles with and without stiripentol. Identifying the species would close the one genuinely open question in the bioactivation branch.
6. **Carbamazepine-specific analysis of folic acid timing.** Re-run the target trial emulation restricted to carbamazepine monotherapy, accepting the loss of power, to replace the transported RR 0.55 projection with a direct estimate. The data already exist in the Nordic registers.
7. → **Implementation trial of preconceptional folic acid in women of childbearing age on carbamazepine.** The quality-improvement approach that raised prescription rates from 41% to 81.6% at one centre should be tested at scale with malformation rate as the outcome. Given 45.7% non-initiation and NNT 45, the achievable absolute reduction exceeds anything the mechanistic work would yield in the next decade.

Appendix: ontology terms for the knowledge-base entry

System	Term	Label	Role
MONDO	MONDO:0018263	Fetal carbamazepine syndrome	The disease
CHEBI	CHEBI:3387	Carbamazepine	Causal agent
NCIT	NCIT:C375	Carbamazepine	Causal agent
HGNC	HGNC:3401	EPHX1	Modifier, not causal
HGNC	HGNC:2637	CYP3A4	Bioactivating enzyme, not causal
HGNC	HGNC:6251	KCNH2	Drug target, not causal
HGNC	HGNC:7436	MTHFR	Downstream of the inhibited step, not causal
HP	HP:0001800	Hypoplastic fingernail	26%
HP	HP:0001792	Small nail	
HP	HP:0002414	Spina bifida	~0.5%, OR 3.6
HP	HP:0002475	Myelomeningocele	
HP	HP:0000175	Cleft palate	OR 2.4
HP	HP:0011800	Midface retrusion	
HP	HP:0000286	Epicanthus	
HP	HP:0000322	Short philtrum	
HP	HP:0000431	Wide nasal bridge	
HP	HP:0000369	Low-set ears	
HP	HP:0000592	Blue sclerae	
HP	HP:0009882	Short distal phalanx of finger	
HP	HP:0000252	Microcephaly	aOR 1.43
HP	HP:0001518	Small for gestational age	aOR 1.25
HP	HP:0001511	Intrauterine growth retardation	
HP	HP:0004325	Decreased body weight	

System	Term	Label	Role
HP	HP:0001263	Global developmental delay	20%
HP	HP:0000750	Delayed speech and language development	
HP	HP:0000717	Autism	Unconfirmed, null under sibling control
HP	HP:0001249	Intellectual disability	Unconfirmed, null under sibling control
HP	HP:0007018	Attention deficit hyperactivity disorder	
HP	HP:0002308	Arnold-Chiari malformation	Secondary to myelomeningocele
HP	HP:0001627	Abnormal heart morphology	
HP	HP:0000077	Abnormality of the kidney	
HP	HP:0001875	Neutropenia	Case-level
HP	HP:0002092	Pulmonary arterial hypertension	Case-level
UBERON	UBERON:0001049	Neural tube	Primary site
UBERON	UBERON:0004141	Heart tube	Site of initiating lesion
UBERON	UBERON:0001456	Face	
UBERON	UBERON:0001705	Nail	
UBERON	UBERON:0004248	Distal phalanx	
UBERON	UBERON:0001716	Secondary palate	
UBERON	UBERON:0002240	Spinal cord	
UBERON	UBERON:0000955	Brain	
UBERON	UBERON:0002113	Kidney	
UBERON	UBERON:0002412	Vertebral column	
CL	CL:0000710	Neurecto-epithelial cell	Neuropore closure
CL	CL:0002494		Arrhythmia site

System	Term	Label	Role
		Cardiac muscle cell of embryonic heart tube	
CL	CL:0000333	Migratory cranial neural crest cell	Craniofacial
CL	CL:0000138	Chondrocyte	Craniofacial cartilage
CL	CL:0000115	Endothelial cell	Perfusion
CL	CL:0000362	Epidermal cell	Nail bed
GO BP	GO:0001843	Neural tube closure	The failed process
GO BP	GO:0086091	Regulation of heart rate by cardiac conduction	The blocked process
GO BP	GO:0071456	Cellular response to hypoxia	Downstream
GO BP	GO:0006979	Response to oxidative stress	Downstream
GO BP	GO:0046653	Tetrahydrofolate metabolic process	Branch 3c
GO BP	GO:0006730	One-carbon metabolic process	Branch 3c
GO BP	GO:0017144	Drug metabolic process	Branch 3b
GO MF	GO:0005251	Delayed rectifier potassium channel activity	Drug target
GO MF	GO:0004301	Epoxide hydrolase activity	EPHX1
GO MF	GO:0004489	Methylenetetrahydrofolate reductase activity	MTHFR
GO CC	GO:0005886	Plasma membrane	hERG location
GO CC	GO:0005789	Endoplasmic reticulum membrane	CYP3A4, EPHX1 location
GO CC	GO:0005739	Mitochondrion	Reoxygenation ROS
NCBI Taxon	NCBI:txid10090	*Mus musculus*	Model
NCBI Taxon	NCBI:txid10116	*Rattus norvegicus*	Model

System	Term	Label	Role
NCBI Taxon	NCBI:txid7955	*Danio rerio*	Model
NCIT	-	Folic acid supplementation	Prevention
NCIT	-	Genetic counselling	Teratogen counselling
NCIT	-	Obstetric ultrasonography	Prenatal detection
NCIT	-	Surgical repair of myelomeningocele	Tertiary
NCIT	-	Cleft palate repair	Tertiary
NCIT	-	Speech and language therapy	Supportive

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